

CLINICAL TRIALS IN PSYCHOPHARMACOLOGY

A BETTER BRAIN

SECOND EDITION



EDITORS MARC HERTZMAN · LAWRENCE ADLER

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Editors

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Introduction

Clinical trials have become the major vehicle by which medical treatments now gain official approval for widespread application. They are the focus of much of the major work by pharmaceutical companies, and certainly their greatest expenditures. Regulatory bodies such as the American Food and Drug Administration (FDA) rely heavily, sometimes almost exclusively, on the results of clinical trials to confer their blessing for purposes of marketing pharmaceuticals.

Psychopharmacology is, in certain respects, a microcosm of developments in clinical trials; more so over the past decade. During that time the extent of trials has expanded greatly. A number of trends have become discernible, largely reflective of the general direction of pharmaceuticals in medicine.

This volume attempts to update and reflect developments in psychopharmacology trials. The authors have selected a series of international experts to assist by preparing reviews of their own areas of expertise. A number of themes emerge from the chapters comprising this collection.

Theme one: clinical trials in psychopharmacology have become institutionalized

Conducting a large trial was unusual half a century ago, not to say controversial. These days, it would be unthinkable to consider the utility of a pharmacological treatment without at least a large (three-digit), usually placebo-controlled, trial and generally multiple experiments. However, the formats for such trials, at least in the United States, have taken on the distinct sense of a cookbook formula. Not only is a microscopically prescribed recipe to be followed, but the focus of review has been more and more upon executing the steps exactly as dictated, without necessarily tailoring trials to the questions at hand or to the populations being treated. The result is to accommodate professional staff at both government agencies, for example the FDA, and at pharmaceutical industry firms who may have limited knowledge of the actual subject matter, of medicine in general and of research.

In addition, a cottage industry has now grown into a sizeable oligarchy of firms which cater to the large, so-called 'ethical' pharmaceutical firms, offering to conduct various aspects of the trials. Their ethos seems to be: this is what the FDA requires.

This may be the case, whether or not it has been tried out with the appropriate authorities. In such fashion, custom becomes encoded as regulatory mandate.

Theme two: clinical trials in psychopharmacology have expanded into new areas of diagnosis and treatment

Compared to the last edition of this volume, the editors have had a much harder time selecting particular areas of explication and, by inference, leaving others (even major areas) for other times and places.

By way of example, the licensure of medications which had been specifically tested on children and adolescents was very limited a decade ago. In fact, it was so limited that regulations were enacted to encourage more such explorations. The incentive was extension of exclusive patent rights on compounds: a potentially powerful tool, indeed. In the present volume, the editors have focused upon certain possibly developmental-related disabilities and their treatments. A case could certainly be made that adult diagnoses in other areas are not reflective of child diagnoses or of their treatments.

Theme three: clinical trials in psychopharmacology have, to a significant extent, become stultified

A more unsettling aspect of the expansion in numbers of trials and subjects is the push to license what are often ‘me-too’ drugs; these crowd out major scientific advances which might be substantially more rewarding in the long run. Alas, psychopharmacology trials are rife with examples of minor variations of themes. Often, they are little-disguised attempts to prolong patent life, with only minor advantages (if any) over previously licensed medications. In fact, these are typically modifications of a firm’s products already on the market, perhaps in danger of shortly becoming generic.

Theme four: progress on clinical trials in psychopharmacology continues apace

Nestled among the tedium of typical trials are other sorties, more promising of genuine progress. These range from taking advantage of general scientific developments (e.g. elaboration of the genome) to innovative analyses of ongoing issues and elaborations of data from large trials (e.g. the collaboratives such as in autism).

The reader has their own opportunity to decide how well these themes are elaborated. The sections and chapters are designed so that they can be browsed, pored over or delved into as reference reviews.

May they be stimulating and thought provoking!

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SECTION I

The Health Care Environment and Medications

1

FDA Reform: Déjà Vu Encore

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Abstract

The Food and Drug Administration (FDA) creates the climate for the development of new drugs and clinical research. A 30 year struggle to bring drugs to the market more rapidly culminated in the 1992 Prescription Drug User Fee Act (PDUFA). While drug review times have shortened, concerns about drug safety possibly associated with more rapid reviews have led FDA and Congress to tighten safety requirements that may well slow or discourage clinical research. The pipeline for new drugs has been shrinking recently because of problems in the translation of fundamental research to pharmaceutical applications, according to the FDA. The FDA has therefore expanded its mandate to embark on a critical path initiative to develop the necessary translational tools. Critics including Congress, the General Accountability Office, the Institute of Medicine and the FDA's own Science Advisory Subcommittee have sharply criticized the FDA's performance, stating that the FDA's science base is inadequate and that the FDA should have greatly increased resources to hire more scientists. After almost 50 years of concern about the FDA's oversight of drugs, it is time to carefully review the structure and organization of the FDA and to consider creating a separate agency dedicated only to the regulation of medical products. To strengthen its scientific resources, the FDA should consider much greater use of non-government scientists and physicians as a more cost-effective way to acquire necessary expertise.

Key Words

FDA; PDUFA; FDA reform; drug safety; critical path initiative; FDAAA; drug lag; drug pipeline problem; streamline clinical trials; comparative effectiveness

1.1 Introduction

The US Food and Drug Administration (FDA) is responsible for the safety of more than a trillion dollars worth of products each year, representing 25% of the US economy.

The FDA's management creates the climate for the development of new drugs and clinical research. The FDA imposed general standards for clinical trials, protects the rights and safety of research subjects and sets other clinical trial requirements by establishing what data are necessary to substantiate safety and effectiveness for marketing approval of a drug [1]. Drug and biologics work of the FDA is carried out by some 5000 employees, assisted by two dozen advisory committees at an annual cost of about one billion dollars.

The FDA's mission has disparate objectives for its control of drugs. Traditionally, the FDA focused primarily on drug safety, efficacy and security. Legislation enacted in 1997 added to its mission new responsibilities to help speed innovations that make medicines more effective, safer and more affordable, and to help the public obtain the accurate, science-based information they need [2]. However, the FDA has not yet demonstrated particular success in achieving these new responsibilities. Indeed, the number of drugs in the development pipeline has been shrinking and, because of safety concerns, the FDA has tightened regulatory requirements which has led to a reduction of the number of new drugs approved.

The emergence of a global economy for pharmaceuticals has complicated the work of the FDA. It no longer deals primarily with US-developed, sourced and manufactured products. Instead, it has to contend with an increasingly global environment for research and development, manufacture and import of drugs and their constituent components. Clinical trial offshoring of FDA-regulated trial sites located outside of the United States was at 41% in 2006, up from 15% a decade earlier.

Ten years ago, the FDA reported a growing US dependence on imported pharmaceutical products. It was noted that as much as 80% of the bulk drug substances, used by manufacturers in the United States to produce prescription drugs, was imported and that the number of finished drug products manufactured abroad for the US market was increasing. In 2007, the Government Accountability Organization (GAO) observed that the United States remains dependent on foreign establishments manufacturing drugs for the US market as the value of pharmaceutical products coming into the United States from abroad continues to increase [3]. However, the FDA lacks the ability to police more than 3000 overseas drug manufacturers to ensure compliance with US requirements. Moreover, increasing adverse public health episodes have been reported due to imported counterfeit and tainted FDA-regulated products.

After a decade of successful efforts in the 1990s to more rapidly review applications for new drugs, the FDA entered the twenty-first century with a swiftly escalating focus on the safety of drugs, the integrity of clinical trial data, the insufficiency of funding and scientific staff, conflicts of interest from advisory committee members, the adequacy of new drug safety reviews, unsafe drug imports and the shrinking pipeline of new medicines. Accordingly, Congress and the FDA have recently added

greater regulatory requirements to address widely publicized safety-related concerns. Congress and the FDA have also sought to address the ‘pipeline problem’ of the diminishing number of new drug applications by adding a new dimension to FDA work for facilitating the translation of scientific discovery into new medical products.

The FDA’s struggle to balance early access to drugs and concerns about their safety has a long history. The 1962 Amendments to the Federal Food Drug and Cosmetic Act established the FDA’s comprehensive authority to regulate human clinical trials and to approve drugs for marketing after finding substantial evidence of their safety and efficacy. Congress enacted this consumer protection in reaction to the tragic tetragenic effects of Thalidomide, resulting from its use in other countries by pregnant women to prevent nausea. Because of the FDA’s caution, slow review and lack of approval for Thalidomide, its detrimental impact was much less in the United States.

After the enactment of the 1962 Amendments, and for the next 30 years, the FDA was criticized for conducting slow reviews of new drugs for marketing approval. As early as the 1970s, doctors and economists complained that the United States had a ‘drug lag’, i.e. that fewer new drugs were approved in the United States than in other countries with modern drug regulatory regimes and that the costs of greater regulatory control were denying the benefits of therapies to Americans. As a practical matter, the impact of a drug’s slow or delayed introduction in the US market provided the FDA with an additional safety net, as the FDA could observe the safety experience of a new drug in other countries before approval in the United States.

The underlying reason for the FDA’s caution was aptly described by former FDA Commissioner Alexander Schmidt in testimony before hearings held by Senator Edward M. Kennedy:

In all of FDA’s history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren’t able to count them... The message to FDA staff could not be clearer. Whenever a controversy over a new drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made [4].

The FDA became less cautious in the mid-1980s, responding to political pressure from aggressive AIDS activists who campaigned for earlier and greater access to clinical trials and new drugs. AIDS patients were emphatic that they would accept higher and unknown health risks that could result from products with less clinical certainty rather than face certain death. In response, the FDA initiated the use of surrogate markers to demonstrate effectiveness as one way to speed up the drug approval process. (The surrogate marker is a substitute for a pivotal clinical measurement, typically prolongation of survival.)

When patients in an azidothymidine (AZT) clinical trial in 1986 were found to be doing much better than those in its control arms, the FDA authorized other patients to receive AZT under the compassionate use provisions of the law. (Shortly afterwards in 1987, AZT received rapid marketing approval.) Subsequently, the FDA

established several new programs that provided more rapid availability of promising new therapies. The following list provides examples.

- In 1987, the FDA began a new program called ‘treatment investigational new drugs (IND)’. Under this program, eligible subjects could receive investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND could be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks provided that: (i) the drug is intended to treat a serious or immediately life-threatening disease; (ii) there is no satisfactory alternative treatment available; (iii) the drug is already under investigation, or trials have been completed and (iv) the trial sponsor is actively pursuing marketing approval.
- FDA also began a ‘Parallel Track’ option as a way to offer wider access to promising new drugs for AIDS/HIV-related diseases under a separate ‘expanded access’ protocol. This protocol parallels the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs.
- In 1992 FDA established the ‘Accelerated Approval’ (Subpart H Approval) regime to make promising products for cancer and other life-threatening diseases available on the market on the basis of preliminary evidence such as a surrogate market prior to formal demonstration of patient benefit.

Some ten years later, responding to an increasing drumbeat of concern about drug safety, the FDA ratcheted up its efforts to ensure the safety of drugs during clinical trials and in the market place. As one critic observed, accelerated approval became ‘decelerated approval’ in 2003. The FDA eliminated the specific clinical development innovations that made accelerated approval possible such as single arm trial data. New requirements for randomized, double-blind, placebo-controlled clinical trials in refractory patient populations and mandatory post-approval clinical trials were also added [5].

From 2003 to 2008 concern for greater drug safety, partly because of concerns about antidepressant use in pediatric patients [6], erupted with proposals for reforms from Congress, the GAO, the Institute of Medicine and the FDA’s own Science Board, among others. They made overarching recommendations to tighten safety oversight, dramatically increase resources for the FDA and improve its management by greater use of information technology (IT). They did not, however, seriously examine the foundational issues of how to improve the basic paradigm for the development and marketing of drugs in light of present and future trends in the science of drug development, and whether government is optimally structured to do this. To its credit, the FDA has initiated some steps in this direction with its Critical Path initiative.

Basic questions about the best ways for the US government to organize, structure and fund its medical products regulation remain to be critically examined. Would a dedicated medical products agency work better and be less susceptible to political pressure? What type of scientific knowledge base does a drug regulatory agency

require for regulatory purposes? Does the FDA's approach, which relies primarily on internal staff, defeat its own goal of having the best science base when better quality scientific technical knowledge is available from outside the FDA? What is the ideal paradigm(s) for drug development considering the constantly expanding base of fundamental scientific knowledge and the need for both regulatory flexibility (to permit the advancement of scientific investigation) and regulatory certainty (to encourage investment in innovative product development)? What should the scope of drug regulation entail for safety and effectiveness, for example the translation of innovation into clinical trials and products, evidence-based health care, drug superiority and other areas? How best can the United States regulation manage to maintain the integrity of imported drugs and ingredients?

1.2 The 1992 prescription drug user fee act adds funds and changes FDA's focus

The chronic 'drug lag', the inadequate level of drug review staff resources at the FDA, the positive experience of more rapid access to AIDS clinical trials and new drugs and the pressure to conduct more rapid reviews of therapies for serious diseases in addition to AIDS in the early 1990s enabled the FDA to charge drug user fees to help fund the acquisition of more drug reviewers.

The FDA had long sought user fees to help fund its operations, which industry had resisted [7]. Other countries with advanced regulatory systems collect user fees for drug and medical device regulatory activities, some cover up to 100% of the costs of the regulatory agency [8].

In 1992, Congress enacted the Prescription Drug User Fee Act (PDUFA) to authorize the FDA to charge pharmaceutical manufacturers user fees, to supplement the annual FDA appropriations. In return, the FDA committed itself to achieving shorter approval time goals. These fees include an application fee, an annual establishment fee and an annual product fee. Because Congress limited authority for user fees to five years, PDUFA has been reauthorized in 1997, 2002 and 2007 by PDUFA II, PDUFA III and PDUFA IV.

Originally, the 1992 PDUFA funds could only be used for the process of reviewing new drug applications. Subsequently, Congress authorized their use for an increasing range of drug-related activities. They now support the full range of FDA activities associated with new drugs from IND application to post-marketing management and surveillance. The size of the fees has increased and they currently support more than 50% of the cost of the Center for Drug Evaluation and Research (CDER).

The FDA has become dependent on user fees. Without them, the CDER would be seriously underfunded and would be unable to function. PDUFA reauthorization has therefore become 'must pass' legislation since the Congress, administration and industry do not want FDA to be denied funds considered essential for the review of new drug applications. Accordingly, PDUFA reauthorization provides a relatively easy opportunity every five years to make changes to the law. Each reauthorization of PDUFA has brought legislative changes to the underlying Federal Food Drug and Cosmetic Act.

- In 1997, PDUFA II added modest regulatory reforms and codified a new FDA mission.
- The 2002, PDUFA III reauthorization broadened the scope of FDA activities which user fees could fund to include preclinical to post-market surveillance for three years.
- The 2007, PDUFA IV authorized FDA to provide funds to the private sector for pursuing FDA's Critical Path Initiative. The FDA's risk management and post-marketing surveillance authority was extensively increased from earliest research through the marketing lifecycle. FDA can now impose this level of control by making approvals conditioned upon agreements by the manufacturer to conduct long-term specific Risk Evaluation and Mitigation Strategies (REMS).

PDUFA has brought unintended effects. Within the agency, for example, organizational components can be divided into the haves and have-nots. Notable differences exist in the resources and level of activity in the FDA for reviews of drugs and medical devices funded by user fees and those FDA components without user fees. In the US Senate, another unintended effect arose in 1992 because of PDUFA's tax-related aspects. The Finance Committee gained jurisdiction over FDA's drug approval activities. Accordingly, Senator Grassley, the most senior Republican on the committee, has been the Senate's strongest FDA critic, conducting extensive investigations and critical hearings and exposing highly publicized weaknesses in the FDA's drug approval process.

1.3 PDUFA shortens drug review times and eliminates the drug lag

By 1997, the FDA claimed that user fees had enabled the agency to reduce the 30-month average time that used to be required for a drug review before PDUFA to just 15 months. This was because of managerial reforms and the addition of 696 employees to the agency's drugs and biologics program financed by \$329 million in user fees from the pharmaceutical industry [9].

While the net result of the PDUFA has been shorter review times for new drugs, although the actual extent to which PDUFA alone was responsible for the shortening is controversial. A Brookings/American Enterprise Institute (AEI) study noted that approval times had been falling at 1.7% per year prior to implementation of PDUFA. Of the total observed decline in approval times between 1991 and 2002, approximately two-thirds can therefore be attributed to PDUFA. Much of this impact in this time period occurred in the initial years from 1992 to 1997 [10].

In 2002, the GAO observed that approval times had declined for both priority drugs (those that the FDA expect to provide significant therapeutic benefits compared to drugs already marketed) and standard drugs (those for which there are no perceived significant therapeutic benefits compared to those for available drugs).

- From 1993 to 2001, the median approval time for new drug applications for standard drugs dropped from 27 to 14 months. The median approval time for new drug applications for priority drugs has remained stable at six months since 1997.
- However, the approval time for standard new molecular entities (NMEs), drugs containing active ingredients that have never been marketed in the United States in any form, had increased since 1998 from about 13 to 20 months. In contrast, median approval times for new biologic applications had fluctuated since 1993, ranging from a low of 12 months in 1997 to a high of about 32 months in 1995. In 2001, the median approval time for biologic applications was about 22 months.

Finally, it is important to recognize that although drug review times have fallen, the total drug development times from drug discovery to marketing approval remains essentially unchanged. The reasons include the longer time necessary to discover NMEs and additional FDA requirements for conducting clinical trials.

1.4 PDUFA timetables feed safety concerns

Concerns began to be raised by 2000 that an increasing proportion of drugs approved under PDUFA timetables were withdrawn from the market for safety reasons. For example, Public Citizen, a consumer safety advocacy organization, testified on 15 September 2000 before FDA that consumers have suffered substantial harm from a large number of redundant ‘me-too’ drugs (e.g. Posicor, Duract, Redux and others) with known safety problems and no more effective than drugs already available [11]. Public Citizen noted in 2002 [12] that an additional three new drugs had been withdrawn from the market for safety reasons – Lotronex, Raplon and Baycol – making a total of 10 drugs withdrawn from the US market since 1992 when PDUFA was enacted.

In 2002, the GAO reported to Senator Edward M. Kennedy in response to his request for a review of the impact of PDUFA on approval times and drug safety. GAO concluded that a higher percentage of drugs had been withdrawn from the market for safety-related reasons since PDUFA’s enactment than prior to this, but that the size of the increase in drug withdrawal rates differs depending on the period examined. The share of more recently approved drugs (1997–2000) that have been withdrawn has risen from 1.56 to 5.34% in the period immediately after PDUFA’s implementation (1993–1996). When withdrawal rates are compared for the eight-year periods before and after PDUFA, the increase is from 3.10 to 3.47%. Drug withdrawals have been affected by several factors. For example, some drugs were removed from the market because doctors and patients did not use them correctly, while other drugs were found to have rare side effects that were not detected in clinical trials [13].

The FDA disagreed with the GAO’s analysis and discussion of drug withdrawal rates. FDA officials said that GAO’s analysis of drug withdrawals for the eight-year period preceding PDUFA compared to the first eight years of PDUFA did not show any real increase, and that GAO’s analysis using the four-year groupings was significantly affected by the small number of withdrawals during each period.

Increasing public and Congressional concerns about drug safety [14] exploded as a result of the widely-publicized alarm raised about cyclooxygenase (COX)-2 inhibitors (e.g. Vioxx and Celebrex), selective serotonin reuptake inhibitors (SSRIs) and Ketek. Congress held multiple hearings on the safety of these drugs and the adequacy of FDA reviews, including testimony from an FDA whistleblower.

A 2006 GAO report stated that the FDA lacks clear and effective processes for making decisions about, and providing management of, post-market safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient control by management and data constraints. GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them [15].

A 2007 Institute of Medicine (IOM) report stated that the drug safety system was impaired by the following factors: serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER that is not optimally functional; and unclear and insufficient regulatory authorities, particularly with respect to enforcement [16].

In late September 2007, the Health and Human Services (HHS) Inspector General issued a scathing report stating that the FDA does little to ensure the safety of persons who are clinical trial subjects. As reported in the *New York Times*, the inspector general said that ‘federal health officials did not know how many clinical trials were being conducted, audited fewer than 1% of the testing sites and, on the rare occasions when inspectors did appear, generally showed up long after the tests had been completed’ [17].

Both the GAO and IOM made recommendations to add greater drug safety requirements and more post-market surveillance. IOM urged a much greater FDA role in surveillance and offered a broad list of recommendations for greater pre- and post-market risk management and other purposes. Likewise, GAO recommended that the Congress consider expanding FDA’s authority to require drug sponsors to conduct post-market studies when needed, track post-market drug safety issues, revise and implement its draft policy on major post-market safety decisions, improve the dispute resolution process and clarify the office of drug safety’s role in scientific advisory committees.

Professor Daniel Carpenter and associates tied the issue of safety to the requirements of PDUFA reviews [18]. They claimed that the PDUFA clock has dramatically influenced FDA review behavior such that a high proportion of approvals are concentrated in the months and weeks just before the deadline, and relatively few occur shortly afterwards. PDUFA deadlines appear to influence FDA decisions that may have an impact on drug safety. Based on an analysis of six measures, including frequency of labeling revisions and safety-based withdrawals from the market, they claim, ‘the rate at which drugs experience post-marketing regulatory events is appreciably higher for drugs approved in the months before the PDUFA clock deadlines, compared to others’.

John Calfee of the American Enterprise Institute strongly disagrees with the conclusion that FDA safety had been compromised. Calfee states that ‘despite its influence and provenance, the IOM report was deeply flawed’ [19]. One problem is

that none of the authors were drug development specialists, which virtually guaranteed that the exigencies of new drug development would be slighted in comparison to drug safety. Worse, the report was remarkably unacademic and provided only cursory scientific support for much of its analysis and recommendations. He argues that the drug safety crisis never existed because (i) the facts do not support the safety claims alleged for the specific drugs of concern or (ii) the risks are greater for newer drugs than older ones. He further raises concerns about the risks that will result for the FDA and the public from the unnecessary expansion of FDA powers, and how that could further discourage new drug development.

1.5 FDA responds to safety concerns

According to Stephen Mahinka [20], the FDA responded to the safety concerns with various actions by:

- increasing its rate of rejections and delays of new drug applications because of safety concerns
- requiring phase IV studies as a condition of a new drug approval
- issuing safety alerts
- issuing more public health advisories requiring label revisions/warnings
- suggesting additional clinical trials
- imposition of restricted distribution programs
- removal of previously approved indications
- market withdrawals.

Moreover, the FDA initiated further actions regarding drug safety by:

- establishing a new Drug Safety Board (March 2007) to provide independent management and advice to FDA on drug safety issues and disseminating safety information
- establishing new associate directors for safety in all 17 FDA drug review divisions
- initiating a new pilot program to prepare safety profiles for several approved NMEs
- establishing a new Risk Communication Advisory Committee to assist the Agency in communicating risks and benefits to the public

- initiating planning to integrate genomic information into drug prescribing
- issuing a new *FDA Drug Safety Newsletter* (September 2007) to report early safety findings.

1.6 The pipeline problem

In 1993, US pharmaceutical research and development (R&D) spending began to surpass the amount of money spent by the National Institutes of Health (NIH) on biomedical research. By 1997, the number of applications for NMEs and biologics license applications (BLAs) received by FDA began to decline, as shown in Figures 1.1 and 1.2.

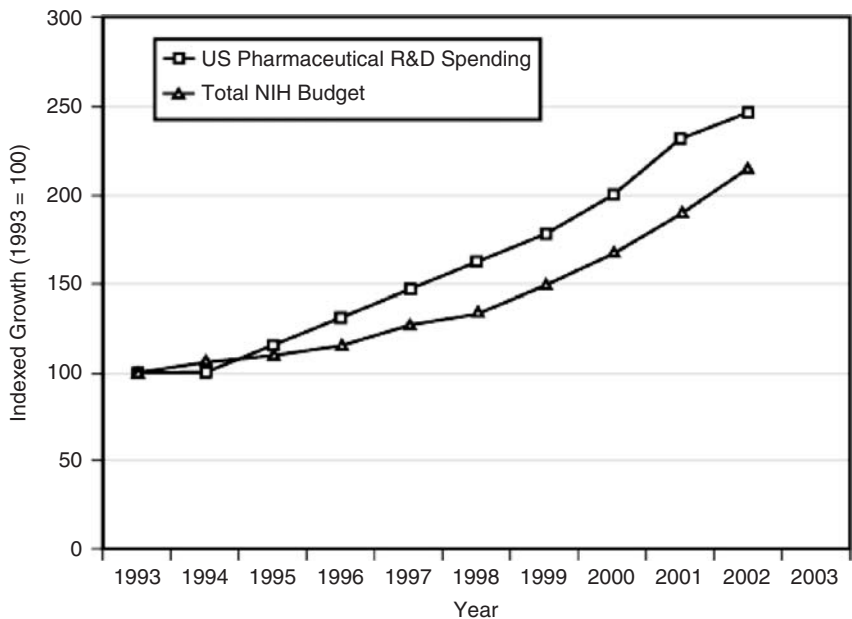


Figure 1.1 Ten-year trends in biomedical research spending. The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993–2003) and by pharmaceutical companies’ research and development (R&D) investment. (Source: PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2002/2003.)

In 2002, the Department of HHS began its own initiatives to accelerate the development of new medical products. Dr Elias Zurhouni, the new Director of the NIH, convened a series of meetings to chart a ‘roadmap’ for medical research in the twenty-first century, particularly translational research.

This process was designed to ask the kind of probing questions that a complex research organization should periodically pose, especially when in transition. The roadmap was

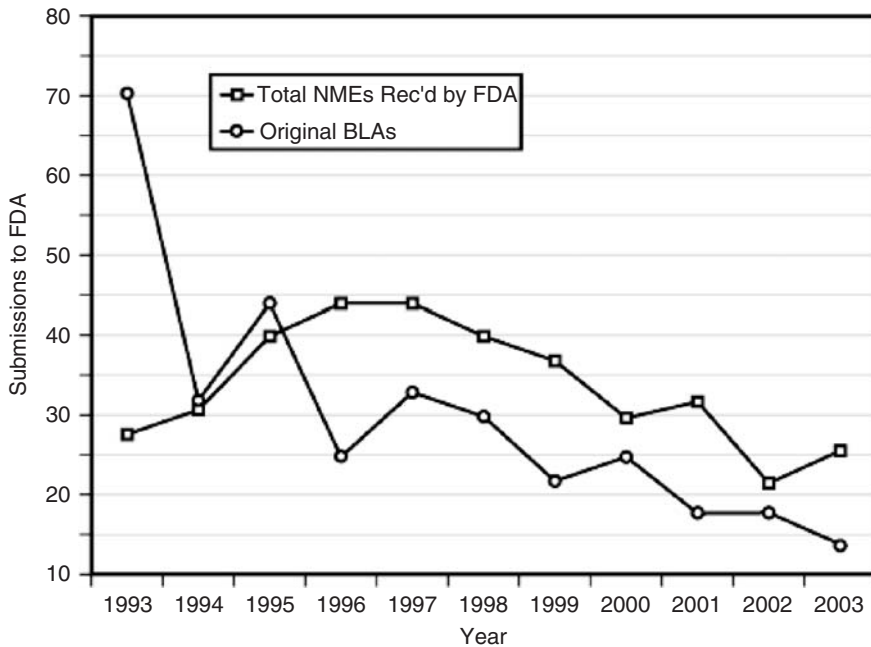


Figure 1.2 Ten-year trends in major drug and biological product submissions to FDA. The figure shows the number of submissions of NMEs (drugs with a novel chemical structure) and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide. (Source: FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Product*, March 2004.)

purposefully focused on efforts that no single or small group of institutes or centers could or should conduct on its own, but that NIH as a whole must address to ensure both efficient and effective discovery. The goal was to define a compelling, limited set of priorities that can be acted on and are essential to accelerate progress across the spectrum of the institute missions [21, 22].

A year later in early 2003, the newly appointed FDA Commissioner Mark McClellan started an effort to improve the development and availability of innovative medical products by improving new product reviews and facilitating new products through clearer, up-to-date guidance for particular diseases and for emerging technologies. The FDA noted a worldwide trend in fewer applications for review of NMEs.

Explanations cited include a weakened investment climate, a trend toward development of relatively minor improvements in types of drugs already on the market, concerns that companies are only interested in products that have the potential to be 'blockbusters', and additional time required for product developers to cope with a 'deluge' of new basic scientific findings in such advanced areas as genetics, genomics, and proteomics. FDA is also cited for the declining application rate, by some who believe that the agency is becoming more conservative in the face of recent drug withdrawals

(although the rate of drug withdrawals has not risen over past years), and that FDA desires to seek increasingly more data about a drug, thus causing larger and longer study trials that consume drug development resources. In addition, recent research has shown that the cost of developing a new drug has increased considerably [23].

The FDA proposed to reduce product development times by (i) reducing delays and cost in product approvals by avoiding multiple review cycles and (ii) improving the review process through a quality systems approach to medical product review. The FDA also proposed plans to enhance three key areas of emerging technology: cell and gene therapy; pharmacogenomics/pharmacogenetics and novel drug delivery systems; and collaborative clinical guidance development.

In 2004, the FDA announced a broader *Critical Path Initiative* to stimulate and assist a national effort to modernize the scientific process (the ‘critical path’) through which FDA-regulated products are developed, evaluated and manufactured. The FDA wanted to improve the critical route from medical discoveries in the laboratory to consumers more efficiently. The Critical Path Initiative would be a collaborative effort between government, industry and academia.

The 2004 FDA report *Challenge and Opportunity on the Critical Path to New Medical Products* blamed the applied sciences for the lack of new tools to obtain fundamentally better answers about how the safety and effectiveness of new products can be demonstrated in faster timeframes, with more certainty and at lower costs.

In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century’s candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures. Finally, the path to market even for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods [24].

According to FDA’s Janet Woodcock, there had been an explosion of scientific discoveries that can help produce more and better medical products. ‘But the efficiency for scientific discoveries being translated into medical products is very low – in fact, it’s worse than it was 10 years ago. . . Today, new compounds that make it through Phases 1 and 2 of clinical trials fail 50% of the time in Phase 3 compared to a 20% failure rate 10 years ago’ [25]. To develop medical products more efficiently, Dr Woodcock responded that:

We need better tools to predict and detect safety problems early in the Critical Path so that products likely to fail are weeded out and developers can focus on products with a high probability of safety and effectiveness. We also need tools to guide the sponsor of a drug in choosing the appropriate dose and regimen or, in the case of a medical device, the right size and placement. And manufacturers need tools to better mass-produce an approved medical product, such as a vaccine, and evaluate the quality of the finished product. . . So we need to build a better tool kit. And the tools must be made publicly available for use by all researchers and product developers.

The FDA's Critical Path initiative began slowly, as noted in the trade press almost two years later in January 2006:

The [critical path] white paper was written with a sense of urgency, and issued with fanfare. A list of research priorities was promised within a matter of months. And then . . . seemingly nothing. The "research opportunities" list never appeared, and Critical Path seemed to drop off the radar as public concern veered in the direction of drug safety, and politicians railed about the "too-cozy" relationship between FDA and the industry. As recently as this fall [2005], Critical Path looked dead or close to it [26].

In March 2006, the FDA issued the *Critical Path Opportunity Report* with a list of research opportunities intended to improve product development in the short- and mid-term. The report presented 76 specific scientific opportunities that FDA stated 'if undertaken, would provide a starting place for collaborative work on modernizing the critical path sciences'. The opportunities were organized into six priority topics and were identified through 'extensive outreach with patient groups, health-related organizations, the pharmaceutical industry, academia and other federal agencies'.

In June 2008, the FDA published the key FDA Critical Path Activities underway in 2007. FDA lists these activities in six categories as follows.

- 1 **Better evaluation tools.** Biomarker development is a major focus. A new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans) and facilitate the development of new types of clinical trials that will produce better data faster.
 - (a) FDA is a founding member of the public/private Biomarkers Consortium that seeks projects to aim to search for and validate new biomarkers to accelerate the competitive delivery of successful new technologies, medicines and therapies for prevention, early detection, diagnosis and treatment of disease.
 - (b) FDA, NCI, NIH and the Centers for Medicare and Medicaid Services (CMS) formed the Oncology Biomarker Qualification Initiative (OBQI) – an agreement to collaborate on improving the development of cancer therapies and the outcomes for cancer patients through biomarker development and evaluation.
 - (c) FDA issued industry guidance in May 2007, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, that provides recommendations to applicants on endpoints for cancer clinical trials submitted to FDA to support effectiveness claims in new drug applications, BLAs or supplemental applications. It also provides background information and discusses general regulatory principles. The endpoints discussed in this guidance are for drugs to treat patients with an existing cancer. This guidance does not address endpoints for drugs to prevent or decrease the incidence of cancer. FDA plans to prepare guidelines for endpoints for specific types of cancer.
 - (d) FDA will seek to better detect and react to safety issues through risk minimization action plans and REMS.

- 2 **Streamlining clinical trials.** Reforming the clinical trial process – both design and trial conduct – would dramatically improve the efficiency of product development.
 - (a) *Adaptive clinical trials* allow those engaged in drug development to respond to what they learn about the safety and potential benefits of new medicines in the development process by making modifications to treatment, endpoint or target population during testing. These tools may help arrive at a positive conclusion about an effective treatment with exposure of fewer patients in the testing process. They also allow drug developers to spend less time and money discovering that a new treatment does not work or must be discarded because of a high incidence of serious side effects.
 - (b) *Exploratory IND studies* were the subject of a January 2006 guidance designed to facilitate very early exploratory scientific studies in people before the standard safety studies (phase 1) begin. Because only small amounts of drugs are used in these early studies, they represent fewer potential risks for people in these trials. The guidance makes recommendations about safety testing, manufacturing and clinical approaches that can be used in these very early studies. The guidance explains how medical researchers can take full advantage of the flexibility built into existing regulations in the amount of data needed when asking the FDA's permission to proceed with such a study, enabling more rapid delivery of innovative products to patients.
 - (c) *Personalized medicine and pharmacogenetics* will allow decisions on which patients should receive what drug and in what dose to be determined based on genetics.
- 3 **Harnessing bioinformatics.** The application of mathematics, statistics and computational analysis to biological information holds the potential to reduce the size and scope of human and animal trials while improving development efficiency and predictability of results. For example, the concept of *model-based drug development* holds vast potential to support more efficient and effective development of drugs and medical devices.
- 4 **Moving manufacturing into the twenty-first century.** The ability to reliably manufacture a high-quality product on a commercial scale is a frequent stumbling block. Critical path tools that help identify and analyze critical product attributes hold the potential to improve both manufacturing efficiency and quality.
- 5 **Developing approaches to address urgent public health.** Needs include antibiotics and counter-measures to combat emerging infections and bioterrorism. Rapid methods for identifying infectious agents will improve our ability to develop new treatments and to respond to emergencies. Models are needed to test new treatments when testing in humans is unethical.
- 6 **Specific at-risk populations – pediatrics.** This will combine and analyze data from existing pediatric studies and look to new genomic technologies for improved diagnosis and treatment of adolescent depression. In addition,

infections in newborns are a significant public health problem and pose difficult development issues that could be overcome with better animal models.

The *Critical Path Opportunities* report also listed the need to clarify the regulatory process and to build a national infrastructure that will support and continually improve the critical path sciences. For example, the critical path needs academic programs in experimental medicine as well as clinician researchers who can work effectively in the laboratory as well as with animal and human studies.

Updates to the Critical Path List are available on the FDA Critical Path web site [27].

1.7 The 2007 FDA Science Board's Subcommittee on Science and Technology report

In December 2006, FDA Commissioner Andrew C. von Eschenbach requested that the Science Board, an advisory committee to the commissioner, form a subcommittee to assess whether science and technology at the FDA can support current and future regulatory needs. Specifically, the subcommittee's charge was to identify the broad categories of scientific and technologic capacities that the FDA needs to fully support its core regulatory functions and decision making throughout the product life cycle, today and during the next decade. The Science and Technology Subcommittee of the FDA Science Board was composed of three members of the Science Board and other experts representing industry, academia and other government agencies, and included individuals with extensive knowledge of cutting-edge research.

The report [28] was a scathing assessment of the FDA's capabilities with the following overarching conclusions.

- The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak.
- The FDA cannot fulfill its mission because its scientific workforce does not have sufficient capacity and capability.
- The FDA cannot fulfill its mission because its IT infrastructure is inadequate.

The subcommittee found that these deficiencies have two sources.

- *The demands on the FDA have soared* due to the extraordinary advance of scientific discoveries, the complexity of the new products and claims submitted to FDA for pre-market review and approval, the emergence of challenging safety problems and the globalization of the industries that FDA regulates.
- *The resources have not increased in proportion to the demands.* The result is that the scientific demands on the agency far exceed its capacity to respond.

This imbalance is imposing a significant risk to the integrity of the food, drug, cosmetic and device regulatory system, and hence the safety of the public.

The subcommittee further noted that the impact of the deficiency is profound precisely because science is at the heart of everything the FDA does. The Agency will flounder and ultimately fail without a strong scientific foundation. That foundation rests on three pillars.

- 1 **Strong selective scientific research programs that are appropriately mission-supportive, in all areas of FDA responsibility.** This research is critical because it is not conducted by other public or private entities, but is fundamental to the discharge of FDA's statutory responsibilities to protect and promote the public health.
- 2 **Excellent staff with cutting-edge scientific expertise appropriate to the mission.** This expertise includes the ability to access, understand and evaluate science; effectively apply this science to the regulatory process; and communicate the implications of its findings for product safety and efficacy to the public.
- 3 An information infrastructure and processing capability that ensures the FDA has access to the best data and information necessary to support the regulatory science required to fulfill the FDA's mission.

The subcommittee argued for vastly increased resources for the FDA for science but provided no specifics other than the obvious conclusion that 'FDA must have the scientific staff and resources to undertake the regulatory research that will provide a basis to: (1) improve capacity for safety and efficacy evaluations and monitoring of candidate and licensed products, (ii) modernize current regulatory pathways and (iii) develop new regulatory pathways where there are currently none'.

The subcommittee also claimed that this research must be undertaken by FDA because it is mission critical, and because it either cannot or will not be done by other government agencies or industry.

The subcommittee did note that more than resources alone would be necessary, but without resources FDA would clearly fail to deal with its precarious situation.

1.8 The FDAAA of 2007 reauthorize PDUFA and provide new authority to address safety and the critical path initiative

The Food and Drug Administration Act Amendments of 2007 (FDAAA) included the reauthorization of PDUFA IV and changes to user fees, FDA's pre-market review of drugs and post-marketing drug safety requirements. Included here are only drug-related provisions of PDUFA IV and the FDAAA [29].

The PDUFA IV amendments for pre-market review performance goals do not differ significantly from PDUFA III. In its commitment for PDUFA IV funding, the

FDA agreed to complete several guidance documents. The new performance goals include the development of a new five-year plan to modernize FDA's drug safety and pharmacovigilance process. The FDA will also seek to reduce medication name confusion with new priority name review initiatives.

PDUFA IV substantially increases the way that FDA can spend user fees to pursue drug safety. Originally only PDUFA I authorized the use of user fee revenues for the review of human drug applications. The 2002 Amendments added limited authority for safety-related activities, namely collecting, developing and reviewing safety information on drugs approved, including adverse event reports, during a period of time after approval of such applications or supplements (not exceeding three years). PDUFA IV removed the three year restriction, thus permitting the use of user fees for the full range of post-market activities including the development and use of improved adverse-event data collection systems and improved analytical tools to assess potential safety problems.

The 2007 amendments expanded the exemption of orphan drugs from the annual product and establishment fees. PDUFA had previously exempted orphan drugs from application fees. Similarly, the FDA may waive or reduce user fees when necessary to protect public health.

The 2007 amendments also reauthorized and amended the 2003 Pediatric Research Equity Act (PREA). PREA had required that most applications for drugs or biologics include a pediatric assessment. Now a new event reports on products whose labeling has changed as a result of pediatric assessment. Similarly, the amendments reauthorize and amend the 2002 Best Pharmaceuticals for Children Act (BPCA). BPCA gives an additional six months of exclusivity or patent protection for new and currently-marketed drugs when applicants conduct pediatric studies on products identified by FDA. The 2007 change added preclinical studies to pediatric studies and shortens the time for sponsors to qualify for exclusivity.

The 2007 amendments addressed concerns about the integrity and transparency of the drug trials and their review. The amendments provide the public with much expanded access to information about clinical trials and their results. The ClinicalTrials.gov database has expanded from only drug trial information on INDs for serious and life-threatening diseases or conditions to all diseases and conditions. In addition, a second database will be established to include results and adverse events on all trials that form the basis of an efficacy claim or are conducted after a drug or device is approved. New conflict of interest rules for FDA advisory committees also were added to promote integrity and transparency.

FDAAA authorized a way to fund FDA's Critical Path initiative. It established the Reagan-Udall Foundation for the FDA, a non-profit corporation to advance FDA's Critical Path Initiative and to identify and address unmet scientific needs in the development, manufacture and evaluation of the safety and effectiveness of FDA-regulated products, including post-market evaluation.

The FDAAA's most expansive provisions responded to concerns about the safety of drugs after approval. The law gives the FDA new authority to require post-approval studies and clinical trials, to request that safety information be added to labeling and to require the submission and performance of a REMS.

FDA is given broad authority to require post-market studies or clinical trials ‘on the basis of scientific data’ deemed appropriate by the FDA, ‘including information regarding chemically related or pharmacologically-related drugs’ to assess a known serious risk or signals of a serious risk or to ‘identify an unexpected serious risk when available data indicates the potential for a serious risk’.

REMS adds substantial new authority. The FDA can require REMS during clinical development or post-approval if FDA determines that specific interventions are needed to ensure that benefits outweighs the risks. The REMS must be submitted with the application for the review of a new drug. Items of consideration for products in clinical development include:

- estimated size of likely patient population
- seriousness of disease or condition
- expected benefit of the drug
- expected duration of treatment
- seriousness of known or potential adverse events
- whether the drug is an NME.

For approved products, criteria can include new safety information that emerges after approval. This includes clinical trial data, adverse event reports, post-approval studies, peer-reviewed literature, risk identification and analysis system or other means about:

- a serious risk or unexpected serious risk that arises after drug approval, REMS required or last REMS assessment or
- effectiveness of the approved REMS (since the last assessment).

FDAAA establishes new civil penalties for violations of these safety requirements. These are capped at \$250 000 per violation or up to a maximum of \$1 000 000 for all violations in a single proceeding with additional penalties for continuing violations.

Finally, in response to concerns that had been raised regarding direct to consumer advertising (DTC), the amendments authorized a new Pre-review of Television Advertisements program with a new user fee. However, because the program failed to reach mandated revenue targets and Congress had not provided other funds for it, the FDA issued a notice in January 2008 that the program would not be implemented because the user fees for the program were not provided. FDA is now authorized to impose civil penalties for DTC advertising that is false and misleading, up to \$250 000 for the first offense and \$500 000 for a subsequent offense. A DTC advert that had gone through the now dormant pre-review program would have been exempt from civil penalties.

1.9 The impact of PDUFA on FDA

PDUFA has not only speeded up the review times for new drugs, but also made fundamental changes to the Center for Drug Evaluation and to the entire FDA. CDER no longer lacks the resources to complete reviews quickly and PDUFA funds can now be used for safety reviews. Industry found the cost of user fees of \$900 000 in 2006 to be an acceptable cost, considering the previous cost of some \$10 million lost for each month of delay.

User fees help provide the resources to expand efforts for the safety of products and assist the Critical Path Initiative. The FDA's role has therefore ventured into new territory in the efforts to facilitate the translation of research into new products through new tools and approaches to clinical trial development. Post-marketing surveillance also expands the FDA's ability to monitor the use of products in the general population.

The user fees available for drugs and medical devices have created a split within the FDA. Those parts of the FDA without user fees are the poor siblings of the user-fee-funded components. Even within CDER, the non-user-fee-funded activities, such as generics, are claimed to receive less attention. Also, because user fee revenues do not cover certain unanticipated cost increases in user-fee-funded activities, appropriated funds from other parts of FDA have had to subsidize this shortfall.

While industry and certainly patients benefit from the availability of new therapies from more rapid reviews, critics complain that by becoming dependent on industry funding, FDA has lost a degree of flexibility and objectivity in its ability to deal with industry. These critics claim that simply receiving industry money creates an appearance of a conflict of interest and places subtle pressures on the FDA. They complain that industry and FDA negotiated the user fee drug review goals required by the PDUFA program through a non-transparent process. They argue that FDA has lowered its safety standards, as is evidenced by claimed increases in the number of products with problems and market withdrawals. Moreover, some believe that merely speculating on the possibility of suboptimal reviews can threaten public confidence in FDA reviews. Adding to the debate are allegations of FDA staff of pressure to meet performance goal deadlines, suggesting to some that safety and effectiveness data are being inadequately evaluated [30].

Other countries and the European Union have user-funded drug regulatory agencies that do not come under these attacks of industry bias. Some of these agencies receive all or most of their funding from user fees [31].

1.10 Comparative medical benefits, comparative effectiveness and FDA

Comparative medical benefits and comparative effectiveness will most likely have a much expanded emphasis by the US government and this will impact pharmaceutical R&D and the FDA. The Obama administration has expressed broad support for increased access to health insurance and administration officials strongly support

comparative studies as a way to determine the value of medical products and to control their costs.

Peter R. Orzag, director of the White House Office of Management and Budget, testified before the Subcommittee on Health in 2007 on the comparative effectiveness of medical treatments while director of the Congressional Budget Office. He concluded at the hearing that comparative clinical effectiveness research, combined with changes in payment incentives, ‘offers a promising mechanism for reducing health care costs to a significant degree over the long term while maintaining or improving the health of Americans’, while emphasizing that significant cost savings from such research would not been seen for many years [32]. While many want to see more comparative effectiveness results for pharmaceuticals, others are wary that comparative clinical effectiveness research is neither necessarily well designed nor sufficiently sensitive to individual differences, and is biased to concluding that cheaper drugs are more effective.

Comparative effectiveness faces many challenges in defining how it is measured, how research is conducted and how to interpret results. For example, effectiveness (use in the medical practice population) differs from efficacy (use in the ideal condition of clinical trials). How should costs be measured – total costs, drug costs, etc.? Are costs monetized (cost benefit) or are they non-monetized (cost effectiveness). The quality and definition of cost effectiveness will vary depending on how results are to be used – for a patient’s decision, for an insurance company decision a formulary decision or for government, etc.

The US government has various programs related to comparative effectiveness within HHS, the Veterans Administration and the Department of Defense. HHS’s Agency for Healthcare Research and Quality (AHRQ) and the NIH are currently the largest federal bodies funding extramural health technology assessments. AHRQ has several ongoing programs for health technology assessments. It funds pharmaceutical outcomes in a national demonstration program for education and research on the optimal use of drugs, biologicals and medical devices through the Centers for Education and Research on Therapeutics. The program is administered by AHRQ in consultation with the FDA. Some of the research is also conducted in partnership with private corporations, such as insurers or pharmaceutical manufacturers. The research compares the health risks, benefits, cost-effectiveness, economic implications and interactions of treatments.

AHRQ also conducts research for the CMS under Section 1013 of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. This law authorizes research, demonstrations and evaluations to improve the quality, effectiveness and efficiency of the Federal-administered Medicare program and two programs for which funding and administration is shared with the States: Medicaid and the State Children’s Health Insurance Program (SCHIP). The law prohibits the Administrator of CMS from using the data produced under the section to withhold coverage of a prescription drug.

The Veterans Health Administration’s Pharmacy Benefits Management Strategic Healthcare Group and the Department of Defense PharmacoEconomic Center (PEC) conduct their own assessments to make formulary and pricing decisions [33].

Recently comparative effectiveness has increasing support from the US Congressional Budget Office, the Congressional Research Service, the Institute of Medicine and the Medicare Payment Advisory Commission [34].

In response to the 2009 economic crisis, the government's 'stimulus package' contained 1.1 billion dollars of new funding for comparative clinical effective research. The funding is to be used for additional research and to accelerate 'the development and dissemination of research assessing the comparative clinical effectiveness of health care treatments and strategies, including through efforts that: (i) conduct, support or synthesize research that compares the clinical outcomes, effectiveness and appropriateness of items, services and procedures that are used to prevent, diagnose or treat diseases, disorders and other health conditions and (ii) encourage the development and use of clinical registries, clinical data networks and other forms of electronic health data that can be used to generate or obtain outcomes data'. The stimulus package also establishes a Federal Coordination Council for Comparative Clinical Effectiveness composed of senior government officials from agencies that support health care services, treatment and regulation of medical products (FDA).

1.11 FDA and non-inferiority trials

While the FDA does not have specific authority to request superiority studies, it does consider non-inferiority trials as the norm in certain situations, for example when it is inappropriate to use a placebo control [35]. 'These situations overlap substantially with situations in which you need some degree of comparative data because lesser effectiveness would be dangerous, a *safety* issue and *not* a relative effectiveness issue (because FDA does not have authority for those).' Other examples include anti-infective trials, some cancer trials and cardiovascular trials where the outcomes with the standard are known and a lesser effect of a new drug would be unsafe.

FDA did not approve Arcoxia, a 'me-too' drug, which had been rejected by the FDA Arthritis Advisory Committee because its safety profile was inferior [36]. At a press conference following the vote, Robert Meyer, M.D., M.P.H. of the FDA's CDER, said he came away with the opinion that the advisory committee intended its vote to resonate beyond Arcoxia. The message, Dr Meyer said, is that the FDA should no longer approve 'just another product in a class if it has the same level of risk as existing products and does not offer a unique benefit' [37].

The FDA also can request the cessation of marketing a drug for safer alternatives, for example Pfizer's Rezulin for new alternatives Avandia and Actos.

Superiority studies are sometimes submitted to demonstrate efficacy for non-responders, particular for a toxic approval of a drug otherwise too toxic unless it has a clear clinical advantage, such as Clozapine for schizophrenics.

Other agencies do pursue comparative studies. For example, the NIH conducted a comparative effectiveness study of two Genentech drugs, Lucentis and Avastin.

1.12 FDA and CMS decisions on Medicare coverage

FDA decisions impact Medicare coverage decisions and coverage decisions impact the pharmaceutical industry and R&D interest. For qualified clinical trials, Medicare (administered by the CMS) covers routine patient care costs for reasonable and necessary items and services to diagnose/treat complications arising from trial participation when certain conditions are met. New product developers will likely increasingly seek to qualify for CMS coverage, by tailoring clinical trials to fit CMS requirements.

CMS coverage decisions are based on a determination of what is reasonable and necessary for the diagnosis or treatment of an illness or injury, which is different from FDA's safety and efficacy standard. Accordingly, CMS is increasingly considering ways to contain costs. For example, when FDA added a 'black box' warning to the label for Aranesp, Epogen and Procrit with instructions for the doctor to prescribe the lowest dose necessary to keep the patient from needing a blood transfusion, CMS restricted coverage based on the FDA 'black box' concerns. When asked by Congress whether this was appropriate, FDA supported CMS as consistent with the available scientific data.

Moreover, CMS has argued in court that CMS 'can set the payment rate by deciding which expenses, associated with the covered item, are reasonable and necessary' [38].

1.13 Preemption: FDA's role in relation to liability litigation in state courts

The FDA is expanding the extent of its influence on consumer protection in liability actions after products are on the market. Two recent cases deal with whether FDA's marketing approval is sufficient to preempt state laws which have in the past permitted liability suits against manufactures and providers of products associated with untoward results. On 20 February 2008, the Supreme Court ruled that a plaintiff may not sue under state law to challenge the safety or effectiveness of a medical device to which the FDA has given 'premarket approval' [39]. A parallel case is currently awaiting a Supreme Court decision about whether the same preemption would apply to a drug product [40]. If the Supreme Court rules in favor of FDA preemption for pharmaceuticals, the additional impact of FDA regulatory decision making as the sole determinant of drug safety will likely add to the weight of responsibility already felt by reviewers, and could encourage more risk-adverse decision making. However, Congress could seek to reverse the Supreme Court by legislation.

1.14 FDA's exclusivity in allowing access to experimental drugs

A recurrent theme in FDA's history is the extent to which an individual has the right to use an unapproved pharmaceutical or an experimental drug. While FDA

broadened access to experimental drugs after the AIDS epidemic, clinical trial access remains limited and periodically patients sue. In January 2008, the US Supreme Court declined to take up the issue of whether terminally ill patients have a ‘fundamental right’ – protected by the US Constitution – of access to experimental drugs that have not yet been fully approved by the FDA, after a lower court in the District of Columbia refused to order access [41]. In 2008, a district court judge ordered a drug company to provide access to a clinical trial drug to a seriously ill patient who was not in the research protocol [42]. The case was reversed on appeal [43]. This, however, is not the end of the issue. With expanding populations of patients desperately needing treatment, issues relating to broadening access will continue and Congress may well intervene with a legislative solution, such as by Senator Brownback’s 2008 proposed Access Act [44].

1.15 Conclusions

The FDA remains a conglomerate federal agency with various expanding consumer protection mandates for drugs and biologics, medical devices, animal drugs and foods. The diverse obligations keep the agency leadership struggling to maintain effective control and consumer protection over a constantly shifting set of emergencies and priorities. In a very real sense, it appears that the FDA is trying to do too much in disparate areas and that perhaps it is time to reconsider its structure and organization.

With more than 50 years of controversy surrounding FDA’s regulation of drugs since the enactment of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, every expectation remains that controversy will continue unless Congress, FDA or the administration deliberately seek to change the structure and organization. During these 50 years, the FDA has not resisted expanding its regulatory turf even although its resources and management are insufficient for the FDA to perform adequately as reported by FDA’s own Science Advisory Board Subcommittee. It has difficulty resisting new regulatory turf that does not fit well with its regulatory expertise and mandates, such as the newly enacted FDA regulation of tobacco (although clearly a serious public health concern, tobacco is very different from the medical products and foods that the FDA currently regulates).

The time has come for a serious consideration of how best to restructure the FDA’s responsibilities. Medical products would form the basis of a reasonable regulatory agency – a *medical products agency*. A major portion of medical products are currently user-fee funded and it is not unreasonable to believe that industry would fund an even larger proportion of a streamlined, dedicated medical products agency. Well-managed medical product user fee agencies do well in other countries, and at significantly less cost and less subject to political pressure than FDA’s current programs. While foods are outside the scope of this chapter, it should be noted that Congress seeks to greatly expand FDA’s regulatory authority over food safety and there has been much discussion that FDA’s food activities could find a better organizational home, possibly combined with other food regulatory responsibilities now at the US Department of Agriculture (USDA).

Although the FDA Science Advisory Board Subcommittee urged a vast infusion of resources to improve science at FDA, it did not conduct a serious examination of the alternative ways a regulatory agency can or should gain the particular scientific expertise it requires to meet its regulatory responsibilities. The FDA basically needs to be able to manage a regulatory process that relies on science and should have staff skilled in gaining the necessary knowledge to make regulatory decisions and conduct market control.

It is unrealistic that a federal regulatory bureaucracy could and should have on its staff the best and brightest in all of the critical areas of knowledge necessary for the understanding and regulation of innovative medical products. The development of pharmaceuticals and their clinical testing has primarily been a private sector responsibility that relies on non-government scientific expertise. Other federal science and science-based regulatory agencies rely heavily on non-government experts to provide assistance on cutting-edge scientific areas. Even the NIH is based on a complex network of non-government grantee institutions and scientists, a host of federal advisory committees to review applications for grant applications and other advisory committees to oversee the work of the NIH. In other countries, medical product agencies typically rely on extensive networks of scientists and other medical experts, instead of seeking to have all of this expertise contained within the staff of the regulatory agency.

The FDA's Critical Path Initiative has added a major new role for the FDA. The agency has moved from being primarily a regulator for clinical trials and market access for new drugs to a resource for translating science into medical products (e.g. the Critical Path Initiative). A Los Angeles Times headline in 2000 asserted 'Once a wary watchdog, the Food and Drug Administration set out to become a 'partner' of the pharmaceutical industry. Today, the public has more remedies, but some are proving lethal' [45].

There are other good reasons to be cautious about how large a role the FDA should play in developing the tools sought for the critical path. The innovation driving the advances in medical products has come primarily from the private sector. Innovation by its very nature does not follow a simple cookbook formula, and the critical path could become an unproductive rut if it discourages the out-of-the-box thinking that will lead to innovative treatments and cures. The development of the critical path, or critical paths, should, to the extent possible, remain as innovative as the innovation that it hopes to engender. And for this, the ideal critical path may be outside of the government bureaucracy.

Drug cost and reimbursement issues are driving considerations of comparative effectiveness, cost-benefit, pharmacoeconomics and other paradigms aimed at improving value from drugs. The FDA currently operates at the edge of these considerations that are under the purview of other federal agencies. The movement to health care reform will be relying much more heavily on this type of information. The extent to which the FDA or other agencies take on major responsibilities to valuing pharmaceuticals will impact on what agencies will influence the climate for drug development and clinical trials.

Finally, the growing and shifting pharmaceutical industry outside of the United States will impact the role, operation and influence of the FDA. This may prove to be the greatest challenge faced by the FDA, its structure and organization. Because of limitations on its ability to oversee research and manufacture offshore, the FDA will need to adapt new mechanisms, likely in concert with other drug regulatory agencies, for ways to protect American consumers and clinical trial subjects.

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2

Do Antidepressants Cause Suicide?

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Read this story/my friend/for you'll find/at the end/that a suitable/moral lies there.
from *Pierre*, by Maurice Sendak, with corruptions, and an apology
<http://www.amazon.com/Pierre-Cautionary-Tale-Chapters-Prologue/dp/0064432521>

Abstract

One of the most controversial subjects in psychiatry has been reignited quite recently. This is the relatively old conundrum: do antidepressant medications actually increase the likelihood of suicide, at least under certain circumstances? The purpose of this chapter is to review the issues involved in this complex question.

Key Words

antidepressants; suicide; adolescents

2.1 Some definitional problems

What is suicide? For present purposes, suicide is taken to mean 'a self-completed act which leads to one's own death'. 'Self-harm' is defined as 'hurt inflicted by someone upon themselves'. An attempt (at suicide) means 'a behavior which a reasonable person would construe as significantly increasing the risk of death from self-harm'. 'Deliberate' implies that the reasonable person would infer intention by the perpetrator of self-harm.

How do we know that suicide has occurred? Here, the usual ways in which causality are invoked apply.

- The dead person has left clues. The obvious ones are suicide notes, or verbal communications which significantly suggest that suicide is about to occur.

- When clues are not immediate, the detective work turns notably more difficult. Forensic science may well be required to make an inference. For example, a substantial percentage of deaths occur in people with blood alcohol levels at autopsy. However, by itself, this is hardly proof of intention. On the other hand, the presence of certain substances – sometimes common household products such as rat poison – would pass the coroner’s test for deliberate self-harm. In between these two examples, we have one of the most common situations, in which someone has swallowed medications (with/without alcohol), which are more easily detectable, but do not necessarily give an indication of the seriousness of intent.

If mortality is the endpoint for determining suicide (and it is clearly, by far, the best), the difference between simply tallying the number of deaths versus the number of suicides is an enormous gulf. The moment a death is deemed a suicide, the statement implies a reasonable likelihood of intent. Unfortunately, there is a vast, murky literature about determining the seriousness of intent. Many claims have been made about the ability of a variety of questionnaires, especially before-the-fact, to determine the seriousness of intent. It is difficult to award credibility to any of them over time. After-the-fact is even more problematic since, apart from suicide notes and verbal statements, the information is generally incomplete.

The limitations of relying upon mortality data have easily led to efforts to assess verbal statements, and behaviors, through questionnaires and interviews. This is especially true in trials of treatment for depression, as well as in a variety of other (usually psychiatric) trials. Typically, a score is rendered, based upon the answers to the questions and/or documentation of suicidal behaviors. The latter are deemed to be actions which might increase the risk of suicide attempts (*vide supra*). Some of these methods incorporate indirect measures, such as ‘Projective Testing’, on the theory that indirect communications can sometimes convey information about brain processes which may not even be consciously available to the suicidal person him/herself. It has proved difficult to confirm assertions about such measures, since replications beyond the original authors of these measures are few and far between if, indeed, they exist at all.

This has not, however, deterred regulatory agencies from encouraging and accepting data about clinical trials and their safety, based upon structured interview and questionnaire data about suicidal ideation and acts. One might argue that this is a case of ‘We’re doing the best we can with what we’ve got’, or that officials have been persuaded that measures of suicidality are sufficiently reliable and valid to be accepted as evidence of safety (or lack thereof).

2.2 A brief history of the concerns of suicidality caused by antidepressants

The first thing to note about this controversy is that it is hardly new. A common belief in psychiatry, which pre-dates the advent of antidepressant medications, is that:

- 1 Some patients are so depressed they cannot muster up the energy or the initiative to commit suicide, even when they have the urge.
- 2 Similarly, when they begin to recover from depression, whether in the natural course of the illness, as a result of psychotherapy or through biological treatments, they may now be activated to the point where they are able to execute the act of suicide, which they had only contemplated previously.

It is difficult to document when this notion of the increased, transient risk of suicide in people beginning to recover from depression first arose. It was present in the literature at least as far back as the advent of electroconvulsive therapy (ECT). By the early 1970s it had become commonplace in psychiatric residency training programs, even though the use of first generation antidepressants was neither widespread nor generally accepted as the standard for treatment of depression.

Specifically in relation to antidepressant treatment, the question of whether antidepressants increased suicide was reviewed retroactively by chart at the Massachusetts General Hospital, by a generally well-respected researcher [1]. In this group of about 1000 patients, five were determined to have completed suicides. We reviewed the brief, published histories of each of these five cases. A reasonable conjecture, based upon this very limited clinical information, was that in at least three of the cases the prescription of antidepressants was at least relatively contraindicated. An example of such a case was a patient with a previous history of borderline personality disorder, including acting out behavior. The general wisdom (once again, poorly documented) is that a patient with such a diagnosis (i) is a poor candidate for a positive response to antidepressants and (ii) is a high risk for using potent medications as a suicidal weapon.

This report stimulated discussion anew on the subject of antidepressants as possible suicidal precipitants [2–7].

In another line of research, a series of clinical papers appeared which reviewed a variety of trials of antidepressants for treatment of children and adolescents diagnosed with depression in various guises. This was a noteworthy and valuable area in which to work because, for many years, antidepressants simply were not tested in anyone but adults during clinical trials toward drug licensure. On the one hand, the reasoning was that minors are too vulnerable and should not be subjected to unconfirmed experimental treatments. However, it has become painfully apparent that not only antidepressants but many other kinds of medication were being prescribed freely by practitioners for those under 18, even where the evidence for their safety and utility was thin. Because of this, the then Director of the National Institutes of Health, Dr Bernadine Healy, pushed an initiative which eventually led to legislation and regulation actually encouraging such drug testing, as a way of both promoting health and protecting the public. In fact, it is now the case that pharmaceutical companies can extend the exclusive patient life of their drugs if they perform the appropriate clinical trials in children and adolescents and the Food and Drug Administration (FDA) approve.

This set of original studies and reviews of antidepressant usage in minors for a substantial period of time was dismayingly discouraging. In fact, it seemed that

(with the possible exception of fluoxetine) antidepressants which appeared to work perfectly well in adults, and to be safe, were ineffective at younger ages.

There are a number of possible hypotheses which could explain these differences. The leading ones are as follows.

- 1 Children and adolescents are not physiologically and biochemically the exact equivalent of adults. While this might seem obvious, the specific mechanisms of difference which might relate to antidepressant responses remain to be elucidated.
- 2 The overall assumption of clinical trials is that they are conducted in equivalent ways in adults and children. This is patent nonsense. Virtually every questionnaire and structured interview for research purposes has had to be significantly reworked in order to be used in child and adolescent research. In fact, a number of the measures are unique to children and adolescents, and have no clearly corollary instrument for adult use. Also, information from adults is typically actively sought and weighted heavily (sometimes exclusively) in evaluating efficacy and safety for children and adolescents. With adults, corroborative information is the exception rather than the rule in most studies. One might argue that this should improve the accuracy and specificity of child and adolescent studies. Once again, this remains to be demonstrated. What is clearly the case is that it makes these studies quite different in their conduct from adult studies.

Notwithstanding this growing controversy, a group of child psychiatric epidemiologists at Columbia University Medical Center was publishing a series of studies of the use of antidepressants by prescription in adolescents at the same time as the evolution of this controversy. The endpoint for these studies was death by suicide in adolescents. The independent variable was prescriptions written for antidepressants, per unit of time, over years.

The first striking finding from this group is that, perhaps contrary to popular belief at the time, the rate of adolescent suicides was actually declining at a substantial and continuing rate through the latter part of the 1990s. When the researchers further stratified the data, in order to rule out a variety of possible explanations, most of the obvious hypotheses were disconfirmed. What remained was the significant increase of prescriptions of antidepressants for adolescents during this decade. The bulk of this increment upwards was accounted for by those written from the offices of pediatricians and family physicians.

The importance of these data will become even more apparent when we consider the implications for public policy (*vide infra*). At this juncture it may be useful to point out the difference in the scales being applied to examine the questions of suicide. The data which suggest the possibility that antidepressants may increase the rate of suicide generally apply to weeks to months, the period of time when most antidepressants are given. On the other hand, the epidemiological data are (i) on a much larger scale of numbers and (ii) measured over years, rather than timeframes of weeks to months. It is therefore possible to imagine that there could be two, apparently contradictory, hypotheses, both of which are true because they apply over different timescales. For instance, if the period of initiation of treatment is (on

average) when patients are at their most depressed, looking out beyond the first few weeks of treatment to months or even years may yield a very different, and even opposite result, if mortality is the outcome measure.

2.3 Politics rears its ugly head

A critical piece of history in the dispute over antidepressants as possible causal agents of suicide is now discussed. The studies which suggested that antidepressants might actually create more suicides in adolescents eventually began to catch the eye of politicians. How this came about is of more than passing interest.

It began with the profession of psychiatry itself. Within psychiatry and related disciplines (notably psychology), there has been a highly vocal minority which over the years has asserted that medications including (or especially) antidepressants are not promoting good health and mental health. Rather, this group claims, they cover up problems without solving them and lead to side effects which can be serious and even irreversible.

Some psychiatrists who have made names for themselves, over a period of time, as spokespersons for this point of view, became quite animated and vocal upon the subject when the adolescent studies began to appear. One example is the Scottish psychiatrist, RD Laing; another is the American psychiatrist Peter Breggin, who has articulated many anti-psychiatric positions over the years. Their statements generated a fair degree of popular press, both in the United States and abroad.

Eventually the clamor of the variety of voices, both from the research community and from the popular press, rose to a pitch where neither US FDA officials nor members of Congress felt that they could be ignored. The FDA, after a series of hearings, commissioned what they hoped would be a relatively disinterested group of scientific experts to re-examine the existing data linking antidepressants to adolescent suicide. Ironically, the impetus to spearhead the work was placed upon Columbia University Medical Center (not the research group mentioned previously, which carries out epidemiological research).

The expert group, upon completion of its task, stated that their review confirmed the point of view which states that antidepressants can increase the likelihood of adolescent suicide [8]. This was a very telling finding, and one that has been a major driving force in socio-political changes in its aftermath.

2.4 The FDA responds

What ensued was yet another series of largely public hearings about the research results and their meaning. The FDA during this time, from 2000 onwards, was under great pressure. The national administrative arm of the government had turned Republican, and was sympathetic to claims that the FDA was an inadequate regulatory body. However, most of this sympathy was being expressed as leaning upon civil servants to be more supportive of industry claims. At the same time, a few politicians saw this as an opportunity to bolster their reputations as protectors of the public good.

One such was Sen. Charles Grassley, [®]Iowa. Grassley's state has little pharmaceutical manufacturing business located within its borders. Grassley represents a set of political ideals that if there is going to be an agency (namely, the FDA) charged by Federal statute with warning the public about possible threats to the public safety, then this agency had better do its job to the utmost of civil servants' abilities.

Officials of the FDA, now under heavy and continuing criticism, began to respond by placing warning labels upon a variety of medications which are used to treat depression. At first, some of these labeling changes were not about suicide at all. The antidepressant Serzone[®] was the subject of a ruling adding a 'black box' warning (e.g. bold type placed in the consumer leaflet which comes with each prescription) about the possibility of liver damage. Not long after this, a similar warning was placed upon Depakote[®]. The former is notable for the fact that, at the time, Serzone appeared to be making significant inroads into the market for antidepressants. In the latter instance, Depakote had been available for years as an anti-convulsant medication. When it was demonstrated to have preventive value as well as a mood stabilizer, and additionally licensed for this use, the FDA also inserted a 'black box' warning on the Depakote package insert. What is also interesting about the Depakote example is that the FDA had no new data on which to base this warning. In fact, they used data which had been publicly available throughout the entire period of Depakote's licensure.

In both instances, I have had informal, discrete discussions with pharmaceutical company representatives. In both, employees within the firms suspect that the impetus for the warning changes may well have come from rival firms, which were concerned about competition. However, there is no corroborative evidence to support these suspicions. (It would be surprising if such evidence was committed to paper, in any event.)

Following on the heels of these warnings, the FDA then began to place 'black box' warnings on antidepressant compounds, about the possibility of increasing suicidality. They also added other recommendations, including the directive that adolescents should be examined weekly by the physician when placed on an antidepressant.

While it is hard to fault such recommendations, they placed the FDA squarely in opposition to the practices of a number of health insurers. Over at least a quarter of a century, health insurers have gradually restricted payments more and more to physicians – especially psychiatrists – who treat patients with mental health problems. Thus, most patients no longer see physicians for psychotherapy but only for medication. The reason for this is that the health insurers pay minimally for psychotherapy time spent by physicians. The practical result of this action by the FDA is to cause subscribers to pressure physicians to see patients more often for less reimbursement, since health insurers are not about to budge on their payment allowances.

2.5 What changes in public policy wrought

Another piece of fallout from the FDA's timidity in the face of political pressure has been that it has likely changed physician practice quite markedly. Malpractice

insurers are, unsurprisingly, liable to pay close attention to pronouncements by the Federal government. Were a case of suicide to come to court, it would be difficult to defend a physician who failed to follow what the FDA had pronounced to be a 'best medical practice'.

Along with this, we are probably seeing a significant shift in day-to-day medical practice around depression. I have now found myself on the receiving end of referrals from primary care physicians who I happen to know formerly treated what they considered routine cases of child, adolescent and adult depression with antidepressants. Sometimes they did this in conjunction with non-physician psychotherapists, and sometimes prescribed medication without other therapy. These same physicians, when I inquired, made it clear that the increased malpractice risk to them, brought on by the FDA's insertions of declarations about practice with medications, made such treatment untenable.

Psychiatrists are under no less pressure, from all sides. On the one hand, patients want to be treated within the reimbursement structures of their health insurance plans. On the other, they want psychiatrists to undertake both the medication and psychotherapy components of their treatment. However, psychiatrists decline to do the latter because of the minimal fees. Many health insurance contracts with physicians forbid physicians from accepting additional payments outside the plan's fee structure for plan subscribers, even if the subscribers are willing to pay the money for additional services. Alternatively, subscribers want psychiatrists to see patients at longer intervals or handle prescriptions over the telephone, in order to save patients' money. These demands can, at times, be mutually exclusive.

The political pressures continue. Public comments to the press and Congressional hearings have not abated as the FDA has succumbed to the temptation to include warning labels. Two recent developments may be indications of possible future changes in FDA policies.

FDA and Gepirone

The first was a decision to reject the application for licensure of an antidepressant called gepirone. This compound has been in use for years in Europe, and the data clearly suggest that gepirone is both safe and efficacious compared to the usual gold standard of placebo in clinical trials. However, the FDA at first cut has rejected the application. How can this be?

The FDA had no major dispute with the data submitted with the application, which appear to follow the FDA's usual and customary formats required to gain approval. Instead, for the first time ever (to my knowledge), the FDA in its public response argued that gepirone brought no clear advantages to the market over antidepressants already presently in use.

The implication of this response is potentially stunning. Without prior announcement of a policy shift, the FDA appears to be saying that the market is sufficiently crowded and that, from now on, the only compounds which will be licensed are those with a demonstrable advantage over those already in use. There are a number of potential problems with this response:

- 1 Why did the FDA wait until after the very expensive developmental work had already been carried out on the compound to announce this apparent major policy shift? Among other things, it seems very likely that the FDA would be forced to reverse this change in policy if the case were to go to court, if simply for fairness of doctrine issues.
- 2 Is the FDA really planning to scrap or very substantially change its criteria for drug review, requiring that new applicants (at least at a certain point in the history of a drug market) demonstrate their value against other competitors? If so, what are reasonable criteria for considering advantages to be sufficient? For instance, it is well known that at least a small group of people who either did not respond well, or could not tolerate other medications in a given class, may yet respond to a new medication when it is produced. Although the common assumption is that this may be the result of random genetic variation in the population, the truth is that (with rare exceptions) no one really knows why this occurs or how to identify such people in advance. Is the fact that a few people might benefit from this drug, and these few alone, not sufficient reason for licensure of an otherwise run-of-the-mill compound?
- 3 How widely does this new dictum apply? In any event, is the public ever to get a chance to comment upon such a radical change in FDA policy? And how is it determined that a market is already super-saturated with look-alike compounds?

Could it be the case that some other competitors have prevailed upon the FDA to take this stand?

FDA: Better safe than sorry

The second instance is represented by a flurry of FDA announcements, followed now by a possible impending retraction.

As time progressed, the theory at the FDA apparently evolved that any medication which changed mood significantly might conceivably contribute to suicidality. The first extension of this doctrine was to begin to add to the warning labels of essentially all licensed antidepressants a cautionary item about possible enhancement of suicidality. The rationale, as best it can be understood, was 'better safe than sorry' and therefore all the class should eventually be treated in the same manner.

Extension to other compounds followed. An obvious step was to take into account the mood stabilizer grouping of compounds. Since depression occurs in cyclic mood disorders, it stands to reason that these compounds are sometimes used to treat depression (whether by intention or inadvertently). It remains the case that many (perhaps even most) instances of bipolar disorder have been treated with specific antidepressants first, usually by primary care physicians, before they are re-diagnosed by psychiatrists [9–11]. In fact, a variety of studies suggest that at least some mood stabilizers may be perfectly acceptable treatments for depression without a history of bipolar disorder [12] (see also Chapter 8).

2.6 A funny thing happened on the way to the forum

When the above suggestion about a change in FDA policy toward mood stabilizers and perhaps some additional (other than antidepressants or mood stabilizer) products was voiced aloud, an unexpected reaction occurred. Some experts actually objected (even publicly) to the creeping gradualism which appeared to be infecting licensed medications, some with quite lengthy and extensive histories of use, based upon assumptions and speculation with absolutely no new data in some cases.

As of September 2008, the hue and cry appeared to have reached the level of Council at FDA, the highest body of relatively disinterested experts to pass upon FDA policy, approvals and statements within the bureaucracy. What follows is at least a temporary suspension of the proposed rules, including postponing any future ‘black box’ warnings for mood stabilizers.

2.7 Meanwhile back at the ranch

One refreshing result of the controversies concerning antidepressants and suicidality is that a number of researchers have now weighed in with reviews, often including new data or a fresh look at a variety of existing databases [13, 14].

More disquietingly, since the FDA began making public pronouncements about the possible dangers of specific antidepressants we now have reports coming in which examine rates of suicidality in certain populations.

- 1 Similar methodology to that of the epidemiological retrospective studies in adolescents is being applied (more or less) prospectively. The results are striking and disconcerting. Whereas the suicidality rates in adolescents were falling for the better part of a decade previously, they now appear to be rising monotonically along a curve that, in some respects, may be mirroring the previous drop.
- 2 The rates of prescription of antidepressants have significantly dropped during the same period of several years.
- 3 If we – perhaps inappropriately and prematurely – put points 1 and 2 together, we come to a reasonable hypothesis: the effect of the FDA change in policy of notification, and the publicity surrounding it, may have led to a dramatic rise in suicidality, particularly in adolescents [15, 16].

The late Robert Merton, Professor of Sociology for many years at Columbia University (in yet another division of the school, outside the Medical Center) wrote of the ‘unanticipated consequences of purposive action’ [17]. Merton was referring generally to intentional interventions via changes in social policy. Among others, he had in mind the universe of medicine, in which he and Frances Fox Piven (later Professor at the University of Pennsylvania) were sociological pioneers.

I propose that the FDA’s change in public policy may have produced precisely the opposite result from what was intended. With (perhaps) all good intentions, or (perhaps) due to political intimidation, it can reasonably be argued that the FDA has

dramatically turned around a happy and felicitous result of medical treatment: the reduction of mortality. Instead, it has produced a rise in suicidality in the United States.

2.8 Moral (maybe)

Well-executed science is neutral. The results should speak for themselves. Of course, science is subject to interpretation, and should be. For that matter, data can be selected which are directed to making a point, sometimes to the exclusion of possibly contrary material. Possible explorations in different directions, which might invalidate the results, can be neglected. However, when data are public, they can be examined and arguments made. In this way, biases can also be uncovered and underscored.

Public policy is not science. Public figures and public agencies need to consider scientific results. They also need to consider the possible limitations of these results.

Most urgently, public policy makers need to project the possible ramifications of their own pronouncements. Although this cannot be done prospectively with data, reasonable thought can be given to the implications of actions. In fact, tools for the projection of possible consequences of public actions are numerous and sophisticated (by means certain, but rather probabilistic). Were such tools applied to the FDA's decision making around these policies? If so, can the public examine these tools? If not, why were the consequences not considered ahead of time?

Finally, is any thought being given to retracting policies which may be having disastrous consequences upon the lives of the mentally ill?

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3

The Genome, Genes and Brain – Tailored Drugs

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Abstract

The Human Genome Project completed sequencing the human genome in 2003; about 25 000 genes were found to comprise the genome. The major psychiatric illnesses are complex polygenic disorders. The elaboration of the genome has facilitated several important domains of research: genetic linkage to psychiatric disorders, the association of variations in the genome to psychiatric symptoms, the elaboration of the proteins encoded by the genes, the understanding of the gene regulation and the understanding of epigenetic effects on gene expression. This research has important implications for assessing vulnerability to specific illnesses, for the treatment of psychiatric disorders, for predicting drug response and adverse drug reactions, for understanding the mechanisms of drug action, for determining targets for new drug development and for the design of new pharmaceutical entities. Future applications include potential gene therapies to prevent major psychiatric disorders.

Key Words

genome; genomics; proteomics; polymorphism; haplotype; linkage; receptors; DNA; RNA; brain

3.1 Introduction

In the last decade there has been a paradigm shift in the approach to the development and testing of new medications for treatment of psychiatric illnesses. This change has been made possible by advances in molecular genetics which have enabled the sequencing of the human genome. The sequenced genome has permitted progress in identifying genes conferring susceptibility to various psychiatric disorders and which

encode the structure of receptors and of messenger systems which are sites of action for new drugs. Also, sequences of the genome which predict individual response or failure to respond to specific drugs have been discovered. The uses of genetic techniques to alter gene expression directly are under study.

In complementary fashion, there have been advances in techniques to explore the structure and function of the human brain. These techniques have included imaging techniques which elucidate brain structure, brain function, neural systems and their interactions and metabolic and bio-energetic parameters. These have converged to increase the understanding of neuronal complexity at the molecular, the cellular and system levels. Additional progress has been made in the ability to define protein structures, to assemble proteins into complex receptors and to synthesize and study these proteins and receptors. These advances are relevant to the need for accelerated development of new drugs by the pharmaceutical industry. The high attrition of potential products during the course of the regulatory process and the high financial investment in product development and testing phases necessitates efficient identification of products which are most likely to be effective, safe and unique in their biological targets.

3.2 Issues in new drug development

The duration and cost of the drug development and approval process requires a staggering investment by the pharmaceutical industry. Of 10 000 entities identified for potential development, pharmacology and safety assessment reduces the number to 1000 compounds entering clinical trials for first human use. Attrition in the clinical trials results in 10 compounds suitable for a new drug application (NDA) submission. Of these, one drug will receive FDA approval. The time line from compound discovery to regulatory approval is approximately 12–16 years. Furthermore, patent exclusivity for a specific indication has been trending downward, and post-marketing identification of safety issues have resulted in the removal of several drugs from the market. Approvals by the FDA decreased to 27 drugs in 2007, the lowest number in 25 years. The overall cost of bringing a new drug to market is estimated at 1.3 billion USD [1].

In the development of drugs for major psychiatric disorders, few psychiatric drugs with novel mechanisms of action have reached the market. Consequently, it is imperative to utilize new technologies to develop medications which target other biological targets.

3.3 Early development of psychiatric pharmaceutical entities

Initially the discovery of medications for treating psychiatric disorders was serendipitous. In the late nineteenth century, excess of urates was believed to underlie various diseases; lithium salts facilitated dissolution of urate stones and were noted

to have a calming effect. This finding was rediscovered by John Cade in 1949, suggesting their use in treatment of manic-depressive illness [2]. Iproniazid and isoniazid were tested as antituberculosis drugs in the 1950s and patients showed improvements in mood and energy [3], leading to the development of antidepressants which were inhibitors of monoamine oxidase [4]. Perchlorperazine and chlorpromazine relieved pre-operative anxiety in surgical patients in the 1950s and were subsequently demonstrated to have antipsychotic ('neuroleptic') properties in patients with psychotic symptoms [5]. A congener of chlorpromazine, imipramine, was developed as a potential antipsychotic, but instead exhibited specific antidepressant properties [6]. Subsequent research in pharmacology demonstrated that the antidepressants inhibited neuronal reuptake of norepinephrine [7] and serotonin [8]. The antipsychotic medications were demonstrated to block binding of dopamine at specific dopamine receptors [9]. The potency of these drugs was directly proportional to the affinity of the drug to block the dopamine type 2 (D2) receptor [10].

Development of new medications for these indications was mainly accomplished by synthesis of structural congeners and subsequent screening for the aforementioned pharmacologic properties. The antipsychotic medications developed and marketed since the first drugs have essentially shared the same mechanisms of action of D2 blockade: medications which treated depression all prevented catecholamine reuptake or decreased catecholamine degradation.

In the late 1960s and early 1970s, early applications of computational analysis were developed to screen potentially active compounds using algorithms of molecular descriptors and pattern recognition. By the middle of that decade, statistical models correlating structural analysis and biological activity were developed. Thereafter, advances in computer analyses and graphics permitted analysis of three dimensional structures utilizing X-ray crystallography and nuclear magnetic resonance (NMR) data [11].

There also was considerable progress in the understanding of brain biochemistry, membrane biology and bioenergetics. Membrane receptors for other neurotransmitters (NTs) were recognized and subtypes of the receptors were identified [12]. Second messenger pathways activated or inhibited by binding of transmitters or drugs to the receptors were discovered [12]. The mechanism for neuronal transduction of substrate metabolism to generate high energy intermediates for neural activity was elucidated [13].

3.4 Advances in research technology

Computerized axial tomography (CAT) scanning was developed in the 1970s and permitted more detailed X-ray imaging of brain structure. In the 1980s, magnetic resonance imaging (MRI) permitted more detailed structural brain imaging. Around the same time, brain scanning utilizing positron emission tomography (PET) and single photon emission computerized tomography (SPECT) permitted functional imaging of the brain. Over the following 15–20 years, the sensitivity of structural MRI increased with advances in scanner design and permitted even more detailed structural

images which could be quantified with greater validity. PET scans achieved important technological advances through improved sensitivity and through the development of more sophisticated tracers and ligands utilized for the scanning. This enabled imaging of metabolic activity by brain region, indirect changes in NT release, receptor distributions and occupancy and ligand binding to pathologic lesions such as amyloid plaques. In the 1990s, the development of functional magnetic resonance imaging (fMRI) was a major advance in imaging real-time changes in coupled blood flow/metabolic activity in subjects at rest and during task performance. Modifications of fMRI led to the development of diffusion tensor imaging, which facilitated imaging of actual brain connectivity.

Non-imaging technologies also progressed during this period. Refined applications of measurement of event-related potentials (ERPs) permitted understanding of information processing and identification of putative markers of illness endophenotypes [14]. Magnetoencephalography measured magnetic field changes associated with patterns of neural electrical depolarization in real time.

Understanding of neurocognition has been increased by the development of refined batteries of neuropsychological testing. A very relevant current example is the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery developed for assessing neurocognitive deficits and changes in schizophrenic subjects [15].

Information from these technological advances converged with the advances in molecular biology which enabled the sequencing of the human genome. The combined use of data derived from these fields of study has not only led to an increased understanding of major psychiatric disorders, but also to an enhanced ability to correlate qualitative and quantitative data on brain structure and function within the atheoretical approach to genetics of the Human Genome Project (HGP).

3.5 Review of genetics

For the purpose of understanding the concepts presented in the rest of this chapter, a brief review of genetics is presented below [16].

Deoxyribonucleic acid (DNA) is a double-stranded macromolecule composed of linear nucleotides (adenine, thymine, cytosine and guanine). A double-helical structure is formed as purine nucleotides from one strand pair with pyrimidine nucleotides on the complementary strand through hydrogen bonding. The sequence of these bases provides the encoding of the genetic information in the DNA.

The is defined as the entire genetic complement of a cell. Genes are sequences of nucleotides which encode for specific protein synthesis. Chromosomes are strands of tightly compacted DNA containing sequences of DNA (genes) which encode proteins and regulation of expression of those proteins. Histones are proteins which bind to DNA in a non-sequence dependent manner; histones are also involved in gene regulation and compacting of chromosomal DNA. Chromosomal DNA is found in the nucleus of the cell, and mitochondrial DNA is located outside the nucleus in the mitochondrion.

The components of a gene are exons, the regions which contain the genetic code, and introns, which do not. Promoters are DNA sequences which initiate and regulate the transcription of the exons into messenger RNA (mRNA) by the enzyme RNA polymerase. DNA sequences which inhibit transcription are suppressors. Exons also contain untranslated regions which are not transcribed into mRNA and therefore are not translated into amino acid sequences.

Promoters may be stimulated by enhancers, areas of DNA distal to the promoter, under the regulatory control of activators or repressors which are DNA binding proteins which bind to enhancer sequences. The promoters and enhancers are located on the same DNA strand as the gene under their control.

Transcription factors are proteins encoded by other genes and bind to DNA sequences in promoters and regulate transcription. Different transcription factors may be activated by different incoming signals. The ultimate activation or suppression of the promoter may reflect the convergence of the signal (e.g. hormone) directed from differing transcription factors.

Transcribed mRNA enters the cytoplasm. Amino acids bound by transfer RNA (tRNA) molecules, whose RNA sequences are complementary to the sequences of the coding triplets of the mRNA, are assembled into proteins at the level of ribosomes. A single gene may encode many alternative transcripts and proteins through alternative splicing and through variation in the initiation of transcription.

3.6 Activation of genes by signal transduction cascades

There are four major signal cascade pathways which are involved in activating nuclear transcription factors, which then in a specific manner activate RNA polymerase for transcribing mRNA [17].

G-protein coupled receptors (GPCRs) respond to NT activation by a change in extracellular conformation. The change in conformation is mediated by the association or dissociation of G-protein subunits which induce an intracellular conformation change. This change ultimately results in the inhibition or stimulation of guanyl or adenylyl cyclase. For example, activation of adenylyl cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosyl monophosphate (cAMP). cAMP activates protein kinase A (PKA) which is then internalized in the nucleus and phosphorylates cAMP responsive element-binding protein (CREB), which in turn activates a transcription factor.

Ion channel-linked NTs bind to ionotropic receptors which results in calcium ion influx. Ionized calcium activates calcium/calmodulin kinase (CaMK) which then is internalized and phosphorylates CREB as described above.

Certain steroid hormones can enter the neuron and bind to hormone nuclear receptor complexes which are internalized into the nucleus. These interact with hormone responsive elements which activate specific genes.

Finally neurotrophins (e.g. brain-derived neurotrophic factor, BDNF) activate kinases which then phosphorylate another kinase cascade (e.g. glycogen synthase kinase-3, GSK-3) which are translocated to the nucleus and activate specific genes.

3.7 The human genome

The HGP (National Human Genome Research Institute) and Celera independently completed the sequencing of the genome. Major goals of this endeavor were to understand: the complex genetics underlying major psychiatric disorders; the biological substrates of these illnesses; the biological basis for the symptoms and abnormal brain functioning seen in these illnesses; the translated proteins from the expression of the genes and the regulation of gene activity. The history of the project development and the methods can be found at the HGP web site (www.genome.gov).

Theoretically, this knowledge could then be used to develop new pharmacologic treatments whose discovery was based on this new genetic paradigm. Specifically, could genomics and proteomics identify potential targets for new drug development? Could identifying subtypes of major psychiatric disorders reduce the heterogeneity of the subjects enrolled in clinical trials of new drug entities? Are there genetic differences which could predict drug response and adverse drug reactions? Could greater knowledge of genomics and proteomics be synthesized with structural and functional imaging findings to understand mechanisms of illness? Could pharmaceuticals be developed to actually change genome expression? Could the genes actually be altered structurally?

3.8 The sequencing of the genome

The expected number of individual genes was estimated at 100 000 genes at the outset of the sequencing; by 2001, the draft sequence estimated 30 000 genes. In 2003 when the sequencing was essentially completed, the final number was approximately 20 000. This was because large spans of the genome were verified as non-coding regions. However, major psychiatric illnesses are complex and appear to be largely polygenic. The only major psychiatric disorder that could be linked to single genes in the sequenced genome is early onset familial Alzheimer's disease. Mutations in the presenilin genes encode secretases which cleave of Alzheimer's precursor protein (APP) at sites resulting in toxic fragments of β -Amyloid [18].

The primary sequencing elaborated the 99% of the genome that humans share. In 2003, the haplotype mapping project (HAPMAP) began to study variability in human's traits. More than 3.1 million single nucleotide polymorphisms (SNPs) and haplotype blocks (regions of the chromosomes containing several different SNPs), were discovered by 2007 [19].

3.9 DNA variation

Trait differences result from variation of DNA sequences in genes, and several types of variants affect heritability. These include SNPs which occur frequently (approximately 1 SNP every 600 base pairs or bp), insertions or deletions of nucleotides, trinucleotide repeats which may increase in length in subsequent generations and

large translocations/duplications/deletions. Depending on their site, DNA variants may alter amino acid sequences, mRNA stability or splicing or RNA processing. Other functional DNA elements include microRNA (miRNA) and small interfering RNA (siRNA), which reduce gene expression by RNA interference. In complex genetic disorders, there may be copy number variations (CNVs) which are microduplications or microdeletions of varying sizes which can increase or decrease gene expression [20].

Additionally, epigenetic factors may result in methylation or acetylation of histone proteins which permit environmental or experiential factors to impact variability in gene expression [20].

3.10 Genes and illness

Different approaches have been utilized in the attempts to find the genetic basis for major psychiatric disorders.

Linkage refers to the phenomenon of chromosomal regions segregating with a specific trait in multiple families. Large samples of families with multiple affected relatives with the illness are studied, diagnostic ascertainment is rigorous and DNA samples are obtained for genetic analyses. A number of areas of on chromosomes have been implicated using this methodology, but replication has been difficult. What is identified is a span of DNA on a particular chromosome in these studies. The completion of human genome sequencing could be applied to these types of studies to identify what gene or genes are encoded in that area. However, there are many methodological problems in linkage studies, not the least of which is the fact that the genes for major psychiatric illness may not be fully penetrant [21].

One promising area was a linkage of schizophrenia on chromosome 22q13.1 in schizophrenia. Abnormal p50 sensory gating [22] or abnormal saccadic eye movements [23] are putative endophenotypes of schizophrenia. When these markers were used to determine whether a subject was affected, linkage at 22q13.1 was suggested [22], [23]. Unfortunately, the linkages are not robust and different markers may have different linkages in the same family cohorts.

Association studies, which compare the frequency of a DNA variant (e.g. SNPs) in patients and controls, are now the standard approach for discovering disease genes. Using microarrays ('SNP chips'), whole genome association studies can now be performed. In these, every gene can be studied in a single study which compares the frequency of 500 000 to 1 million SNPs in a cohort of patients and controls. In these studies sample sizes must be very large, including thousands of patients and controls [21].

The sequencing of the human genome also provided the opportunity for 'top-down' studies in studying brain abnormalities in post-mortem brains of persons who had suffered psychiatric illnesses. This work can look at mRNAs in brain regions. Patients could be compared to controls in a between subject-design or different brain regions within the same subject can be compared.

The essential technique in studies comparing mRNAs of affected versus control brain tissues involves extraction of mRNAs from the brain tissue in the region under

study. Reverse transcriptase, an enzyme which transcribes RNA into double-stranded DNA, is utilized to obtain complementary DNA (cDNA) sequences of the extracted mRNAs. The cDNAs are amplified by polymerase chain reaction (PCR) and separated by gel electrophoresis. Clones which are differentially expressed are sequenced and identified through searches of HGP and other large databases for target validation. It is also possible to study transgenic mice in which the genes identified by the differentially expressed cDNA are overexpressed or knocked-out.

The results obtained from linkage studies, the association studies, the whole genome association studies and the post-mortem studies are described in the following sections.

3.11 Genomic findings, potential targets and new drug development

Schizophrenia

A number of candidate genes have been identified which have important implications for the pathogenesis of schizophrenia and imply potential targets for new drug development.

Neuroreglin (NRG1), Dysbindin-1 (dystrobrevin-binding protein or DTNBP-1), D-amino acid oxidase activator (DAOA) [21] and Glutamate receptor, metabotropic 3 (GRM3) [24] are candidate genes for schizophrenia. Although these genes encode for diverse functions in the brain, they converge on regulation of glutamatergic neurotransmission. The clinical observation that N-methyl-D-aspartate (NMDA) antagonists such as phencyclidine and ketamine can provoke psychotic symptoms converges with functional neuroimaging findings [25] and post-mortem mRNA analyses in implicating glutamatergic dysfunction in schizophrenia [26]. It has been postulated that NMDA hypofunction resulted in decreased dopaminergic activity and increased subcortical dopaminergic activity [27].

Augmenting glutamatergic activity then seemed to be a reasonable strategy for development of a novel non-dopaminergic treatment of schizophrenia. A phase II trial of an agonist of the mGlu2/3 receptor showed efficacy equal to olanzapine and superior to placebo [28].

A novel concept is that schizophrenia might be treatable by targeting the epigenetic changes in the illness being expressed. This concept is based on the hypothesis that experiences or illnesses during gestation or later life may lead to enzymatic methylation or acetylation of proteins which promote gene expression. DNA methyltransferase catalyzes histone protein methylation, which reduces gene expression. Conversely, histone acetyltransferase catalyzes histone protein acetylation, which augments gene expression. These changes are conserved when the DNA replicates which would result in permanent alterations of gene expression.

Post-mortem studies of gene expression of persons affected with schizophrenia have revealed decreased expression of reelin [29]. Reelin is an extracellular matrix protein which influences development and cognition. Brains of schizophrenics show

hypermethylation of the reelin promoter which would reduce reelin expression. These results suggest the hypothesis that reelin promoter may be subject to continuous repression by deoxyribonucleic acid methyltransferase (DNMT) [30]. Development of an inhibitor of DNMT therefore becomes a potential target for treating (or reversing) schizophrenia.

Neurocognitive impairment is a core symptom of schizophrenia and represents the symptom domain that most strongly predicts functional outcome [31]. Genomics has identified candidate targets for treatment in this illness domain. Examples are catechol-O-methyltransferase (COMT) and the α -7 nicotinic receptor.

COMT has been identified as a candidate gene in schizophrenia in both linkage [32] and association studies [33]. In the frontal cortex enzymatic deactivation of dopamine is the main mechanism for reducing intrasynaptic dopamine. This is distinct from limbic areas where neuronal reuptake is the dominant mechanism [34].

A specific SNP, val158met, is clearly involved in the efficiency of the prefrontal cortex in working memory tasks [35]. The val allele is the high activity allele and breaks down dopamine more rapidly, leading to less intrasynaptic dopamine and reduced efficiency of executive cognition. Schizophrenic patients, their siblings and normal controls all show the same effect of genotype on working memory on the n-back paradigm [35, 36]. In this test of working memory, subjects are presented with a series of digits. The 0-back task requires the subject to recall the last digit. The 1-back task requires recall of the next to last digit, and the 2-back task requires recall of the second to last digit [35]. On the 2-back test, performance is most impaired in individuals with the val/val genotype, intermediate in those with the val/met genotype and best in those with the met/met genotype [36]. Controls performed better than siblings of patients, who performed better than schizophrenic patients [36]. Impaired executive cognition was tightly correlated with impaired frontal lobe activation on blood oxygen level-dependent (BOLD) fMRI studies during task performance [37].

In addition, val/val is associated with increased mid-brain dopamine in vivo when measured by PET scans measuring 6-fluorodopa uptake, conducted simultaneously with fMRI studies described above [38]. In post-mortem studies, val/val predicts increased expression of tyrosine hydroxylase mRNA expression, suggesting dopaminergic hyperactivity [34].

The val/val genotype therefore results in decreased pre-frontal dopamine correlated with decreased working memory performance and in increased subcortical dopamine synthesis which is implicated in psychotic symptoms. For this reason, a COMT inhibitor might be useful in treating the neurocognitive deficit in schizophrenia in a genotype-dependent manner. Tolcapone has been demonstrated to improve cognition in normal controls in a genotype-dependent manner [39]. Phase II trials are ongoing in patients.

Another potential target for neurocognitive impairment is the α -7 nicotinic receptor. Positive linkage on 15q13-q14 was first noted with the p50 deficit schizophrenia endophenotype and subsequently with schizophrenia [21]. The region includes cholinergic receptor, nicotinic, alpha-7 or CHRNA7, the gene encoding the α -7 nicotinic receptor [21]. The clinical observation of the frequency of nicotine dependence in schizophrenics is consistent with the relevance of this receptor [40]. A post-mortem

study of the hippocampus in schizophrenic patients reported decreased receptor density [41]. Furthermore, the impaired cholinergic neurotransmission in patients with Alzheimer's disease suggests cholinergic mechanisms are involved in cognitive impairment. α -7 nicotinic receptors are located on dopaminergic neurons in the pre-frontal cortex [42]. Activation of these receptors by acetylcholine results in enhanced dopamine release [42]. Increased dopamine release in the pre-frontal may improve cognitive deficits in schizophrenic patients [38]. Agonists and positive modulators of the α -7 nicotinic receptor are in development as cognitive enhancers [42].

Bipolar disorder

Advances in genomics have led to a change in the understanding of the neurobiology of bipolar illness. The associated genes converge on pathways involved in neurogenesis, neuroprotection and regulation of synaptic plasticity. The molecular understanding of bipolar illness has shifted from understanding bipolar disorder as an illness with polarity-defined symptomatic states to the concept of bipolar disorder as an illness characterized by impaired neuronal resilience and neuronal plasticity [43]. This changing understanding has implications for selecting targets for new drug development.

Identified genes include GSK-3 β , diacylglycerol kinase ϵ (DGKH), bcl-2, nucleoredoxin (NXN) and whirlin (deafness, autosomal recessive or Dfmb31) [44]. These genes are involved in the phosphatidylinositol signaling pathway and the wingless or wnt/ β -catenin pathway; there is 'cross-talk' between these pathways mediated by protein kinase C (PKC), which is activated by diacylglycerol [45]. These pathways are involved in regulation of BDNF, nerve growth factor (NGF) and B-cell lymphoma-2 (bcl-2) which promote cell survival and neurogenesis [45].

Preclinical and clinical studies suggest that lithium may possess neuroprotective properties [46]. Lithium protects neurons in cell culture from damage from glucose deprivation and excitotoxicity. Lithium also enhances hippocampal neurogenesis. Chronic lithium treatment increases gray matter volume and neuronal N-acetylaspartate (a putative marker of neuronal viability and function) in brains of patients with bipolar disorder [46].

Lithium and valproate share important pharmacologic properties. Both inhibit GSK-3 β and inhibit PKC signaling [47]. Each activity may be relevant for targets for new drugs. PKC inhibition may target manic symptoms, and GSK-3 β inhibition may be more important for resilience and neuroplasticity [45].

Inhibition of PKC is a putative antimanic mechanism. Tamoxifen both blocks estrogen receptors and inhibits PKC [48]. In two placebo-controlled trials, tamoxifen was superior to placebo in efficacy and was well tolerated [48], [49]. A variety of PKC inhibitors are currently under development.

Association has also been reported with the glutamate receptor, ionotropic, AMPA1 (GRIA1) with psychotic bipolar disorder in a cohort of 23 families [50]. Preclinical studies have revealed that action at α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors is complex, and it is likely antimanic and antidepressant drugs have differential effects at the receptor [51]. Drugs

which are allosteric modulators of this receptor hold promise as novel agents. There is potential for treatment of acute symptoms as well as for long-term mood stabilization, resilience and plasticity with these drugs [51].

In summary, bipolar disorder is a complex polygenic disorder which has several domains of pathology. The illness is now viewed as a chronic illness which reflects disturbances in the resilience and plasticity of neurons and complex neuronal circuits.

Major depressive disorder

Since the discovery that monoamine oxidase (MAO) inhibitors and imipramine possessed antidepressant activity, no antidepressant with a non-aminergic mechanism of action has reached the market. Advances in research technology and genomics should facilitate the new understandings of the illnesses and new targets for the treatment of depressive disorders.

Association and linkage studies have not consistently identified candidate genes for major depressive disorder. However, there are reports of association with BDNF [52] and the serotonin transporter (SERT) [53].

There is evidence that there is association to genes encoding cyclic nucleotide phosphodiesterases (PDE), which are involved in the degradation cAMP and cyclic guanosine monophosphate (cGMP). The strongest association was for PDE 11 [54]. Given that G-coupled protein receptors are involved in serotonergic neurotransmission, development of new drugs which act on cGMP-related PDEs would be a reasonable approach to non-aminergic treatments for depression.

Analysis of post-mortem brain sections from persons who suffered major depressive disorder (MDD) have revealed decreased expression of several genes which include genes involved in glutamate transport and genes encoding mitogen-activated protein (MAP) kinases. Additionally, there was decreased expression of genes involved in neurotrophic signaling: fibroblast growth factor (FGF), vgf and BDNF [55]. As in the case for bipolar disorder, neurotrophic signaling cascades provide a novel target for drug development.

The involvement of genes functioning in glutamate transport converges with imaging studies demonstrating reduced glutamate in the anterior cingulate cortex of depressed patients measured by magnetic resonance spectroscopy (MRS) [56]. Targeting glutamate receptors could therefore be a rational strategy for novel antidepressant development. Intravenous ketamine administered to treatment-refractory depressed patients resulted in rapid improvement in mood which persisted for seven days [57]. Memantine, a non-competitive blocker of the glutamate NMDA receptor, was as effective as escitalopram in treating major depression with co-morbid alcoholism [58]. NMDA antagonism remains another rational target for antidepressant development.

Post-mortem sections of brains from humans suffering depression showed reduced expression of glucocorticoid mRNAs [59]. Association studies have shown that depression was also associated with polymorphisms in the glucocorticoid receptor [60]. This finding, in conjunction with long-standing evidence of dysregulation of the hypothalamo-pituitary-adrenal axis in patients with major depression, suggests that

development of corticotrophin releasing factor (CRF) antagonists may be a fruitful strategy in new drug development.

An interesting observation is the overall change in the understanding of schizophrenia, bipolar disorder and major depression. While differing in symptomatic presentation, there emerges the common aspect of alterations in neural plasticity, neurogenesis and resilience. This is mediated by overlapping genetic mechanisms and has implications for targets for new drug development.

Pharmacogenetics and personalized medicine

Can genomic information predict response to pharmacotherapy? Three examples of how genes or their variants can predict drug response or adverse effects are described below.

Cytochrome P450 2D6

Many psychiatric medications are metabolized by this isoenzyme; there are over 100 genetic variants. Differing mutations affect the activity or stability of the enzyme. These variations can be ascertained by microarray or ‘gene chip’. Of particular importance are the differing allele frequencies by ethnicity. Rapid metabolizers may have inadequate response at standard doses; slow metabolizers may have adverse effects at standard doses. For medications with a narrow therapeutic index, this prediction can be crucial for patient safety [61].

COMT

The COMT genotype is predictive of improvement in neurocognition in schizophrenics treated with olanzapine. As detailed earlier in this chapter, the met/met genotype is associated with slower metabolism of dopamine in the prefrontal cortex; met/met predicts improvement on the 2-back working memory task at 4–8 weeks for patients taking olanzapine [62].

Serotonin 2A receptor gene (5HTR2A) and kainate-type glutamate receptor gene (GRIK4)

In the first analysis of the results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial, subjects who were homozygous for the A allele at 5HTR2A showed an 18% reduction in absolute risk for non-response compared to subjects homozygous for the other allele [63].

A follow-up analysis on a larger sample demonstrated that subjects who were homozygous carriers of both the GRIK4 C allele and the 5HTR2A allele were 23% less likely to exhibit non-response than subjects who did not carry these marker alleles [64].

The future

Finally, there are some speculative potential targets for future drug development which involve either directly altering genes, or altering the expression of genes involved in psychiatric illnesses.

Use of viruses as vectors for gene therapy

There are two strategies involving use of viruses as vectors for gene therapy.

The first strategy utilizes a retrovirus as the vector to deliver genes which are incorporated in the DNA of human cells. Retroviruses have RNA as their genetic material. Their RNA includes genes encoding reverse transcriptase and integrase. Reverse transcriptase catalyzes the synthesis of DNA from the viral RNA. Integrase catalyzes the insertion of the DNA into the host genome. If RNA corresponding to the DNA of a healthy human gene is inserted into the viral genome, it is theoretically possible to insert that sequence into the human genome.

The second strategy utilizes adenoviruses. The genetic material of adenoviruses is in the form of double-stranded DNA. Adenoviruses deliver their DNA to the nucleus of human cells without inserting it into the host DNA. A healthy gene could be inserted into the nucleus of the cell by this technique. However, this DNA is not replicated with the cellular DNA and would require repeated delivery.

However, there are technical and ethical issues regarding the use of these approaches. These methods, their medical applications and related technical issues and ethical concerns are discussed on the HGP information web site (www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml#whatis).

Pharmacologic gene therapy

An alternative strategy in gene therapy is the use of pharmaceuticals to alter gene expression.

The possibility of reversing epigenetic re-methylation of nuclear DNA by inhibiting DNMT [30] was discussed previously in this chapter.

An exciting strategy is the use of specific siRNAs to prevent expression of genes which confer illness risk. siRNAs are double-stranded RNAs which silence homologous mRNA transcripts by inducing their degradation or by halting their translation [65]. This technology is currently under development.

3.12 Conclusion

The sequencing of the human genome and the subsequent cataloguing of human genetic variability have changed the approach to understanding illness and to the development of new therapies.

There has emerged a more complete understanding of the biological basis for many illnesses. It is possible to ascertain which persons are at genetic risk for developing illnesses. Ability to identify new brain targets for drug development is enhanced. It is possible to focus on ‘personalized medicine’, that is interventions specific to the affected individual. Finally, there is an increased capability of developing treatments to prevent illness.

These advances mirror the current National Institutes of Health mission of developing interventions which are pre-emptive, practical and personalized.

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4

Patenting and Licensing Concerns in Psychiatric Genetics

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Abstract

Recent years have seen a proliferation of patent filings in the field of psychiatric genetics. Patents have already been issued on isolated wild-type or mutant human genes believed to correlate with susceptibility to psychiatric disorders, as well as on methods of diagnosing susceptibility, pharmacogenomics or drug screening using such genes. If experience in other areas of diagnostic genetics is any indication, it is expected that there will arise in psychiatric genetics issues relating to exclusive licensing of important correlation patents and also relating to the fragmentation of patent rights. Such fragmentation occurs when multiple patents on diagnostic correlations are controlled by multiple owners, in a situation where all or many of the correlations are deemed necessary for a universal diagnostic panel. Non-judicial avenues for solving these problems include the formation of so-called patent pools in which multiple owners collaborate to give each other and third parties rights to all patents necessary for testing a given disease. Professional associations such as the American College of Medical Genetics or the American Psychiatric Association may play a facilitating role in the formation of such collaborative patent arrangements.

Key Words

patents; licensing; pharmacogenomics; psychiatric genetics; patent fragmentation; patent pools; isolated genes; susceptibility; diagnostics; patent thickets

4.1 Genetic diagnoses in psychiatry

After the entire human genome had been sequenced and published, it did not take long for biological scientists of all disciplines to proclaim that a genetics revolution was upon us and to predict all manner of fast advances, especially in medicine. The relatively new field of psychiatric genetics was no exception. Its focus is on the role of genes in psychiatric illnesses. Psychiatric geneticists believe that, with careful and systematic study of the human genome, it will be possible to find increasingly meaningful correlations between genes and mental disorders.

While genetic linkages for certain phenotypes such as attention deficit disorder, autism or schizophrenia have been postulated, there is a clear recognition that not only are psychiatric disorders phenotypically complex, but their genotypic correlations are clearly due to the interactions of multiple genes. When these multiple genes are turned on, due to development or environment (such as nutrition or stress), they shed expression products into the body that generate a bewildering array of so-called *endophenotypes*. These are often internal and not always easily observable features, such as protein levels, and even aggregated or modified forms of the proteins. The endophenotypes, in turn, may give rise to yet another layer of observable traits, such as anatomical brain modifications. Ultimately, these may lead to the composite set of behavioral symptoms observed in mental disorders.

To make matters even more interesting, the expression of endophenotypes is not only influenced by the environment, but by other endophenotypes in what has become known as *epigenetics*, the interplay of multiple internal and external factors on the production and sustainability of the ultimate phenotype. For a given psychiatric disorder, the resulting multidimensional picture that takes all of these factors into account over the span of a human life has been called by Gottesman *et al.* a ‘reaction surface’ [1] – and a pretty complicated surface it is.

In psychiatry – as in other clinical areas – there is the realization that, given our present limited understanding of epigenetics, the best we can hope to reveal by gene analyses is a *susceptibility* or *predisposition* toward disease. With the tools of genetics, we may be able to discover variants from the norm, such as gene mutations or polymorphisms that occur more prominently in populations or families with a psychiatric disease than in those without. To coin an elegant phrase of Gottesman, we may call such genomic modifications ‘vulnerable risk states for future dysfunction’, recognizing that factors outside of our genes *may* then ‘convert vulnerability to actuality’.

Schizophrenia may be used as an illustration. About two dozen candidates for vulnerability genes have been identified, with the catechol-O-methyl transferase (COMT) gene being a good example. The COMT gene, which is present on chromosome 22, encodes for COMT, one of several enzymes that degrade catecholamines such as dopamine, epinephrine and norepinephrine. A single nucleotide polymorphism (SNP) in the COMT gene correlates with phenotypic frontal lobe functions such as cognitive task impairment. This SNP changes the amino acid valine (Val) to the amino acid methionine (Met) at position 158 of the gene sequence, and the SNP is therefore denoted as *Val158Met*. Neurons with a COMT enzyme having the Val158Met polymorphism show higher levels of activation during certain cognitive

tasks, requiring higher levels of firing to achieve the same level of stimulation. It is not surprising then, that an inherited variant of COMT is thought to be one of the genetic factors that may predispose someone to develop schizophrenia later in life.

Another interesting aspect of the impact of genetics on psychiatry is the concept of *pharmacogenomics*, also known as ‘personalized medicine’. In this approach, a patient having an established diagnosis in need of drug therapy is tested genetically to evaluate if they are likely to be a good responder to one medication or another, or would be susceptible to side effects.

For example, Arranz and deLeon [2] describe the development of genetic tests to determine a patient’s metabolic status and the first attempts at personalization of antipsychotic treatment. The most significant results are the association between drug metabolic polymorphisms, mainly in cytochrome P450 genes, with variations in drug metabolic rates and side effects. For example, patients with genetically determined poor metabolizers (PMs) status may require lower doses of antipsychotic. Alternatively, ultrarapid metabolizers (UMs) will need increased drug dosage to obtain therapeutic response.

Testing for the presence or absence of the Val158Met SNP, or of PM or UM status, can be routinely carried out in modern genetic diagnostics laboratories using state of the art sequencing methodology. Indeed, the numbers of genetic tests for all diseases, and of laboratories offering them, have grown explosively in the last nine years. In late 1999, it was estimated that genetic testing was available for more than 300 diseases in over 200 US laboratories and, by late 2008, the numbers had grown to 597 laboratories carrying out clinical tests for 1635 diseases [3]. Expecting future growth in psychiatric genetics, the diagnostic and pharmaceutical industries have become actively involved in research and development in the field. Given the commercialization programs of most US universities, private industry is also enthusiastically supporting and developing a great deal of academic research. With this level of industrial interest come patents and, not surprisingly, there has been a proliferation of patent activity in psychiatric genetics.

4.2 The evolving patent landscape in psychiatry

We now turn to the core of our chapter, the evolving patent landscape in psychiatry and what it portends for the future of the field. We biotech patent attorneys tend to be optimistic, perhaps even more so than the experienced and seasoned scientists who are carrying out the research that we are charged with patenting and protecting. The nature of the patent system is such that we tend to file patent applications early to prevent losing rights due to premature publication. We also tend to file a lot of applications ‘just in case’ a gene test turns out to be commercially useful. The concept of *usefulness* under most patent systems of the world is far short of the standards of clinical effectiveness required by the health authorities, such as the FDA. As a consequence of the rush to file before publishing and the relatively lower standard of usefulness, there are already a large number of pending and issued patent claims on tests for genetic susceptibility and for personalized medicine in psychiatry. We will explore some of them after a brief (and simplified) primer on patents and patent protection.

The nature of patent rights

A patent is a private property right granted by the government that gives exclusivity of limited scope and for a limited period of time to inventors for their disclosure of an invention that has met the government's patentability requirements. If an inventor wishes to obtain exclusivity in several countries, then he or she must obtain a patent in each country and satisfy each country's patentability requirements. Our discussion will be focused on US patents.

A patent may be granted to anyone who invents any new, useful and non-obvious process or method, machine, article of manufacture or *composition of matter*. Compositions of matter include chemical compounds, pharmaceutical formulations and purified natural products such as proteins or genes. The patent must conclude with *claims* that define, in technico-legal words, the scope of the protection conferred by the patent, or the protection sought in a patent application. Similar to the language in a deed for land, the claims set out the 'metes and bounds' of the *intellectual property* protected by the patent.¹ For example, a patent could be issued with claims on a method of diagnosing disease X, or a composition of matter for use in such a method.

Relevant to our discussion, patents have been and continue to be granted on isolated and purified products of nature, including isolated human genes or portions of genes that encode proteins or peptides. Patents are also granted on methods of using such genes or their information for diagnosing, preventing or treating diseases [4]. Specifically, and as we will shortly demonstrate, many patents and patent applications contain claims to methods of diagnosing the *susceptibility* of an individual to develop a psychiatric disorder, by detecting in the genome of the individual the presence or absence of a particular genetic sequence that correlates to the disorder.

A patent on a psychiatric diagnostic test would be granted by the US Patent and Trademark Office (USPTO), an agency under the auspices of the Department of Commerce. At present, the grant of a US patent on a test gives its owner the right to exclude others from making, using, offering for sale or selling the test in, or importing kits embodying it into, the United States for 20 years from the filing date of the patent application. It is important to understand that what is granted by the USPTO is not the affirmative right to make, use and so on, but the right to *exclude* others from undertaking these activities. The patent rights of the owner are always subject to the greater patent rights of others, and the owner, while holding a patent, may still need licenses from other patent holders before they can commercialize the diagnostic test. Once a patent is issued, the patentee may enforce the patent in the federal courts.

The goal behind granting exclusionary patent rights to an inventor of a test is to protect the time and money that an individual or company may have to put into its commercial development. This guarantees that only the applicant of the patent has the opportunity to produce and market the test for the limited term of the patent.

¹ Intellectual property is broadly defined by the World Intellectual Property Organization as including 'creations of the mind: inventions, literary and artistic works, and symbols, names, images, and designs used in commerce' (<http://www.wipo.int/about-ip/en/>, accessed 28 October 2008). Patents for inventions are therefore one of the multiple forms of intellectual property.

Exclusivity is seen as essential to encourage investment in and development of new services and products, especially of risky inventions in the health sciences.

One interesting constraint, among many, of the ability of the USPTO to issue genetic correlation claims is the so-called *phenomenon of nature* limitation. We will briefly discuss this next.

Patent claims cannot preempt a phenomenon of nature

It is undisputed in law that a patent claim cannot be issued if it excludes others from operating a natural phenomenon, such as a basic law of nature. The Supreme Court has ruled several times that ‘...phenomena of nature...are part of the storehouse of knowledge of all men...free to all men and reserved exclusively to none’ [5]. For example, a valid patent could never issue on ‘a method of exchanging matter for energy, such that for every unit of matter (m), the amount of energy (E) obtained is denoted by $E = mc^2$ ’. Had Einstein improperly applied and obtained such a patent from the Swiss Patent Office (with someone else examining it), the patent would have given him a 20 year monopoly on all uses of his interconvertibility law. This is clearly nonsense. The relation between matter and energy, as well as other natural relations such as gravity or electromagnetism, have been in existence since the formation of our universe. Einstein discovered the mass/energy equivalency; he had, however, nothing to do with inventing it.

The difficulty arises in defining what is a phenomenon of nature (not eligible for patents) and what its application is (eligible). Had Einstein or someone else, after the discovery of $E = mc^2$, invented a novel nuclear reactor with a clever mechanism of channeling the energy extracted from mass toward other useable forms of energy such as electricity, they would have been able to obtain a patent (even although the reactor would be based on Einstein’s famous discovery). That is because the invention of the reactor would have been ‘made by the hand of man’, a phrase coined by the Supreme Court in the famous *Diamond v. Chakrabarty* case, which decided that artificial, oil-degrading microbes were patent eligible subject matter [6]. Similarly, while a gene sequence by itself is a phenomenon of nature and therefore not patent-eligible, once the gene is isolated from its natural environs and purified to homogeneity it is, in such a state, no longer a natural material and becomes eligible for a patent as a ‘composition of matter’. Its practical applications to diagnose susceptibility are also eligible as ‘method of use’ patents.

The prohibition against preempting a phenomenon of nature informs the all-important wording of method claims in genetic diagnostics patents. A claim drawn to a method of determining susceptibility to schizophrenia might (incorrectly) be drafted as follows:

A method of determining the presence or absence of the single nucleotide polymorphism *Val158Met* in the DNA of the COMT gene of a patient wherein the presence of the SNP is indicative of a susceptibility to Schizophrenia in the patient.

Such a claim is probably invalid for preempting a natural phenomenon, namely the relationship between the SNP and schizophrenia. The relationship itself is a product

of evolution and is not anything ‘made by the hand of man’. Now compare such a claim with a more clearly patentable version:

A method of determining the susceptibility of a patient to suffer Schizophrenia, which comprises:

- 1 obtaining a sample of DNA from cerebrospinal fluid of the patient;
- 2 confirming that the sample contains the COMT gene;
- 3 sequencing, by polymerase chain reaction (PCR), the region of the COMT gene around codon 158; and
- 4 determining if the sequence encodes the *Val158Met* polymorphism.

This claim would likely pass muster in that it goes beyond the simple natural correlation between the SNP and the disease. The claim includes a number of ‘man-made’ steps, such as obtaining samples of cerebrospinal fluid (CSF) and sequencing by PCR the COMT gene around codon 158. While ongoing patent litigation has already focused on the possible invalidity of several diagnostic claims under this ‘phenomenon of nature’ prohibition, no major court precedent has yet been reported [7].

Patent licensing

As we have seen, the owners of diagnostic patents are the only ones who may commercialize the patented diagnostic tests. All others who make, use or sell such tests with commercial intent are considered patent infringers and may be enjoined by a court of law from continuing their infringement. There is a limited and narrow exception to this rule and it applies to those who may study the diagnostic test with nothing but *philosophical intent*, for example, to evaluate how the test works. However, even the continuing use of a patented invention in a university context to further the basic business of the university, that is to teach, has been held to be patent infringement and subject to an injunction [8]. The phrase ‘philosophical intent’ is therefore, to use a legal term, narrowly construed.

If the inventors or owners (in the case where the inventors have assigned their rights to a company or university) have a pending patent application or have been granted a patent, they may *license* their patent rights to others, called licensees.² A patent license is, in effect, an agreement that the patent owner will not sue the licensee for patent infringement, as long as the licensee fulfills its obligations such as using their best efforts to commercialize the technology. Licenses may be limited regarding time, geographical area or field of use. They may be exclusive, partially exclusive or non-exclusive. An exclusive license restricts the use of an invention to a single licensee and, in essence, transfers the right to exclude from the owner to another party. A partially exclusive license allows multiple licensees, but may restrict the use of the invention by any single licensee to a particular geographic area

² It is not uncommon to license patent applications while they are still pending. If properly drafted, such a license ensures that if and when a patent is issued, it will also be licensed.

or to a particular use. Finally, a non-exclusive license can be issued to any number of licensees.

Patent licensing is the most frequent vehicle used by academic institutions to commercially exploit the patents that are generated by their professors and scientists. Under the Bayh–Dole Act of 1980, US universities have the right to own all inventions made in their laboratories using federal funds, and have the right to license the resulting patents exclusively to companies in order to facilitate – in the words of the statute – their ‘practical application’ [9]. As we will see, the *manner* of licensing diagnostic patents has caused much difficulty and will be discussed in detail below.

Meanwhile, with a basic background on patent law in place, let us now explore US patents in the field of psychiatry and, more specifically, gene-based patents (or pending patent applications) involving the diagnosis of psychiatric disorders.

Examples of patents and patent applications in psychiatric genetics

Consistent with the goals of psychiatric genetics, that is, to find and exploit the relationship between disease and genotype, the most common types of patent claims that have already been granted or are pending are drawn to isolated genes and their diagnostic or pharmacogenomic correlations. We will provide examples, first by type of patent claim and then by type of psychiatric disorder.

Types of patent claims

Genes

These are claims to isolated and/or purified wild-type or variant human gene sequences that have been determined to be associated with certain psychiatric disorders. For example, claim 1 of US Patent 6,555,316,³ owned by Genset SA, France, is drawn to a biallelic marker named A56 that is present in a gene of unknown function named g35030 which seems to correlate with schizophrenia and reads:

An isolated, purified and recombinant polynucleotide comprising a contiguous span of at least 30 nucleotides between nucleotide positions 199122 to 249803 of SEQ ID NO:1 [Sequence Identifier No. 1 is the sequence for the g35030 gene], wherein said contiguous span comprises the biallelic marker shown as A56.

Susceptibility

These are claims to methods of determining the susceptibility/risk/predisposition of a patient to develop a particular psychiatric disorder based on the presence of certain gene mutation(s) or polymorphism(s). For example, claim 1 of US Patent 6,274,352, owned by Garvan Institute of Medical Research, Australia, reads:

³ This patent as well as all other patents mentioned in this paper may be downloaded free of charge from the website of the USPTO: <http://patft.uspto.gov>. Select ‘Patent Number Search’ and enter the number.

A method of assessing an individual's predisposition to Bipolar Affective Disorder (BAD), comprising detecting the presence or absence of at least one BAD-linked allele at 4q35 on chromosome 4 of said individual wherein the presence of a BAD-linked allele is indicative of [an] individual's predisposition to BAD.

Diagnosis

These are claims drawn to methods of diagnosing a psychiatric disorder based on the detection of certain gene mutation(s) or polymorphism(s). For example, claim 1 of US Patent 6,566,065, owned by McGill University, Canada, reads:

A method of diagnosing schizophrenia in a subject, said method comprising the steps of: (a) analyzing the methylenetetrahydrofolate reductase (MTHFR) nucleic acid in a sample obtained from said subject; and (b) determining the presence of a heterozygous C/T mutation at position 677 of MTHFR in said subject, wherein the presence of said mutation is indicative of said subject having said Schizophrenia.

Pharmacogenomics

These are claims drawn to methods of predicting a patient's likelihood of responding to drug treatment for a particular psychiatric disorder. For example, claim 5 of US Patent 6,136,532, jointly owned by the University of California and the University of Costa Rica, reads:

A method of predicting a patient's likelihood to respond to drug treatment for Bipolar Mood Disorder (BP) comprising: determining a patient's genotype in a region on the long arm of chromosome 18, wherein said determining comprises determining an allele size in a DNA sample derived from said patient at a marker located between markers D18S469 and D18S554, inclusive; and comparing said patient's genotype to a genotype of an affected individual, wherein a sharing of an allele size at a marker located between markers D18S469 and D18S554, inclusive, is an indication of an increased likelihood that a drug treatment for BP will be effective.

Another example of a pharmacogenomics claim is claim 1 of US Patent 6,399,310, owned by Akzo Nobel NV, Netherlands, which reads:

A method for improving the therapeutic response to mirtazapine in a human patient with Major Depression comprising administering mirtazapine, in an amount effective to treat Major Depression, to said patient, wherein said patient has been determined to be a carrier of the gene for apolipoprotein E4.

Drug screening

These are claims to methods of screening for drugs that could be useful in treating a psychiatric disorder by using the expression products of human genes or gene fragments in the screen. For example, claim 1 of US Patent 7,052,853, owned by Myriad Genetics, Inc., Salt Lake City, UT, reads:

A method of screening for drug candidates useful in treating Depression, said method comprising: measuring, in the presence and absence of a test compound, apoptosome activation of an apoptosome comprising wild-type APAF1 having SEQ ID NO:2, an APAF1 having SEQ ID NO:3, or an APAF1 having an amino acid substitution at a position selected from the group consisting of (a) Cys 450; (b) Gln 465; (c) Glu 777; (d) Asn 782; (e) Thr 953; (f) Leu 415; (g) Ser 357; (h) Asp 479; and (i) Glu at position 625; wherein if the level of apoptosome activation is less in the presence of said test compound than in the absence of said test compound then said test compound is a drug candidate for treating Depression.

Types of psychiatric disorders

There exist large numbers of gene-based patent filings for the diagnoses of psychiatric disorders believed to have genotypic correlations. These disorders include, for example, depression, schizophrenia, autism, bipolar disorder, anxiety disorders (including obsessive compulsive disorder), eating disorders (such as anorexia and bulimia), alcoholism and learning disorders (such as attention deficit hyperactivity disorder).

To illustrate the nature and ownership of the patent filings, we will look closely at three disorders: bipolar disorder, schizophrenia and autism. Numerous institutions (private industry and academia) have received US patent protection regarding the psychiatric genetics of these three disorders. Table 4.1, at the end of the chapter, presents a summary of 10 different patents that have been granted on genes allegedly associated with bipolar disease. Table 4.2 presents a summary of 10 patents for schizophrenia and Table 4.3 presents a summary of two patents and seven pending applications for autism. (The tables are far from all-inclusive, and each one shows only up to 10 representative genes. There are many more.) The tables include the US patent numbers, the patent owner and the types of claims that have issued. Also indicated is whether or not the research was funded with US government funds. This, as we will discuss shortly, is a legally relevant issue.

Even a quick look at Tables 4.1–4.3 confirms both the caution and optimism of the legal departments of pharmaceutical companies such as Millennium, Integragen or Bristol Myers Squibb, or the academic technology transfer offices of universities such as California, McGill or Rockefeller. For each disorder, there are multiple issued patents or pending applications on different genes and their correlations. As explained, the patent system does not have the time to wait until each of the correlations has been proved or disproved to be effective under the more exacting standards imposed by the FDA or by journal referees. Patent examiners will issue patents for diagnostic susceptibility tests based on evidence that is much less rigorous than that elicited by large-scale clinical trials.

The purpose of the patent system is not to weed out the diagnostically effective from the ineffective tests. The purpose of the system is to provide exclusivity for a limited period of time in order to promote investment and commercial development. Ultimately, the risk of diagnostic ineffectiveness or downright irrelevancy falls on the companies making the investments. If the tests turn out to be useless, the patents are irrelevant and no one will care. If the tests turn out to be useful and are then copied

Table 4.1 Representative gene-based patents for bipolar disorder.

Gene(s):	DRD4	BDNF	DBH	PNMT	Short arm chromosome 18	Long arm chromosome 18	BAD-linked allele on chromosome 4	fsh05	PAPAP	TRPC7
Patent number	6,998,235	7,101,666	6,913,885	6,660,476	6,750,010	6,136,532	6,274,352	5,955,355	7,220,581	6,548,272
Owner of patent	Centre for Addiction and Mental Health (Toronto, CA)	Centre for Addiction and Mental Health (Toronto, CA)	Whitehead Institute for Biomedical Research (Cam- bridge, MA) Johns Hopkins University (Baltimore, MD) The General Hospital Corporation (Boston, MA)	City of Hope (Duarte, CA)	The Regents of the Univer- sity of California (Oakland, CA) and Univer- sity of Costa Rica (San Jose, CR)	The Regents of the University of California (Oakland, CA) and Univer- sity of Costa Rica (San Jose, CR)	Garvan Institute of Medical Research (Dar- linghurst, AU)	Millenium Pharma- ceuticals (Cam- bridge, MA) and the Regents of the University of California (Oakland, CA)	Serono Genetics Institute SA (Evry, FR)	Eiken Kagaku Kabushiki Kaisya (Tokyo, Japan)
US gov- ernment funded?					YES	YES		YES		
Type of claim(s)	Suscep- tibility	Suscep- tibility	Suscep- tibility	Suscep- tibility	Suscep- tibility	Suscep- tibility Diagnosis Pharmaco- genomics	Suscep- tibility	Genes	Genes	Genes

Table 4.2 Representative gene-based patents for schizophrenia.

Gene(s)	PRODH	KalphaM1	MTHFR	PNMT	HOPA	Synaptogyrin 1	TH	fsh05	PAPAP	DISC1
Patent number	6,395,482	7,329,490	6,566,065	6,660,476	6,566,061	6,764,824	6,210,879	5,955,355	7,220,581	7,279,305
Owner of patent	The Rockefeller University (New York, NY)	Bristol-Myers Squibb Company (Princeton, NJ)	McGill University (Montreal, CA)	City of Hope (Duarte, CA)	The University of Iowa (Iowa City, IA) and USA, Department of Health & Human Services	Council of Scientific and Industrial Research (New Delhi, IN)	Rhone-Poulenc Rorer S.A. (Antony Cedex, FR)	Millenium Pharmaceuticals, Inc. (Cambridge, MA) and the Regents of the University of California (Oakland, CA)	Serono Genetics Institute. SA (Evry, FR)	N.V. Organon (Oss, NL)
US government funded?					Yes			Yes		
Type of claim(s)	Susceptibility	Susceptibility	Susceptibility Diagnosis	Susceptibility	Susceptibility	Susceptibility Genes	Susceptibility Diagnosis	Genes	Genes	

Table 4.3 Representative gene-based patents and published patent applications for autism.

Gene(s)	HoxA1 and HoxB1	HNL3	SLC6A1 and SLC6A11	PRKCB1	PITX1	SLC6A7	SLC6A4	NBEA	SLC25A12
Patent or application number	6,228,582	7,384,740	20080213765	20080193464	20070218068	20070134664	20070037194	20060194201	20070248956
Patent owner	University of Rochester (Rochester, NY)	Institut National de la Sante et de la Recherche Medicale (Inserm) (Paris, FR); Institut Pasteur (Paris, FR); Assistance Publique-Hopitaux de Paris (Paris, FR)	IntegraGen (Genavenir, FR)	IntegraGen (?) (Evry, FR)	IntegraGen (Evry, FR)	IntegraGen (Evry, FR)	Vanderbilt Univ. (Nashville, TN)	K.U. Leuven Research and Development (Leuven, BE)	Beatrice and Samuel A. Seaver Foundation (New York, NY)
US government funded?	Yes						Yes		Yes
Type of claim(s)	Diagnosis Genes	Susceptibility Diagnosis	Susceptibility Diagnosis Drug screening	Susceptibility Diagnosis	Susceptibility Diagnosis Pharmacogenomics drug screening	Susceptibility Diagnosis Pharmacogenomics drug screening	Susceptibility Diagnosis Genes drug screening	Susceptibility Diagnosis	Susceptibility Genes drug screening

by commercial free riders, who did not make the initial investments, the patents will be quite relevant. Investors will be pleased to have obtained patents, even though the inventors may not have had more rigorous data at the time of filing. The idea is that, if several years after the initial patent filing, a given diagnostic susceptibility test (by itself or in combination with others) turns out to be successful, there will then be in existence an issued patent to protect the investment that brought it into the stream of commerce.

Such a situation, however, will not preclude a company which later copies the patented test from defending against a charge of patent infringement by arguing at any time during the life of the patent that the patent is invalid, and should never have been granted by the USPTO. Patent invalidity defenses include: evidence that, at the filing date, the test was not novel in that it had been previously published or disclosed; that it would have been obvious to one skilled in psychiatric genetics; that it had not been sufficiently described in that, additional work absent, it was not yet fully reproducible; or that the test as claimed violates the ban on preempting a natural law. These are all very common and often successful litigation defenses to an accusation of patent infringement. What is not as common, and is much less likely to succeed, is for a copier of the patented test to allege, in defense, that the patent is invalid because the test is not useful. Even judges who are not scientifically trained can readily see the contradiction in such a position. A company that is making a profit by copying a diagnostic test patented by another will have a hard time arguing that the test is useless.

Patent issues that may arise in psychiatric genetics

The existence of gene-based patent rights in psychiatry is a relatively recent phenomenon. The field has not yet experienced certain issues that are starting to permeate other clinical areas, such as cardiology or cancer, where genetic diagnostic patents have been around longer. These issues transcend common litigation defenses, such as those of patent invalidity that we just discussed, but are more closely linked to the nature of the diagnostic genetics field itself. We will now describe two of these unique issues and explain how they might also arise in psychiatry.

Are patent applications being examined properly?

A first issue is related to whether the USPTO is doing an adequate job of examining the ever-growing number of patent applications dealing with genetic diagnostics. This issue relates to the nature of the proofs submitted to the USPTO to demonstrate the admittedly low threshold of ‘usefulness’ required by the law. Sometimes the submitted proofs have come under attack by others, as is the case with the BiDil patent of NitroMed. In 2004, the USPTO issued US Patent No. 6,784,177 to NitroMed of Bedford, Mass. The patent has the title ‘Methods [of] using hydralazine compounds and isosorbide dinitrate or isosorbide mononitrate’. Claim 1 of the patent reads as follows (emphasis added):

A method of reducing mortality associated with heart failure *in a black patient in need thereof comprising administering to the black patient* hydralazine or a pharmaceutically acceptable salt thereof in an amount of about 30 milligrams per day to about 300 milligrams per day and isosorbide dinitrate in an amount of about 20 milligrams per day to about 200 milligrams per day.

This claim – as well as other similar claims in the 6,784,177 patent, drawn to methods of reducing hypertension, improving oxygen consumption or improving exercise tolerance – is for administration of BiDil, a previously patented cardiac drug, to black patients. It is in essence a pharmacogenomic method claim.

The issuance of this patent has caused criticism on the basis that it used race instead of much stricter genomic correlations, such as SNPs or gene mutations, and that it was sought primarily to extend the patent exclusivity of an earlier, non race-based BiDil administration patent that expired in 2007 [10].

The issuance of this controversial patent sounds a note of warning to applicants of pharmacogenomic patents in psychiatry. As we have seen, the USPTO generally uses standards of usefulness that are more relaxed than those of the FDA. The USPTO, however, is not immune to public criticism and, because of the heated debate around the 6,784,177 patent, is likely to be somewhat stricter in issuing future patents in personalized psychiatric genetics.

How are the patents controlled?

A second issue likely to arise involving patents in this field is related to the *manner* in which patents to genetic diagnostics, once issued, are controlled, and how the tests are made available to the public. Two licensing situations have caused concern in other clinical areas. In one situation, all the necessary patents for a diagnostic genetics test are controlled solely by one owner (or the owner's exclusive licensee). In another situation, multiple patents which in the aggregate are necessary for a universal diagnostic test, are controlled by multiple owners (or their licensees). We will look at these in turn.

Single owner/exclusive licensee

The classic (and well-publicized) example of singly controlled patent rights to a genetic diagnostic test is that of the BRCA1 and BRCA2 (breast cancer) genes. BRCA1 and BRCA2 are tumor suppressor genes involved in the signaling and repair of DNA damage. During the 1990s, it was discovered that mutations in these genes result in a predisposition to breast cancer, ovarian cancer and other cancers [11]. The BRCA1 and BRCA2 genes were discovered with the help of funding from the National Institutes of Health (NIH) and were patented. There are multiple patents in the BRCA portfolio, including many owned or co-owned by Myriad Genetics of Salt Lake City, UT. Several of the Myriad patents are co-owned with the University of Utah; others are co-owned with other academic institutions [12]. Myriad, however, reserved the sole right to develop, use and commercialize the diagnostic tests for BRCA1 and BRCA2 and, in 1996, opened a \$30 million laboratory in Utah to do so.

From the start, Myriad attempted to suppress BRCA testing at competing laboratories by threatening patent infringement litigation. The clinical and scientific communities considered these actions particularly aggressive given the short amount of time it took for Myriad to assert their legal rights once the patents issued. As a result, the scientific community (not always legally correct) spoke out against Myriad's stand, stating that it would prevent researchers from developing improved tests, assessing the quality of Myriad's tests and developing treatments for breast and ovarian cancer [13]. Concerns regarding Myriad were particularly strong in Canada, Europe and Australia, places with public healthcare systems that differ markedly from those in the United States. In Europe, many groups filed patent opposition proceedings to Myriad's European patent on the isolated BRCA1 gene. (An opposition proceeding is uniquely European and is not available in the US.) In November 2008, however, Myriad succeeded in retaining the BRCA1 patent in amended form. More specifically, the patent now relates to diagnostic methods for detecting a predisposition for breast and ovarian cancer caused by a specific group of frameshift mutations in the gene. The patent no longer contains claims to the normal BRCA1 gene itself or to the mutated forms, *per se* [14]. Two other patents on the BRCA1 gene were amended to exclude diagnostic methods, a decision that Myriad is appealing. A patent on BRCA2 was allowed to stand in amended form [15].⁴

Ultimately, according to industry observers, Myriad's objectors in Europe took issue not so much with the *validity* of the patents themselves, but with the *commercialization* of those patents. Myriad's critics charge that its licensing policy and the high prices it demanded for its tests essentially barred other laboratories from conducting BRCA1 and BRCA2 testing. We should note, however, that it is not unlawful for a patent holder to prevent others from commercializing its patented inventions – quite the contrary; that is in the very nature of a patent. The right given by a patent to exclude others for a term of years is a delicately crafted compromise designed to promote investment in new technologies. It is when the right to exclude competitors collides with the public health (and not just with the commercial health of the competitors) that troubles may arise. We will address the public health issues later in this chapter.

Multiple owners/multiple exclusive licensees

It often arises that diagnostic correlations among disease and gene sequence variants work well only if multiple variants are tested in multiple genes. It is not uncommon for there to be multiple patents, each claiming one of these sequence variants, and each owned by, or exclusively licensed to, different institutions. This may give rise to the phenomenon known as a *patent thicket*, where a potential market entrant,

⁴ Until recently, the US patents have not been challenged. On 12 May 2009, however, the American Civil Liberties Union (ACLU), the Public Patent Foundation and several other plaintiffs filed a lawsuit against the USPTO, Myriad Genetics and The University of Utah Research Foundation, alleging that the patents on BRCA1 and BRCA2 genes stifle research that could lead to cures and limit options regarding medical care. The lawsuit argues that the patents on these genes are unconstitutional under the first amendment of the US Constitution, as well as invalid on other grounds (<http://www.reuters.com/article/pressRelease/idUS267791+12-May-2009+PRN20090512>).

such as a diagnostic laboratory, needs to seek and obtain multiple licenses from the different patent holders in order to test broadly for the disease. The transaction costs of investigating and obtaining multiple licenses to multiple variants can quickly become prohibitively expensive – and has been referred to as a ‘nightmare’ [16]. Further, if one or more of the owners or license holders refuses to grant a license, as is their right under the law, the test offered may not be as complete as desirable. With the rapid growth of the field, it is evident that the problems of thickets arising out of multiple patents on different variants will only get worse.

A recent example of a thicket is the diagnostic testing for inherited Long QT⁵ Syndrome (LQTS), a disease that may cause fatal cardiac arrhythmias when undiagnosed and untreated. LQTS has been correlated to numerous mutations in at least three sets of genes, leading to three genotypic forms of the syndrome: LQT1, LQT2 and LQT3. Most of the patents on the isolated genes and their susceptibility correlations are owned by the University of Utah Research Foundation. The Foundation has granted exclusive licenses to test for LQT1 and LQT2 mutations to one company, and exclusive licenses to test for other mutations in these genes as well as LQT3 to another company. It is believed by commentators that no one company alone is able to offer a complete set of gene tests. The dispute has reached the US Congress [17].

It is easy to see that a similar thicket might easily arise in psychiatric genetic testing for any of the three diseases illustrated. If for example it is determined that a universal multigenic diagnostic test for schizophrenia requires testing sequence variants in just 5 of the 10 genes in Table 4.2, say, proline dehydrogenase (PRODH), tyrosine hydroxylase (TH), fsh05, PAPAP and disrupted in schizophrenia (DISC1), a diagnostic lab wishing to place such a test on the market would need to negotiate licenses with Rockefeller University, Rhone–Poulenc, Millennium, Serono Genetics and Organon NV. This would be a daunting – and, quite possibly, unprofitable – proposition. The result would be that the market would have multiple laboratories offering different tests, or one laboratory offering less than a complete set of tests. Indeed, a complete set might not be readily available at all.

4.3 Approaches to solving potential problems

We have described some of the problems that have arisen when genetic diagnostics patents have been issued in clinical fields other than psychiatry. We will now analyze potential solutions being discussed in those fields. We will conclude by recommending certain guidelines and policies for psychiatric genetics that might avoid some of the problems.

We can roughly divide the proposed solutions into those suggested: (i) for the period before patents are issued; (ii) for the period after they are issued; and (iii) independent of time period, and involving collaborative approaches.

⁵ The term QT refers to the time interval between the start of the Q wave and the end of the T wave in the heart’s electrical cycle, as measured by ECG. The ECG measures electrical impulses as five distinct waves, known as P, Q, R, S and T waves. Most individuals with LQTS have a prolongation of the QT interval on ECG.

Before patents are issued: prevent issuance as a matter of law

Legislative attempts have been made to prevent or severely restrict the issuance or enforceability of human gene patents. For example, on 14 March 2002, former Representative Lynn Rivers (D-MI) introduced two bills with the stated goal to ‘carve out some limited exceptions to the applicability of gene patents . . . designed to minimize some of the negative impacts of patents on the practice of medicine and the advancement of science’ [18]. The first bill, HR 3966, The Genomic Science and Technology Innovation Act of 2002, would have required the Office of Science and Technology Policy to conduct a study that assesses the impact of federal policies, including intellectual property policies, on the innovation process for genomic technologies. The study would have explicitly considered various alternative levels of intellectual property protection for genomic materials and the likely impact of the various levels on increased costs of licensing. The second bill, HR 3967, The Genomic Research and Diagnostic Accessibility Act of 2002, would have exempted from patent infringement those individuals who use patented genetic sequence information for non-commercial research purposes. Another section of the bill would have exempted medical practitioners using genetic diagnostic tests from patent infringement remedies. There was no further action on either of these two pieces of legislation during the 107th Congress, and the bills died.

On 9 February 2007, Representatives Becerra (D-CA) and Weldon (R-FL) introduced House bill HR 977, The Genomic Research and Accessibility Act of 2007 [19]. This bill proposed prohibiting patents on ‘a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies’. No further action has been taken on this bill.

The failure of these bills is not surprising. The pharmaceutical and biopharmaceutical industries have already obtained thousands of patents on isolated genetic sequences and their uses, and have enforced these patents through hundreds of infringement lawsuits. Many of the patented sequences encode for blockbuster drugs, such as erythropoietin or tissue plasminogen activator, and serve as production templates for these proteins. Removing patent protection from all ‘gene sequences’, broadly, as the 2007 Becerra bill proposes, is not something that these industries would ever support, and for good reason. Without patent protection, it is simply too risky a financial proposition to move down the path of research and clinical development of *any* drug (proteins or otherwise). Prohibiting all patents on gene sequences would be analogous to a severe amputation rather than delicate surgery.

After patents are issued: control of the licensing process

A better and more subtle approach than forbidding gene patents altogether would be to try and influence how such patents are exploited and licensed *after* issuance. This can be attempted either voluntarily, confrontationally (by enlisting the power of the courts or of government agencies) or collaboratively. We address these in turn.

Voluntarily: licensing guidelines

Discussions on how to address the present and anticipated patent problems in diagnostic genetics voluntarily are taking place both in the United States and Europe.

US proposals

In the summer of 2006, technology transfer representatives from a select group of US research universities (Caltech, Cornell, Harvard, MIT, Stanford, University of California, University of Illinois, University of Washington, Wisconsin Alumni Research Foundation, Yale and the Association of American Medical Colleges) met at Stanford. After careful discussion, the group issued a white paper entitled 'In the Public Interest: Nine Points to Consider in Licensing University Technology' [20]. This 'Nine Points' document contains a set of recommendations to be considered when universities license patented technology to industry. In 2007, the Association of University Technology Managers embraced the Nine Points and recommended to all of its members that they try to use them in their corporate support and licensing contracts.

A discussion of all nine points is beyond the scope of this paper. For example, the document suggests to universities that they: reserve the right to practice licensed inventions; that they structure exclusive licenses in order to promote development and use; ensure broad access to research tools; weigh patent enforcement actions carefully; and address unmet needs such as those of neglected patient populations, especially those in the developing world. In one of the Nine Points, there is a comment on the licensing of genetic diagnostic patents that is highly relevant to our discussions of psychiatric genetics. Recognizing that, at times, diagnostic tests may have to go through the regulatory approval process and so may warrant exclusive licensing when the costs of test development require substantial investment of capital, the document nevertheless states:

Exclusive licensing of a single gene for a diagnostic may be counterproductive in a multi-gene pathology where only a panel of genes can yield an adequate diagnosis, unless the licensee has access to the other genes of the panel.

The document further comments that a university might consider granting an exclusive license to a company to manufacture a kit for the diagnostic test, but remain free to license non-exclusively to others the right to use the patented test. It concludes:

In general, when no alternative testing strategy is available for a given indication, consideration should be given to means of ensuring reasonable access for patients and shielding individual healthcare providers from the risk of suit for patent infringement.

The suggestion to try to avoid exclusively licensing a single gene, where only a panel of genes can yield adequate diagnosis, addresses the problem of expected patent thickets in psychiatric genetics head on. If different patents owned by different parties cover different genes (or their correlations) needed for an adequate panel, the

Nine Points document clearly suggests that exclusive licenses are not the way to proceed.

European approaches

In 2008, the European Society of Human Genetics (ESHG) also issued recommendations on genetic test patents [21]. After commenting on what they call the ‘bad’ licensing practices with regard to the BRCA case, the document states that ‘given that a considerable number of patents on disease genes and genetic tools have been granted, or are in the process of being granted, the ESHG considers that the issue (i.e. the availability of genetic tests) cannot be ignored’.

The ESHG’s recommendations would continue to allow researchers to patent their genetic tests, while at the same time ensuring that the patents do not restrict a patient’s ability to access such tests. The recommendations also include establishing an ethics committee to assess the scope of patents, fomenting more interaction among the patent authorities in the different countries in order to align their patent systems, prohibiting patents for disease genes and promoting new models for licensing to promote research, such as patent pools and clearinghouses. In an effort to assess the full scope of ‘bad’ licensing practices in the field, the ESHG has urged the ‘genetics community and governments [to] . . . analyze the availability and accessibility of genetic tests in the public sector, and identify the responsibility of the patent system if tests that exist are not available or affordable’.

Confrontationally: compulsory licensing in the public interest

If a patent holder controls a diagnostic test used in psychiatric genetics but is unwilling to grant a license to a testing laboratory, there is very little that the laboratory can do. Marketing a test without a license is patent infringement, and will subject the laboratory to a lawsuit and a permanent injunction. Refusal to license patented technology is, generally, not a violation of law. The courts have historically supported an absolute right to exclude others, regardless of economic consequences. There is a notable exception to this right. It arises from the recognition that there are times when the public interest, such as health, may trump patents. This exception can be raised either in court proceedings or in federal agency proceedings.

Court proceedings

In 2006, in the US Supreme Court case of *eBay, Inc. v. MercExchange, LLC* [22], Justice Thomas wrote that a permanent injunction may be entered in a patent case, but only *as long as the public interest is not disserved* [23]. Since public health is a major ‘public interest’, it follows that the holder of a psychiatric genetics patent who refuses to license a willing laboratory is not guaranteed to get an injunction. If the laboratory can successfully argue in court that its test is better, more complete, more thorough, complementary to other tests in a panel and so on, and that the public health would be severely harmed without its test, then, like it or not, the patent holder will have to obey the court. Our hapless owner may well win the patent infringement case against the laboratory but, if the owner fails to obtain a permanent injunction,

the court will force a so-called *compulsory license* on them. They will have to allow the laboratory to market the laboratory's test under court order. The laboratory will have to pay them a royalty of course, but, in the interest of the public health, the owner cannot stop the laboratory from commercializing its own diagnostic.

Federal agency proceedings

The other forum in which to raise the public health exception to the absolute right of a patent holder to exclude others comes from the Bayh–Dole Act of 1980. As we have seen, under this Act, US universities have the right to own all inventions made in their laboratories using federal funds, and have the right to license the resulting patents exclusively to companies. The Bayh–Dole Act, however, also includes a mandate to ‘...protect the public against nonuse or unreasonable use of [federally funded] inventions’ [24]. This mandate is achieved by the funding agency through so-called *march-in rights*, under which the agency can compel a Bayh–Dole patent holder to license the patent to a third party [25]. This is another form of *compulsory licensing*, except it is limited to patented inventions made with federal funds. The statute that controls the funding agency's march-in right says that (emphasis added)

...the Federal agency...shall have the right...to require the [patent holder]...to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant,...and if the [patent holder]...refuses such request, to grant such a license itself, if the Federal agency determines that such...(2) *action is necessary to alleviate health or safety needs which are not reasonably satisfied by the [patent holder]*....

In other words, if the patent holder (say, a US university or its exclusive licensee) has failed ‘to alleviate health or safety needs’, then the funding agency (e.g. the NIH) may initiate march-in proceedings and compel the holder to grant a license to a responsible laboratory. To date, the NIH has taken an essentially hands-off approach to utilizing its march-in right and has never exercised it, even though applications for march-in proceedings have been filed a few times.

Whether the NIH will choose to march in when an appropriate genetic diagnostics case comes before it remains to be seen. Such a case might well arise from an NIH-funded research program at a university, leading to the patenting and exclusive licensing of a psychiatric diagnostic test using a gene correlation. If a responsible laboratory requests a license from the university or its licensee and is turned down, the laboratory may approach the NIH and ask that it commence march-in proceedings. If the laboratory proves that the lack of testing is causing health or safety problems, it might succeed in forcing a compulsory license on the university or its licensee.

Collaboratively: patent pools and standard setting

We have described how at one end of the spectrum, by following the carefully crafted Nine Points, universities might voluntarily alleviate some of the problems that have arisen in genetic diagnostics patenting; the same problems that may well arise in

the future in psychiatric genetics. We believe that universities are indeed trying their best to follow the Nine Points, although it is too early to tell if these practices are having an impact upon psychiatric genetics. At the other end of the spectrum, and by using confrontational approaches through the courts or through march-in rights, a diagnostic laboratory might be able to force a compulsory license on a recalcitrant patent holder. Because the field of genetic diagnostics patenting is relatively young, there have not yet been any clear precedents in either of the two confrontational areas.

We now wish to propose a third, more collaborative, approach for solving the problem of anticipated patent thickets in psychiatric genetics: the use of so-called *patent pools*. A patent pool is a legal arrangement in which two or more patent owners agree to license certain of their patents to one another. The patent pool may be formed into a corporation, which is then able to license the pooled patents to third parties.

Patent pools are frequently used in the manufacture of consumer electronics products such as DVDs, MPEG, Blue-Ray discs and high definition TVs. If consumer electronics manufacturers wish to create a market for their products, they must collaborate with each other. For example, CDs made by one company must be able to play in a CD player made by another. This necessary interdependence means that manufacturers, in cooperation with each other and with the aid of independent experts, form standard-setting organizations and then make their products following agreed-upon arbitrary standards. The standards are arbitrary in the sense that, for example, there is nothing *a priori* functional about the diameter of a CD disk being 120 mm, or its standard sampling rate being 44.1 kHz. Yet, to sell even one CD player, everyone needs to abide by the standard or no-one sells anything. The electronics patent pools are then organized around these industry standards. All patents that are necessary for manufacturing products in accordance with the standard belong in the pool.

We have previously recommended the use of patent pools to resolve the problem of thickets in diagnostic genetics [26]. We believe that, if appropriately constructed, such pools would also go a long way toward solving the coming thicket problem in psychiatric genetics. Return to Table 4.1, which describes 10 patented genes presumably correlated to bipolar disease. Let us assume initially that all 10 genes are needed for a universal test panel. The patents in Table 4.1 are therefore said to be *complementary* to each other in that each patented correlation complements all others in the panel. The gene correlations work together to produce a diagnostic result and their patents cannot be substituted for each other. Let us further assume that, of the 10 genes, one is actually essential in that its presence or absence is critical for the end result. The patent covering that gene would therefore be said to be an *essential* patent.⁶ Our concept for a pool in psychiatric genetic diagnostics follows a basic principle. In a case where multiple correlation patents for the same psychiatric disease are owned by different owners, then a pool should be formed for that

⁶ An example of an essential diagnostic gene and its patent in a different clinical area is the Δ -F508 mutation in the cystic fibrosis (CF) gene, which is the most ubiquitous mutation involved in the disease. The purified gene and its testing are patented in US Patent No. 6,984,487. Without this essential patent in a pool, the pool cannot offer a universal test for CF.

disease (and no other diseases) and the pool should contain only *complementary* and *essential* patents (and no other patents) for that disease [27].

It is critical that, with the assistance of independent experts, a 'genetic diagnostic standard' be established for each disorder. Such a standard will help decide which gene sequence correlations are necessary for a state-of-the-art test panel and which ones are not and, therefore, which patents belong in the pool (complementary or essential patents with claims that are needed to comply with the standard) and which do not. These genetic diagnostic standards are not quite the same as the arbitrary industry standards used in the consumer electronics industry. In the genetic diagnostics field, they would be akin to medically-driven 'best practices', in that they would determine which sequence variants are significant for diagnosing susceptibility or for identifying a carrier, and therefore which combination of variants should be considered the 'best practice' when performing a test.

A best practice or consensus statement could be issued by an independent medical organization such as the American College of Medical Genetics (ACMG), the American Psychiatric Association (APA), the American Academy of Child and Adolescent Psychiatry (AACAP) and/or the International Society of Psychiatric Genetics (ISPG). The ACMG routinely issues laboratory standards and guidelines for disease testing. For example, in 2001 and 2004, it issued policy statements recommending a 'standard' panel of 25 mutations for identifying carriers of CF [28]. The ACMG has, over the past decade, issued additional policy statements with 'standards' for the significant mutations to be employed in and genetic testing of a variety of other diseases, including Alzheimer's, breast cancer, Canavan's, colon cancer, factor V Leiden, fragile X syndrome, newborn hearing screening and uniparental disomy [29].

The APA, which publishes practice guidelines for the assessment and treatment of psychiatric disorders in adult patients [30], and the AACAP, which issues practice parameters for the treatment of children and adolescents with psychiatric disorders [31], can play the same role in psychiatry that the ACMG is playing in other clinical areas. For example, a consensus statement by one of these psychiatric societies might conclude that only 3 of the 10 genes affecting bipolar disease in Table 4.1 are needed for a universal panel for diagnostic testing of susceptibility. Let us say that the three genes are phenylethanolamine N-methyltransferase (PNMT), fsh05 and PAPAP. The consensus may also decide that the PNMT gene is actually essential to the panel. Once this independent expert decision has been made and announced, it is a simple matter to recognize that only the patents of City of Hope, Millennium and Serono should go into the pool. Their three patents are complementary and the City of Hope's patent is, in addition, essential. The other seven patents in Table 4.1 would not go into the pool and would then quickly lose their commercial value.

Another advantage of an independent scientific standard for multi-gene test panels is that it would coerce the owners of individual correlation patents to collaborate with the other holders of essential and complementary patents rather than offering tests separately. No-one can force a patent holder to join a pool; it is entirely voluntary. However, if a psychiatric scientific society issues a 'best practice' that requires the testing of no less than all three of the PNMT, fsh05 and PAPAP genes in combination, there will be stronger incentives for each of the three patent holders

(City of Hope, Millennium and Serono) to cooperate with each other, rather than going it alone.

4.4 Conclusions

Psychiatric genetics is susceptible to facing intellectual property challenges because the correlations between disorder and genotype are not of the one-disease-one-dominant gene variant that is seen in non-psychiatric diseases such as CF or Huntington's. Instead, a plethora of genes (and, thus, a plethora of possible variations/mutations in those genes) with small effects – not just one dominant gene with a large effect – seem to underlie most psychiatric illnesses. In fact, a major theme at the ISPG-sponsored 15th World Congress on Psychiatric Genetics (October 2007) was the need for scientists to share DNA samples in order to make progress toward pinpointing psychiatric genes and to help overcome obstacles associated with definitively identifying them. As noted, this 'multi-gene' scenario in psychiatry has already led to multiple gene correlation patents for the same disorder, owned by multiple owners. All or a subset of these patents may be needed for the commercial development of scientifically acceptable diagnostic susceptibility panels in the future.

Given our increased understanding of epigenetics, it is also likely that an acceptable susceptibility test may have to include endophenotypic measurements (such as the presence or absence of a protein shed into the blood) or of a downstream form of the protein (such as a misfolded or aggregated version). The commercialization of correlative genetic assessments in the field of psychiatry will therefore require careful planning in order to avoid patent thickets that could potentially hurt or slow valuable diagnostic testing.

Professional societies can play a crucial role in this respect. The APA, AACAP, ISPG or ACMG should consider forming task forces charged with studying the coming intellectual property problems. They could recommend the adoption of guidelines for voluntary licensing practices, along the lines of the Nine Points enunciated by US research universities. They could also be instrumental in determining strict scientific standards for universal gene panels for each psychiatric disorder. Such standards would go a long way toward facilitating the formation of patent pools, and help solve the thicket problems by collaboration rather than by confrontation. Maybe, with farsighted action by these societies, it will be possible to heed the experience of others in diagnostic genetics, and prevent the psychiatric community from repeating their mistakes.

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5

Women's Issues in Clinical Trials

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Abstract

In the last 50 years, opinion about whether or not to include reproductive-age women in trials of new drugs has swung back and forth. The inherent risk to a potential fetus can never be entirely eliminated. On the other hand, women are autonomous agents and, in consultation with their spouses and knowledgeable others, are capable of deciding for themselves whether or not to participate. Once fully informed, it is their right to make that decision. Related issues covered in this chapter include the history of thalidomide, the challenge of including lactating women in trials, contraceptive options and recruitment strategies.

Key Words

autonomy; breastfeeding; contraception; drug trials; ethics; pregnancy; recruitment; teratogens; women

5.1 History

The history of women and clinical drug trials probably begins in the 1950s with the story of thalidomide. In the middle of the twentieth century, bacteria seemed, for a period, to be the most likely cause of almost all human diseases. Sir Alexander Fleming had won the Nobel Prize in 1945 for his discovery of penicillin and every pharmaceutical company in the world, including Chemie Grünenthal (a small West German pharmaceutical company), set out to discover new antibiotics. The director of research at Chemie Grünenthal, Heinrich Mückter, had experience working with a vaccine against typhus, experiments carried out in extermination camps in Poland during the War. Because so many of his 'patients' died, there was a public warrant

out for his arrest in Krakow. He managed to flee to West Germany, however. With colleagues Kunz and Keller, he obtained a derivative of glutamic acid from Chemische Industrie Basel (CIBA) in Switzerland, hoping to develop the compound as an antibiotic [1]. They named it thalidomide.

Unfortunately, thalidomide showed no antibiotic properties when tested in experimental animals but, on the plus side, it appeared to be innocuous. None of the animals died. At that time, new drugs were cleared for marketing in most countries on the basis of safety claims alone, so thalidomide was, by definition, ready for use [2]. But what use?

Because its chemical structure resembled that of barbiturates, Grünenthal marketed it first as an anticonvulsant. It proved ineffective for that purpose, but it seemed to make people somewhat sleepy. The drug was therefore launched as a tranquillizer, a market recently made attractive by the immense popularity of the newly released meprobamate [3]. Grünenthal began by distributing free samples of thalidomide to doctors in Switzerland and West Germany in 1955. An employee of Chemie Grünenthal brought samples home to his pregnant wife, and 10 months before thalidomide was put on the market in Germany, on Christmas Day 1956, their child was born with no ears. The connection was not made; the company began selling the drug over the counter in Germany in October 1957 and, because of its much-touted absolute safety [4], it became the drug of choice for pregnant women upset by morning sickness.

Thalidomide...is a new sedative hypnotic drug which produces no toxic effects when administered orally to animals in massive doses...The drug has a quietening effect on the central nervous system,...promoting sleep... It has no deleterious side effects and does not affect the heart, respiration or autonomic nervous system [5].

By 1960, thalidomide was being sold all over the world – except in the United States. A US company, Richardson–Merrell, applied for Food and Drug Administration (FDA) approval for thalidomide. The case was given to Frances Oldham Kelsey who had joined the FDA, which oversees all industry-sponsored trials, one month earlier. Dr Kelsey, a Canadian pharmacology graduate of McGill University, had worked as a malaria researcher before beginning her work at the FDA and had studied the effects of quinine in pregnancy. She had found that adult rabbits metabolized quinine rapidly, but pregnant rabbits were slower metabolizers and rabbit embryos could not metabolize the drug at all. In addition, she had found that quinine passed through the placenta which, at the time, was considered improbable. This experience alerted her to the potential effects of new drugs on the developing fetus.

Thalidomide was Kelsey's first drug review assignment for the FDA. The agency had 60 days to reach a decision that safety data were adequate or to notify the sponsor of any observed deficiencies in their application. Failure to communicate by the 60th day would result in automatic approval of the drug [2].

Kelsey rejected the thalidomide application because its description of the drug's chemistry, metabolism, toxicity, absorption and excretion was inadequate. Richardson–Merrell resubmitted the application, but it was turned down once more. Kelsey continued to request more data and, with each request, the 60 day

clock began again. Three months after Richardson–Merrell first applied for FDA approval, the British Medical Journal published a letter reporting peripheral neuropathy in patients who had taken thalidomide over a long period of time [6]. Kelsey immediately requested information about this from Richardson–Merrell. Years later, she recalled that:

...the recognition of peripheral neuritis developing, particularly after long-term use of thalidomide, raised in our mind the question as to what effect the drug might have on the fetus who might be exposed to it for up to nine months [7].

In total, the company resubmitted its application to the FDA six times. Kelsey turned it down each time. On 30 November 1961, the drug was removed from the market in Germany because of new reports of a teratogenic effect [8]. Richardson–Merrell withdrew its US application in March 1962, but continued to make the drug available in Canada where it had been approved. By that time in the US, Richardson–Merrell had distributed thalidomide to over 1200 doctors to be used for investigational purposes – a custom permitted under US law pending market approval. The law of the time also permitted pregnant women to be included as research participants after the first three months of the investigational period. Two and a half million tablets were distributed in the US for experimental purposes and nearly 20 000 patients received thalidomide, including several hundred pregnant women. The window of danger for congenital problems turned out to be quite narrow, but the amount needed to cause problems was very small: infants of women who took thalidomide (one tablet was sufficient) between the 20th and 36th day after conception were at risk for malformation. The result, thanks to Kelsey, was that only 17 children in the US were born with thalidomide-related deformities.

By contrast, in the rest of the world, an estimated 8000–12 000 infants were born malformed due to their mother's use of thalidomide and, of those, only about 5000 survived beyond childhood. Approximately 40% of thalidomide victims died before their first birthday.

Because of what happened with thalidomide, the Kefauver Harris Amendment was passed by Congress and signed by President Kennedy on 10 October 1962 [9]. It strengthened the FDA's control of experimentation on humans and changed the way new drugs were approved and regulated. Since the thalidomide tragedy, all drugs and other chemicals with which humans come into contact have to prove a lack of teratogenic potential before they can be marketed. In addition, new drugs have to be shown to be not only safe, but also effective. Informed consent is now required of all participants in clinical trials, and adverse drug reactions have to be reported to the FDA.

In 1977, the FDA recommended exclusion of women of childbearing potential from early (phase I and early phase II) drug trials. Women were also excluded from later phase II and phase III studies if animal studies had not been completed. Exceptions were allowed for trials of drugs for life-threatening diseases [10]. Even women on reliable contraception, women without partners or women whose husbands had vasectomies or were using condoms were excluded. Although these FDA

guidelines pertained mostly to the early phases of drug development, in practice the participation of women in all clinical trials was negatively affected [11]. Reproductive age women could enter phase 3 trials but, in that case, the dose range appropriate for women, generally established in earlier phases, would not be known. In addition, it could be argued that because most drugs fail early trials, the exclusion of women from early phases could potentially limit the identification of drugs specifically useful for women [11].

5.2 Perceived advantages of excluding women

For the researcher, there were advantages to not including women in clinical trials. Because women's age-specific mortality rates are lower than men's, in order to represent a population, a sample that includes women needs to be larger, consequently leading to longer and more costly studies. Recruiting and retaining women in trials has always been more difficult than recruiting men because of women's caretaking responsibilities and, in the United States, their relative lack of medical coverage and paid sick time from employment. In addition, menstrual fluctuations meant more variability among women, again resulting in the need for larger sample sizes [12]. Most importantly, the teratogen risk could be greatly reduced if women were excluded. More than 90% of the drugs approved by the FDA between 1980 and 2000 carry an undetermined teratogenic risk, meaning that the risk is essentially unknown [13].

5.3 Change in perspective

Despite such seeming advantages, it was soon recognized that excluding women was neither practical nor ethical. It was not practical because exclusion meant that relatively little was known about women's reactions to new drugs before these drugs became freely available on the market. Nothing was known (except by extrapolating from animal studies) about women's potential responses over the life course, and that included undetermined effects on fetuses and neonates. Ethically, excluding women constrained their autonomy, should they wish to take part in a trial, and went against the principle of nonmaleficence, since treatments to which women were ultimately exposed had not been appropriately tested for them [14].

Every year, more information becomes available about the extent to which women and men differ in their absorption, metabolism, excretion, distribution and end organ reaction to drugs, and that there are differences between pre and postmenopausal women in this regard [15, 16]. Metabolic differences specific to pregnant women are being found [17, 18] and it has become apparent that effects on the human fetus cannot always be predicted by results in laboratory animals.

A change in perspective toward the inclusion of women in clinical trials occurred in the mid 1980s, to a large degree an outgrowth of a report by the Public Health Service Task Force on women's health [19]. A new National Institutes of Health (NIH) policy began to urge inclusion of women and minorities in clinical research.

By 1989, NIH required a rationale for the exclusion of women and minorities and a congressional caucus for women's issues requested a report on the implementation of the new guidelines in 1990. In 1992, a survey by the US General Accounting Office, the body responsible for the audit, evaluation and investigation of Congressional policy and funding decisions, found to their dismay that less than half of publicly available prescription drugs had ever been analyzed for sex-related response differences [20].

Between 1991 and 1993, Bernadine Healey was director of the NIH. During her tenure, NIH established the policy of only funding clinical trials that included both men and women whenever the condition being studied affected both genders. In 1993, the NIH Revitalization Act, section on Women and Minorities as Subjects in Clinical Research, mandated that Phase 3 clinical trials required adequate numbers of women and minorities in order to enable a valid analysis of differences among groups. The same year, the FDA guideline ended the restriction on the inclusion of women of childbearing potential in early clinical trials and emphasized appropriate representation of the two sexes in order to facilitate detection of clinically significant differences. In 1994, the FDA created an Office of Women's Health, which oversees correction of gender disparities in drug research and administration policies [21]. The Centers for Disease Control (CDC) revised their regulations in 1995 and, in 2001, the Department of Health and Human Services (DHHS) followed suit, emphasizing the importance of the research participation of women.

The interpretation of what had caused the thalidomide disaster changed. The problem was not that pregnant women had been included in investigational trials with the result that babies were born malformed. In fact, the drug had been released in most countries with no investigational trials whatsoever, and this was the root of the problem. It was the *lack* of trials with pregnant animals and with pregnant women, rather than the inclusion of pregnant women in trials, that had caused the worldwide tragedy.

5.4 Have things changed?

In spite of regulatory changes, women and researchers continue to worry about the potential risk to a fetus born as a result of the mother's use of an investigational drug, for example a drug for which there are better tested alternatives. This can be demonstrated by the extensive documentation of contraceptive practices that are often required in clinical trials. Many industry-sponsored studies have required that women of childbearing age use two forms of contraception during their participation. Analogous risks to the progeny of a participating male who might impregnate his partner during the course of a trial have never attracted the same attention. The implication is that, in contrast to men, having been informed about potential risks to a fetus, women are not responsible enough to ensure that they do not become pregnant (or, alternatively, to welcome the pregnancy should it take place). A special committee of the Institute of Medicine in 1994 recommended that both men and women of reproductive potential be informed as fully as possible about potential developmental risks to a fetus (and to a breast-fed infant) and that they then make their own decisions about both participation and about choice of contraception during

the trial (as long as there are no scientific reasons, e.g. drug interactions, for excluding certain contraceptive methods).

It was recommended that the possibility of pregnancy termination in the case of unwanted pregnancy be discussed as part of the consent process. Furthermore, existing pregnancy and/or lactation should not, according to the report, be an *a priori* exclusionary factor in clinical trials, as long as the woman was fully aware of all known risks and still volunteered to participate. The committee recognized that, where there was no prospect of benefit to the pregnant woman or where significant harm to potential offspring could be inferred from preclinical studies, pregnant women could and perhaps should be excluded from participating in a trial. However, apart from such circumstances, the report recommended that participation be a matter of personal choice, as long as the participant was fully informed of potential risks [22].

5.5 Progress since 1993

Prior to 1993, the exclusion of women from clinical research studies contributed to the relative scarcity of information on women's health. Because of this, the US Office of Women's Health now strongly advocates for the participation of women in clinical trials since, assuming the prevalence of the disease being studied is gender-equal, women are just as likely as men to use the therapy once it is on the market. The Office also argues for analysis of data by sex because this allows researchers to determine if sex difference in drug response exists, as is often the case [23]. In a study of articles published in *The New England Journal of Medicine* from 1994 to 1999, researchers found women's enrollment rates to be approximately 25%. Gender-specific data analysis was performed in only 14% [24]. Somewhat later, when the new guidelines had been in place longer, a Canadian study examining research ethics applications (1995–2000) took place. The study found that while almost all researchers intended to recruit both men and women, only one in five planned to analyze the data by sex. This proportion (planning to analyze by sex) actually decreased from 30% in 1995–1996 to 17% in 1999–2000 [25].

In 2006, in a survey of researchers, 69% responded that the new NIH mandate has been successful in increasing gender diversity in clinical trials; 7% felt that, thus far, it had failed to increase the research participation of women and 24% were unsure [26]. Also in 2006, another group found inadequate compliance with the NIH guidelines on women and minorities [27]. The results of a 2008 NIH funded survey show that NIH guidelines have been successful in that ethics research boards appear to agree that the guidelines are important and adequate [28]. Reviewing 379 studies funded by the National Institute of Mental Health (NIMH) between 1995 and 2004, Mak *et al.* found that most of the studies did report gender information and that gender representation was balanced across studies. However, fewer than half the studies were designed in a way that would permit subgroup analysis by gender [29]. As in the US, Müllner *et al.* in Europe found no gender discrepancy in clinical trial representation. This study did not report on analysis by gender [30].

A recent Australian inquiry likewise found no paucity of women participating in research [31]. The total sample comprised 546 824 subjects in 400 different studies conducted in Australia between 2003 and 2006. Seventy-three percent of the participants were female; 36 studies were male only, 78 were female only. In the 286 studies that were not sex-specific, 56% were female. Of 114 sex-specific studies, segregation by sex was considered biologically necessary in 62%. A little over one-quarter (28%) of studies with 30 participants or more published covariate adjustment or subgroup analysis by sex. In 7%, there was sex-specific reporting of results. In summary, although women are increasingly being recruited in appropriate numbers into research studies, few of the results of these studies are being analyzed or reported by sex.

This is true even with respect to cardiovascular studies, where significant differences have been found in the responses of men and women [32]. The percentage of publications reporting sex-specific results in cardiovascular research was 37% for general medical journals and only 23% for cardiovascular journals. Among NIH-sponsored research, however, 51% of trials did analyze their outcomes by sex. This suggests that strong NIH oversight works.

One reason for the difficulty researchers experience when attempting to recruit women into clinical trials is that frequently used exclusion criteria, such as residential instability and substance abuse, correlate positively with socioeconomics. In other words, the poorer the person the more likely he or she is to be excluded; women are typically poorer than men. A recent paper reported, for instance, that women and minorities were disproportionately excluded by poverty-related eligibility criteria in an alcohol treatment trial [33].

In a recent review, common medical conditions and their associated treatments were found to be the basis for exclusion in 81% of trials [34]. More women than men suffer from comorbidities (arthritis, thyroid disease, chronic pain, insomnia, allergy) that require the use of prescribed medication, and this may render them ineligible. (This same review found that exclusion criteria were omitted from the reporting of 12% of the trials.) Conditions related to being female (contraceptive use, potential pregnancy) were grounds for exclusion in 39% of trials. Of all the exclusion criteria, only 47% seemed justified by the review authors. Industry-sponsored trials were more likely to exclude individuals as a result of concomitant medication use, medical comorbidities and age. Drug trials involving multiple centers were the most likely to specify extensive exclusions.

In mental health, where women are more commonly affected than men, proportionately few women participate in research. In schizophrenia, where the prevalence of men and women is equal, we reviewed clinical trials of the atypical antipsychotic medications. The median percentage of women in the total sample was only 33%. Worries about fertility were one issue; eligibility criteria may have been another [35].

5.6 Reported current difficulties in including women

In reviewing the literature in 2008, it is clear that potential risks to offspring continue to be of concern when women of reproductive age take any drug, including an

experimental one. Because of the inherent limitations of animal studies and *in vitro* techniques, and because developmental problems can be both subtle and rare, the risks can be impossible to detect before the drug is already in widespread use.

Reproductive studies in animals are not always valid for determining whether a drug is safe for humans. Some drugs that appear to be reproductively or developmentally toxic in animals may not be in humans. The metabolic pathways of drugs differ in different species, so hazardous outcomes also differ. (It is the case, however, that all known human teratogens are also teratogens in at least one animal species). Genetic differences among humans may further modify the risk to reproduction and to development. Timing of exposure to risk as well as the dose and duration of exposure that are required to produce bad outcomes are of critical importance.

Potential danger to the fetus also exists when men are given a teratogen. Information provided to would-be trial participants, male or female, in order for the consent to be 'informed' should include known fetal effects of the drug in question set against background facts about the chances of adverse reproductive or developmental outcomes in a comparable population not exposed to the trial agent. The incidence of adverse outcomes in the general population is often higher than many potential study subjects probably realize. They need to know, for instance, that 15% of couples fail to conceive after one year of trying (a common definition of infertility), that 20–30% of pregnancies end in miscarriage, that 3–8% of all babies are born with physical birth defects and that 1% are born with severe mental retardation. This is the background against which the additional risk of the study drug needs to be understood [36].

5.7 Contraception in clinical trials

Cain *et al.* surveyed the type and frequency of use of contraceptive requirements for entry into clinical trials between 1994 and 1997. Assurance that women participants in drug trials were not and would not get pregnant was demanded routinely in the early post-1994 era [37]. Requirements have loosened in the intervening years but have not disappeared. In the 1990s, contraception or sterility for women was required in almost half the protocols without explanation of the reason and, in a further third, it was required reportedly because of the nature of the study drug. Less than 10% of trials did not require contraception. Certification of contraceptive use was required in approximately one-quarter, usually with two signatures. Another 50% required certification of understanding the contraception requirements. Signature certification documenting no pregnancy at enrollment was required in 234 protocols. There were no requirements for signatures from male subjects. Celibacy and sexual orientation were not recognized as reasons for waiving the signature requirements.

The emerging consensus among women's health advocates now appears to be that men and women participating in trials should be free to use the contraceptive of their choice to avoid (or not) a pregnancy they may or may not want. They need to be made aware, however, by the researcher, of the available options in contraception and of their relative effectiveness.

Hormonal contraceptives may introduce complications into the evaluation of some study drugs and may, under such circumstances, need to be excluded. Women need to be informed about the side effects of hormonal contraceptives. New epidemiological findings show that women using the estrogen patch, for instance, are at higher risk of developing venous thromboembolism (VTE) than women using birth control pills [38]. Because hormones from a skin patch do not go through the liver, the estrogen level is effectively increased by 60% more than that of the pill and high estrogen levels raise the risk of all estrogenic side effects, not only blood clots.

Recommendations are for contraceptive methods with the fewest side effects that, at the same time as protecting against pregnancy, also protect against sexually transmitted diseases. Feminist leaders advocate for methods that are under the control of the users (thus increasing women's autonomy); university and industry researchers, by contrast, are likely to give priority to methods that *minimize* users' control, thus providing stronger safeguards against pregnancy.

An ethical issue for some women is the mechanism of action of contraceptive methods; some methods may produce an early abortion and, therefore, be contrary to the woman's beliefs. Some barrier techniques require the male partner's active cooperation or support. In these cases, the obligation to prevent unacceptable risks to future children should be borne jointly by the woman and her male partner who should, logically, be part of the information sharing procedure [39]. Depending on the relationship between the woman and her partner, this may not always be possible.

Prevention of pregnancy when trial drugs are contraindicated in pregnancy because of known risks to the fetus (FDA categories D and X) or potential risks to the fetus (FDA categories B and C) is an important concern in study design. The woman's autonomy is paramount, but needs to be balanced by the obligation of the researcher to consider the best interests of the mother-child unit [39].

Pharmaceutical companies continue to be extraordinarily careful because they do not want to be sued should an infant be born malformed. It is also possible, conversely, that they are potentially liable for putting too many obstacles in the way of women wanting to take part, should evidence emerge later that a drug on the market is more risky or less effective in women than in men. Informed consent does not necessarily protect against liability [40].

In 1991, the US supreme court unanimously held (*International Union vs Johnson Controls Inc.*) that discrimination on the basis of fetal protection was not permissible in a workplace where potential fetal toxins were present. The verdict stated that informed parents should make the decision rather than the company making certain jobs unavailable to women. The burden for fetal protection was thus placed on exposed individuals [37]. Even requiring a negative pregnancy test at the start of a trial, as is often done, may be considered unreasonable by women who are in a position to know that they are not pregnant [41].

5.8 Drugs in lactating women

There is concern about how much of any drug enters the infant during breastfeeding and also about potential effects on the quality and amount of mother's breast milk.

For these reasons, lactating women are rarely recruited into clinical trials of new drugs. Therefore, when they need medication, they are either advised to discontinue breastfeeding (which deprives the infant of the benefits of breast milk) or to take drugs that have not been systematically evaluated in lactating women. It is perhaps time for a mandate to deliberately include lactating women in new drug trials. Clinical studies that do so should advise these women of the potential risks to the nursing child, including those of cessation of breastfeeding.

5.9 How often do women take drugs during pregnancy?

Between 1996 and 2000, in a survey of 152 531 deliveries in the US, over 3% of women were found to be receiving a category D drug and 1% were taking a category X drug (according to the FDA risk classification system, this means that there are known risks to the fetus) at the initial prenatal care visit [42]. A more recent study from Italy reported that, among 33 343 deliveries identified in 2004, 70% of women were exposed to at least one prescription medication during pregnancy [43]. Almost half (48%) were exposed to at least one prescription medication other than vitamins and minerals. The most commonly used medications were antibiotics, such as amoxicillin, fosfomycin and ampicillin. Nearly 1% of women were exposed to drugs contraindicated (i.e. category X) in pregnancy, including 189 women (0.6%) who received these drugs during the first trimester. Several statin medications were among the most common contraindicated drugs of exposures.

5.10 Ethical issues: risk/benefit analysis

Assessing the potential risks and benefits of clinical research is not a straightforward exercise. Depending on perspective, the risks and benefits are weighed differently. The probability of occurrence of side effects is based upon experience from earlier studies. Once a sufficiently large population has been studied, some degree of agreement on magnitude of risk can be reached. This varies among individuals, depending on their values: the importance they give to health, for instance, versus freedom of choice; altruism; and meaning of life. Because a woman's autonomy is ethically important, any form of birth control she chooses, including abstinence, should remain an option for reproductive age women. Requiring women who report being sexually inactive to use birth control strongly implies that they cannot be believed. Under such circumstances, it is not surprising that many women refuse to participate in research. Sexually active male study participants are not submitted, at present, to the same requirements as women regarding birth control. But all males exposed to drugs with a suspected teratogenic potential should be advised to practice effective birth control during the exposure and one or two cycles of spermatogenesis beyond the exposure and to avoid all semen contact with vaginal walls during their partner's first trimester of pregnancy [44].

5.11 Adequate information

The disclosure statement of consent forms for all studies needs to include thorough information about potential risks to children who may be born to trial participants. This means a conservative weighing of the available data (animal studies on effects of reproduction and development, reproductive or developmental effects of similar drugs, chemical structure and properties of the drug in question, mechanisms of action, sites and mechanisms of toxicity and dose response relationships). A pregnant woman should be encouraged to consult with her obstetrician and with the baby's father before agreeing to take part. It is important that she understand the relevant risks and benefits and the fact (if this is the case) that the trial may be of no direct benefit to herself or her child-to-be.

The FDA has proposed inclusion of the following on consent forms:

It is possible that your participation in this study may cause damage to children if you choose to have them. You have already been told what is known about this possibility, and you are encouraged to ask further questions. (Include as appropriate: We urge you or your partner not to become pregnant while you are part of this study.) You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this study to discuss this possibility with you and anyone else you want to have present [45].

5.12 Adolescent women

There are particular challenges for studies that enroll adolescents under the age of 18 who usually are not adults under applicable law, although this varies among jurisdictions. Federal regulations require permission of parents and assent of the child for enrollment. State law may allow for counseling about prevention of pregnancy without a parent being present or even notified. Investigators need to be fully aware of the potential legal issues that could arise and should seek competent legal advice on how to manage them responsibly [39].

5.13 Recruitment and retention of women

The literature on recruitment and retention identifies three major influences when women are considering participation in health-related research: barriers to entry, incentives and deterrents [46]. According to the existing literature, women are motivated to participate by (i) the desire to be altruistic, (ii) the compensation, whether monetary or other and (iii) the change to their routine.

Lack of transportation and childcare has been described as a barrier. Minority women, depending upon the minority to which they belong, may face further challenges. These include distrust of the medical establishment, traditional customs

that undermine women's autonomy, language barriers and requirements for female assessors. Focus groups conducted with African American women produced 10 clear challenges to recruitment: lack of information about ongoing trials, mistrust, need for easy access to the site of the trial, need for perceived benefit to themselves, their family or their own community [47], need to hear about the trial from sources perceived to be safe [48], need to understand the importance of the trial, compensation, minority representation on the research team and the need to prioritize health. Making health a priority means putting other preoccupations (children, family, finances) aside, and this is perhaps more difficult for women than for men.

A similar study of Mexican women also found 10 trends, some the same as above and some different [49]. In Britain, researchers studying the problem of recruitment among South Asian immigrants suggest using multi-recruitment strategies; defining the demographic and social profiles of the population to be included; using focus groups to identify any potential barriers; consulting representative community members to provide assistance in the study; ensuring eligibility criteria are set as wide as possible; developing educational and recruitment approaches to attract ethnic minority health professionals; ensuring health professionals are adequately trained in culturally and ethnically orientated service provision; determining the most effective mass media to use in study promotion and recruitment; and targeting inner-city, one-person practices [50]. Certain strategies seem to work in recruitment across the board, with women of all ages and with minorities. Of the various clinical trials, drug trials usually do well with respect to recruitment, as do cancer studies of all types. A dedicated trial manager is crucial and, finally, recruitment is easier if the intervention is only available as part of the trial. The most commonly reported strategies to improve recruitment were newsletters and mailouts, but it was not possible to assess whether they were causally linked to changes in recruitment. Good groundwork and excellent communications were considered to be extremely important. Interpersonal issues are probably even more significant for women than they are for men, so that the communication style of the interviewer becomes key to the recruitment of women [51].

In summary, women are now being recruited into drug studies in large numbers around the world, but gender-specific analysis of results lags behind. Although recruitment and retention of women deserves attention, the main challenges continue to be safety and ethics. Trying to be overly safe with respect to pregnant or lactating women risks limiting their autonomy and imposing strictures that are not imposed on men, contrary to the assumption of gender equality. This is a difficult area for researchers. It requires a transparent approach with full disclosure of potential risks and benefits, and relies on treating trial participants as colleagues in a joint scientific endeavor.

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SECTION II

Clinical Trials and Mood Disorders

6

Issues and Clues in the Pharmacological Treatment of Mood Disorders

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Abstract

As with many psychiatric disorders, ‘mood disorders’ refer to a group of syndromes characterized by a diverse combination of emotional, cognitive, somatic, behavioral and physiological symptoms. The core symptom is an altered mood which may manifest in different ways: a prolonged sadness with an unbearable psychological pain (‘psychache’); a feeling of uncontrollable and persistent irritability and anger; or an unusual intense sense of well-being. Anhedonia without psychache is also considered to be a sign of mood alteration under current classifications. Mood impairment is associated with a constellation of other symptoms ranging from: negative or positive thoughts; increased or decreased energy; motor agitation or retardation; modified appetite, sleep and libido; and a significant functional impairment. We will begin this chapter with an overview of epidemiological and neurobiological data with current or future therapeutic implications, while considering issues that complicate the treatment of mood disorders. We will then review some factors that may influence the choice of available drugs, mostly in depressive disorders (bipolar disorders will be addressed elsewhere). Finally, we will conclude with a brief review of treatment interventions which show great promise.

Key Words

mood disorders; depressive disorders; neurobiology; treatment; issues; diagnostic categories; targets

6.1 What do we know about mood disorders that may be relevant for their pharmacological treatment?

Epidemiological data

Mood disorders are frequent, affecting up to 10% of the general population over the last 12 months in the United States and Europe [1, 2]. Moreover, it is now clear that mood disorders are recurrent in more than 80% of cases and chronic in 10% of patients [3]. Individuals with mood disorders are symptomatic more than half of the time, mostly at a sub-syndromal, yet often disabling, level [4]. Mood disorders are frequently associated with other comorbid conditions, ranging from anxiety disorders to alcohol and substance abuse [2]. From the time of puberty, they are more prevalent in women [5]. Moreover, age at onset of mood disorders is young, with 50% of patients experiencing a mood disorder before the age of 30 years and some during childhood or adolescence [6].

Long-term follow-up studies show that over 10% of individuals with mood disorders commit suicide [7], and mood disorders represent more than 60% of all psychiatric disorders associated with suicide. Mortality is also significantly higher in this population for causes of death other than suicide (accident, homicide or natural causes) [8].

Depression is frequently associated with somatic illness, including cardiovascular, metabolic or neurologic diseases [9] in complex and deleterious relationships. Among chronic diseases, depression appears to be the leading cause of decrement in health. It also significantly increases the disability associated with other comorbid conditions, for example angina or diabetes [10]. The first cause of death in individuals with bipolar disorder is cardiovascular diseases, followed by suicide and cancer [11].

Regarding their prevalence, morbidity and mortality, it is not surprising that mood disorders are costly for society. For instance, a recent review estimates the annual cost of depression per individual to be \$1000–2500 for direct costs and \$2000–3700 for indirect costs (loss of productivity at work, unemployment and loss of family/caretaker productivity) [12]. It is estimated that mood disorders will be the leading causes of disability in developed countries by the end of the next decade [13].

Neurobiological data

Mood disorders may be conceptualized as the expression of a dysfunctional network of brain regions (including medial, dorso- and ventrolateral prefrontal cortex, anterior cingulate gyrus, amygdala, hippocampus and striatum) [14]. These networks underlie mental processes (cognitions and emotions) enabling the relationships between the individual and a complex environment, as well as homeostasis within an individual. The diffuse alterations in brain functioning found in mood disorders may explain the constellation of possible manifestations [15]. Psychotropic medications lead to a modification of the impaired activity of some brain regions which is correlated with clinical improvement [16]. Interestingly, medication and psychotherapy may have

different as well as common effects in term of brain activations [17], supporting the relevance of treatment combination.

At the biochemical level, these networks are significantly modulated by monoamine projections from midbrain and brainstem nuclei [18]. Mood disorders have been associated with the dysfunction of other biochemical systems, for example the hypothalamic-pituitary-adrenal (HPA) axis [19], and appear to involve many more neurotransmitters, neuromodulators and hormones besides the monoamines. The conceptualization of mood disorders has therefore evolved from simple theories of inadequate amounts of neurotransmitters to more complex theories of imbalance in biochemical systems.

Modification in sizes of different brain regions has been reported [20]. Some of these structural abnormalities have been correlated with the duration of the pathological state, while some may also have been found in healthy relatives of patients. Structural abnormalities may, therefore, represent both a developmental risk marker for mood disorders and the effect of prolonged pathological states. These findings have been interpreted as the result of a neurotoxicity induced by chronic glucocorticoid secretion, a decreased neurogenesis or a loss of plasticity [18]. Mood disorders have been associated with the alteration of several intracellular signaling pathways and the expression of transcriptional factors [21]. These findings largely come from the observation of the *in vitro* intracellular effects of chronic administration of antidepressants and other drugs, including lithium or valproate [22].

Mood disorders are highly heritable [23]. Moreover, genes and early negative environmental factors (like childhood maltreatment) interact on the risk of adult depression [24], underlying the developmental feature of mood disorders. These factors may impair the normal development of emotional and cognitive processes. The activation of brain regions, such as the amygdala in response to fearful faces, is modulated by genetic variations [25], suggesting an individual variability in vulnerability to external stressors and consequently to mood disorders.

Recent results suggest that childhood maltreatment may have a specific effect on the biological mechanisms of adult mood disorders. For instance, depressed women with a history of childhood abuse show different neuroanatomical (hippocampus volume [26]) and biochemical (HPA reactivity [27] and inflammatory markers [28]) impairment in comparison to non-maltreated depressed women. These results suggest that new therapeutic strategies according to the patient's developmental history may be warranted.

Although suicidal behaviors are strongly associated with mental disorders (notably mood disorders), data support the notion of a specific neurobiological vulnerability [29]. For instance, male normothymic patients with a history of unipolar depression and suicidal acts show increased activity in the right lateral orbitofrontal cortex in response to angry faces in comparison to normothymic patients without a history of suicidal behavior [30]. These results (and others) suggest that: (i) suicidal behavior should be considered a specific pathological entity and not only a criterion for the diagnosis of major depressive episode and (ii) specific treatments may be necessary for these patients.

What do we really treat?

The main issue in the treatment of mood disorders, as for other psychiatric disorders, is a lack of understanding of the physiopathological processes underlying these syndromes [31]. Although mood disorders have been described since antiquity and research in neurobiology has exploded over the last decade, they remain largely misunderstood. One reason is that categorical entities used in neurobiological research have been consensually constructed on a clinical basis in a (justified) attempt to improve diagnostic reliability among clinicians/researchers. However, this has been carried out without any biological or etiological validity [32]. As a consequence, what we define as a mood syndrome may be the ‘final common pathways’ of different biological processes necessitating different treatments [33], just as fever may be the expression of diverse etiologies ranging from infection to cancer. Use of categorical entities in human clinical and biological research therefore increases the risk of heterogeneous and flawed results.

This lack of biological validity in diagnostic entities has direct critical implications in clinical practice and pharmacological trials. For instance, current clinical categories are not effective in everyday practice for predicting the course of mood disorders. Long-term follow-up studies have shown that the course of depressive disorders is rarely clear cut [3]. The majority of patients display a complex sequence of sub-threshold depression, dysthymia and major depressive episodes. Of note, one study showed that many outpatients with a major depressive episode remit without any medication within three months [34]. Numerous patients obviously do not fit into our current nosology.

This biological heterogeneity is also responsible for our inability to predict the response to a treatment in a given patient, because patients with possibly different ‘diseases’ (but diagnosed with a common syndrome) are examined together in pharmacological trials. Consequently, current treatments of mood disorders are largely based on trial-and-error (and bias in doctors’ and patients’ selections of medications), but not on etiological or biological targets [33].

Biomarkers are needed to guide clinicians in diagnostic and therapeutic decision making. This may be reached through the study of more ‘basic’ clinical dimensions found during mood episodes such as anhedonia (which is also found in normal individuals as a trait) [35] or the study of endophenotypes, that is ‘hidden’ (biological, neuropsychological, etc.) trait markers found in patients and their unaffected relatives [36]. This may be more fruitful and may avoid becoming ‘overwhelmed by the heterogeneity of illness’ [18]. Furthermore, a multidisciplinary use of modern techniques ranging from neuroimaging to genetics and animal models may offer a clearer and more complete picture of the altered mechanisms of mood disorders [18, 33, 37].

From what is known to what is done

A second (partly related) issue in the treatment of mood disorders is the low proportion of patients correctly diagnosed and treated according to current classifications and guidelines. In primary medical centers, depression has been found to be

underdiagnosed in 36% of cases and overdiagnosed in 13% of cases in comparison to guidelines [38]. Another problem is the low use of medical services, as 60% of patients with mood disorders have never consulted a professional for treatment [5]. Adequate programs may improve correct recognition and treatment of mood disorders [39].

When correctly diagnosed and effectively treated, patients may choose to discontinue their treatment. As with many chronic diseases, good therapeutic compliance in mood disorders is not the rule. For instance, only one out of two normothymic bipolar patient are totally compliant in a specialized center over a two-year follow-up [40]. Denial of being ill is a frequent cause of non-compliance [41]. Improving therapeutic adherence in people suffering from recurring, chronic and disabling disorders is a major goal which may be reached through specific educational programs [42].

6.2 Are there clues for the pharmacological treatment of mood disorders?

Despite the lack of a unified understanding of the etiology of mood disorders, doctors are being presented with various treatment options. Guidelines have been edited and are frequently updated to help clinicians choose the best possible treatment strategy. However, these guidelines are largely based upon the heterogeneous clinical entities criticized above.

In the absence of biological or genetic tests, we would like to focus here on some specific clinical and demographic factors that may influence the choice of a pharmacological treatment for a mood disorder. Although the evidence for some remains scarce, we chose to review those that may be relevant in practice. Other factors have been omitted due to limitations of space, for example age at illness onset, seasonality, atypical features, psychotic symptoms, pregnancy, psychiatric comorbidity including personality disorders and substance/alcohol abuse, somatic comorbidity, social functioning and cognitive impairment.

In our opinion, treatment of mood disorders should aim to:

- decrease current symptomatology, notably suffering and impairment
- decrease residual symptoms/chronicity and associated disability
- prevent relapse of episodes
- improve social functioning and
- limit side effects and improve the long-term somatic prognosis.

Bipolarity

One-third of patients with bipolar disorder are initially misdiagnosed as having major depressive disorder [43]. Bipolar patients who first present with a depressive episode

appear to have a more severe course of illness (more episodes, more rapid cycling and more suicidal behavior) compared to patients who first present with mania [44]. One possible explanation is that the initially depressed patients have been treated with antidepressants without mood stabilizers. Indeed, antidepressants alone seem to increase the risk of switching into a mania or mixed state, cycle acceleration and poorer outcomes in general [45, 46].

Recognition of potential bipolarity is therefore of major importance in the context of individuals first presenting with a depressive episode. No particular symptom discriminates bipolar from non-bipolar depressions, but some clinical symptoms should raise the question of potential bipolarity: earlier age of illness onset, mood lability, psychiatric comorbidity, family history of bipolar disorder, higher number of prior depressive episodes, family history of completed suicide, greater prevalence of atypical features or reverse neurovegetative symptoms (increased appetite and hypersomnia), greater prevalence of melancholic symptoms, irritability, anger and psychosis [47].

The treatment of bipolar disorder is discussed in Chapter 8.

Anhedonia

The motivational system involves the dopaminergic system which interacts with the noradrenergic, serotonergic and cholinergic systems [48]. Drugs which enhance dopamine or norepinephrine actions – either directly or indirectly – are suggested in the treatment of anhedonia. Psychostimulants (such as dexamphetamine or methylphenidate) as well as other drugs including the norepinephrine and dopamine re-uptake inhibitor bupropion, have been shown to significantly improve symptoms of energy, pleasure and interest in depressed patients with predominant baseline symptoms of decreased pleasure [49]. Monoamine-oxidase inhibitors such as phenelzine or moclobemide [50], as well as amineptine, reboxetine [51] and desimipramine [52], have been found to be effective in treating depressed patients with pervasive anhedonia.

Psychache (psychological pain)

Psychological pain is an important feature of depression that may increase the risk of suicidal acts [53]. Chronic physical and psychological pain can lead to depression while, at the same time, depression may intensify chronic physical pain [54]. Functional imaging studies have provided evidence that psychological pain activates many of the same brain regions as physical pain [55]. In addition, noradrenergic antidepressants are widely used in the treatment of physical pain including cancer pain in terminal/palliative care, migraine and so on. Furthermore, opiates have been successfully used in the treatment of depressive symptoms [56]. Although the opioid system has been involved in the pathophysiology of depression [57], no study to our knowledge has specifically explored the effect of treatments directly targeting the opioid system in psychological pain.

Sleep disturbances

Sleep disturbances is a frequent symptom of depression [58]. It is also associated with suicidality. Some authors have shown a difference in the remission of depressive symptoms, including sleep, between newer antidepressant compounds such as nefazodone and selective serotonin reuptake inhibitors (SSRIs). Nefazodone has also been shown to be superior to a cognitive behavioral psychotherapy for the improvement of the disturbed sleep in chronic depression [59]. Nefazodone may have a direct positive impact on disturbed sleep associated with depression. Molecules in trials including melatonergic receptor agonists may also warrant further investigation.

Hypersomnia has been reported as a feature of bipolar depression [60]. Increased sleep is one of the atypical symptoms most strongly associated with bipolar family history [61]. Recent studies suggest that hypersomnia could be a phenotypic marker of early onset depression and, therefore, should lead to the consideration of mood stabilizing agents.

Anxiety

Anxious depression is a subgroup of depression in which patients manifest depression with prominent anxious symptoms or a comorbid anxiety disorder. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 46% of patients met criteria for anxious depression [62, 63]. Emerging evidence suggest that anxious depression should be considered a particular subgroup. Patients with anxious depression may demonstrate a specific clinical symptom profile and treatment response, including: higher depression severity; more suicidal ideation; melancholic features; greater functional and occupational impairment and a slower or lack of antidepressant response, with residual anxiety [64, 65]. Depressed patients with prominent symptoms of anxiety or with comorbid anxiety disorders can be treated effectively with newer antidepressants (SSRIs and serotonin-norepinephrine reuptake inhibitors or SNRIs) [66].

It has been suggested that combining SSRI or SNRI with benzodiazepines is more effective than antidepressant monotherapy for anxious depression. It has been argued that combination therapy offers more clinical benefits, more rapid control of anxiety, a reduction of SSRI-induced anxiety/agitation (that can occur early in the course of therapy), improved adherence to antidepressant therapy and improved control of episodic or situational anxiety [65]. Other pharmacologic treatments include tricyclic antidepressants, buspirone and atypical antipsychotics [67].

Severity of the episode

Psychotherapy and psychosocial interventions should be considered a first line treatment for patients with mild to moderate depression [68, 69]. It can be used in combination with antidepressants for patients suffering from more severe forms of depression and for those who have had a partial antidepressant response, or who

have had adherence problems. Structured problem-focused psychotherapies (such as cognitive therapy) in which patients learn specific skills have been shown to be particularly effective in the acute phase of depression and in preventing future relapse [70].

Depression severity has been identified as a significant predictor of remission [71]. For patients presenting with a melancholic form of depression, pharmacological treatment are first-line choices. There is some evidence that tricyclic antidepressants and venlafaxine may be more effective than SSRIs for melancholic patients [72]. Augmentation strategies (i.e. association of molecules with different mechanisms) are often necessary in severe cases. In addition, electroconvulsivotherapy is probably underutilized in this indication.

Recurrence of episodes

The rate of recurrence of depression is over 75%, making recurrence the rule rather than the exception [73]. Recurrence has been shown to be related to a positive family history of depression and an earlier age of onset. Patients meeting criteria for chronic depression may be less likely to have recurrent depression [74]. Risk factors for subsequent recurrence (onset) may be different from those that govern the capacity for remission (offset) and the length of the episode.

Efficacy in long-term maintenance treatment for recurrent unipolar depression has been demonstrated for antidepressants [75] and lithium [76]. However, patients in these studies were usually selected as they first achieved remission in acute/continuation phase with the same drug. The newer antidepressants have shown a superior long-term efficacy and a better tolerability compared to traditional tricyclic antidepressants [77]. Lithium prophylaxis may reduce suicide risk and normalize the high mortality rate of recurrent mood disorders [78]. Carbamazepine may also be indicated in prophylaxis in recurrent depression [79].

Lack or insufficient response (residual symptoms and chronicity)

Residual symptoms are common in patients treated for mood disorders. Only 25–50% of patients in clinical trials achieve full remission of their depressive symptoms even after prolonged therapy (more than six months). Patients with residual symptoms appear to be at higher risk of non-compliance, relapse, suicide and functional impairment and use more health care resources compared to those who have no residual symptoms [80]. Typical residual symptoms include sleep disturbance, diminished pleasure, loss of interest, fatigue or loss of energy and decreased motivation [81]. Some authors suggest that these symptoms, inadequately addressed by the serotonergic system, are associated with the dysregulation of the dopaminergic and noradrenergic systems [82]. Treatments that enhance dopaminergic and noradrenergic activity such as moclobemide, reboxetine or bupropion could be of particular interest [83].

Risk factors for delayed remission of a depressive episode are: a longer duration of the current episode; higher recurrence; older age; incorrect diagnosis; inadequate dose or duration of treatment; psychiatric and medical comorbidity; and a higher severity [84, 85]. Switching, combining and augmenting antidepressants are usual

strategies in these cases. Switching to a second antidepressant (within the same class or to a different class) may be effective in achieving response in 40–60% of cases. Combination therapy refers to adding another antidepressant from the same or a distinct class to enhance the antidepressant effects [86].

Several drugs can be used in an augmentation strategy including: lithium (in augmentation of tricyclic antidepressants and SSRI) [87]; anticonvulsivants (lamotrigine, divalproate and carbamazepine) [88]; thyroid hormones (T3) in augmentation with tricyclic and SSRI antidepressants [89]; atypical antipsychotics (risperidone, olanzapine, ziprasidone and aripiprazole) [90, 91]; dopamine agonists (pramipexole) [92]; and others (pindolol, psychostimulants, buspirone, modafinil, testosterone and estrogens) [93]. The drugs most commonly used for augmentation are lithium and thyroid hormones (T3).

Some non-pharmacologic treatments of resistant depression have been studied: electroconvulsivotherapy (possibly the most effective treatment for resistant depression with higher response rates than pharmacologic treatments alone) [94]; vagus nerve stimulation (which has shown efficacy in monotherapy or in combination with antidepressants) [95]; transcranial magnetic stimulation [96]; deep brain stimulation; and magnetic seizure therapy.

Psychotherapy [97] used alone, or in augmentation of pharmacological treatments, is also recommended. Switching from pharmacological to non-pharmacological treatments or vice versa has also been found to be an effective strategy (e.g. nefazodone following non-response to cognitive behavioral psychotherapy, and vice versa) [98].

Family history of treatment response and side effects

As the pharmacodynamic and pharmacokinetic properties of a drug are genetically modulated, it can be hypothesized that a given individual may inherit the response and side effects to a particular treatment. Studies suggest that this is the case in mood disorders. Several studies have demonstrated that response to antidepressants tend to be similar in patients and their relatives [99]. Response to lithium has also been shown to cluster in families with bipolar disorder [100]. Although the literature is rather scarce on this topic, when possible it may be useful to use information on the therapeutic response in close relatives to guide the choice of medication in patients.

Prevention of suicidal behavior

As previously discussed, a large literature supports the idea that there is a specific neurobiological vulnerability to suicidal behavior, independently of comorbid mood disorders [29]. Therefore, prevention of suicide, especially in identified high-risk individuals (e.g. patients with a past history of suicidal acts), should be specific. However, the development of specific pharmacological treatments is still needed. The exclusion of suicidal patients from trials on mood disorders has partly precluded the discovery of specific treatment intervention for this population.

Lithium has been shown to reduce the number of suicides in patients with mood disorders [101]. Also, increase in antidepressant use has been associated with a decrease in suicide rates in many epidemiological studies around the world [102].

Long-term follow-up studies have found that the treatment of mood disorders, whether by lithium, antidepressant or neuroleptics, significantly reduce suicide rates in mood disorders [7]. However, it is not clear if these treatments specifically target the vulnerability to suicidal acts or the stress represented by a mood episode. Thus far, the best evidence-based prevention strategies have been the education of physicians on the recognition and treatment of depression and the restriction of patients's access to lethal means [103]. In addition, some psychotherapeutic interventions in suicide attempters have shown efficacy in the prevention of recurrence [104].

Children and adolescents

Pharmacological trials on mood disorders have primarily included adults. Much less is known about children and adolescents. Concerns about increased suicidal ideation with antidepressants in adolescents were addressed by the British and North American regulatory agencies in 2003 and 2004. Following these warnings, antidepressant prescriptions decreased, while there was an increase in the rate of adolescent suicides [105]. The cause of this association between antidepressants and suicidal ideation emergence remains unclear. One explanation may be the difficulty in diagnosing bipolar disorder in adolescents who first present with a depressive episode.

A reanalysis of randomized controlled trials suggest that benefits generally overcome risks [106]. However, recent analyses of randomized controlled trials suggest that antidepressant efficacy may be inferior in children than in adolescents and, overall, efficacy is modest in depression [106, 107]. Therefore, it seems sensible to propose antidepressants as a first-line treatment of only moderate to severe depression in adolescents associated with close clinical monitoring. Non-pharmacological therapies may be a first-line treatment in children.

Late-life depression

Depression in the elderly raises a series of difficulties ranging from recognition of depressive symptoms, disentangling depression from somatic diseases (notably cognitive impairment) and a higher sensitivity to side effects. At the same time, depression is associated with a significant functional impairment and increased risk of suicide [108], complicating diagnosis and treatment in this population. Another issue leading to complexity in this group is the multiplicity of potential etiologies of late life depression, for example depression from vascular origin [109].

Regarding the pharmacological treatment of depression in older-aged people, a recent Cochrane Review suggests that both SSRIs and tricyclic antidepressants have the same efficacy, with the latter showing more side effects [110]. In addition, older and younger patients seem to have similar rates of remission [111]. However, older people appear to relapse more often [112], leading to the recommendation of treating a first depressive episode for at least 12 months following remission [113]. Non-pharmacological interventions (psychoeducation, family counseling and visiting nurse services) are also recommended [113].

Gender

Gender is obviously a relevant variable in mood disorders. Expression, prevalence and course of mood disorders are different in males and females [114]. In addition, although there may not be many behavioral differences in healthy individuals [115], gender-based neurobiological variations (including structure, activity and biochemistry) [116] may have physiopathological consequences (e.g. acute tryptophan depletion leads to depressive symptoms more often in women than men [117]) and treatment response in mood disorders.

One study reported a better response (efficacy and dropout) to specific serotonergic reuptake inhibitors in women and to serotonergic and noradrenergic reuptake inhibitors in men [118]. However, replications have shown mixed support. Although women tend to show a better response to SSRI [119, 120] and possibly to monoamino-oxidase inhibitors [121], evidence that men have a significantly better response to adrenergic antidepressants is less consistent [120, 122]. Other studies have found no gender difference in serotonergic or noradrenergic drugs [111, 121]. It could, therefore, be recommended to use SSRI as a first-line treatment in women.

Menopause

Several studies have suggested that menopause may influence the response to antidepressants [123]. Specifically, SSRIs may be more efficacious in younger women while more noradrenergic antidepressants may be more beneficial for menopausal women [118, 124]. However, other studies have not found any difference according to the menopausal status for serotonergic or noradrenergic antidepressants [121, 122].

Hormones alone, or in augmentation, have been proposed as a treatment of depression in perimenopausal and post-menopausal women. So far, results have been inconsistent. Estrogens alone have been more efficacious than placebo in perimenopausal women [125], but not in postmenopausal women [126]. Antidepressant augmentation by hormones has also yielded mixed results [124, 127].

Ethnicity

In addition to problems regarding differential expression of mood disorders in ethnic minorities [128] and their lower access to and quality of mental health care [129], ethnic differences in response to psychopharmacological agents has also been demonstrated. Indeed, variation in the distribution of genetic polymorphisms according to the ethnic groups leads to variation in pharmacodynamics and pharmacokinetics properties of drugs [130]. Cultural aspects such as diet (e.g. some herbal remedies in Asians) may also interfere with pharmacological outcomes.

Few studies have specifically addressed the question of ethnic differences in the outcome of the treatment of mood disorders [131]. One study examining depressed HIV patients [132] reported: a lower response to fluoxetine in black compared to white patients; a higher response to placebo in Latinos compared to both other

groups and no group-differences in adverse events. A pooled analysis of several clinical trials using paroxetine for depressive and anxiety disorders [133] found no group difference between African American, Asian Americans and Latinos. Finally, it should be noted that ethnic minorities tend to dropout from pharmacological trials more often, even if the reasons are not clear [134].

Clinical evidence is therefore still poor for an ethnic difference in efficiency and tolerability. However, clinicians should be aware of ethnic pharmacological variability, for example the low metabolism of drugs interacting with the cytochromes P450 2C19 (substrate of benzodiazepines) and 2D6 (substrate of several antidepressants) in East Asians [131]. Another related issue is the reported higher lithium ratio in African Americans than in Caucasians [135].

Childhood maltreatment

As explained above, depressive episodes in women with a history of childhood maltreatment seem to be associated with particular physiopathological correlates [136]. As a consequence, it is expected that treatment of depression should differ according to this developmental factor. However, only one study has investigated this question. Nemeroff *et al.* [137] showed that cognitive behavioral therapy was significantly superior to nefazodone in chronically depressed patients with a history of childhood trauma. More investigations of this important issue are needed.

6.3 Perspectives

Over the last 50 years, we have seen the discovery of a significant number of drugs for the treatment of psychiatric disorders. These medications have changed the life of millions of patients and families around the world. In the field of mood disorders, antidepressants and lithium have all been major advances. However, questions remain regarding efficacy, tolerability, delay of onset, resistance and remission maintenance. For instance, the STAR*D study, which prospectively assessed real-life effectiveness, revealed that only 30% of outpatients treated with citalopram for unipolar depression achieved complete remission [138].

No clear pharmaceutical innovation has been developed over the past two decades [139]. The monoaminergic system has been the main focus of attention in physiopathological and pharmacological studies of mood disorders since the discovery of the serotonergic properties of the first antidepressants [140]. Recent advances in the understanding of mood disorders and their treatment suggest that new molecules with no direct monoaminergic properties may be promising. Lists of molecules in phase I, II and III trials can be found on www.clinicaltrials.gov.

Drugs in trials notably target the glutamatergic system (glutamate-modulating agents, N-methyl D-aspartate or NMDA receptor antagonists and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid or AMPA receptor potentiators), HPA axis (Corticotropin Releasing Factor antagonists, glucocorticoid II receptor antagonists), Substance P (Neurokinin receptor antagonists), vasopressin-system (Vasopressin IB

receptor antagonists), melatonergic system (melatonin M1/M2 receptor agonists) and various intracellular pathways (phosphodiesterase inhibitors, etc.) [140]. As discussed above, these drugs may be particularly beneficial if specific (clinical and neurobiological) targets can be identified, as opposed to heterogeneous clinical categories [141]. This also implies that pharmaceutical companies should consider investing in research that is not solely based on clinical entities.

Advances in the treatment of mood disorders would also be aided by improvements in understanding the biological mechanisms mediating psychotherapeutic and other non-pharmacological response (e.g. the effect of social interactions, food, omega-3, physical exercise, light). In addition, other non-pharmacological techniques are promising, such as repetitive transcranial magnetic stimulation, vagal nerve stimulation or deep brain stimulation [142]. However, targeting specific evidence-based neuroanatomical regions will be necessary to improve the efficacy of these techniques. Finally, pharmacogenetics may help clinicians predict efficacy and side effects of drugs in a given patient [143].

Advances in knowledge regarding the physiopathological correlates of mood disorders, the biological actions of various available therapies as well as the discovery of new molecules and therapeutic modalities, will ultimately help doctors develop more comprehensive, targeted and efficient therapeutic strategies. A long but exciting road lies ahead.

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7

Bipolar Disorder

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Abstract

The pharmacological management of bipolar disorder encompasses the acute treatment of mood episodes, the continuation phase after initial response and the longer term prevention of recurrences. Lithium salts have been the first treatment in the modern era in this field, and still represent the gold standard for the various phases of bipolar disorder 60 years after their introduction in the treatment of mania. Alternatives to lithium have been investigated, often following serendipitous observations. Classical neuroleptics and antidepressants have long been used for the treatment of mania and bipolar depression, respectively, even if relevant controlled trials have been rare. Treatment of acute episodes with antidepressants or neuroleptics has been associated with switch into the opposite phase and with cycle acceleration. After the first description of the effects of valproate in the 1960s, several other anticonvulsants have demonstrated antimanic, antidepressant and mood stabilizing properties in bipolar patients. Several second-generation antipsychotics have already been approved by regulatory authorities from different countries for the acute treatment of mania. On the other hand, acute treatment of bipolar depression has long represented a difficult task, even though current trials of various agents are promising. Controlled trials of prophylactic efficacy of bipolar recurrences are difficult and expensive. The duration of a drug in the market has markedly influenced this field. Discrepancies in the definitions of treatment phases reflect the difficulties of long-term studies. Current trials are designed to investigate maintenance effect of treatments after initial response without a clear separation between prevention of relapse and prevention of recurrence. Long-term outcome can perhaps be investigated by naturalistic studies alone, as effectiveness and efficiency are not addressed by controlled trials. Moreover, bipolar disorder often requires combined treatments. Additional issues can be addressed by naturalistic studies alone, including the potential development of resistance after prolonged treatment or after discontinuation of prophylaxis, and the potential poorer outcome when there is a delay in starting prophylaxis or in the presence of

atypical features. Observations from specialized facilities support a potential effect of lithium against the otherwise increased mortality of bipolar patients, especially due to suicide. No similar evidence is available regarding currently prescribed alternatives to lithium.

Key Words

bipolar disorder; mania; depression, bipolar; lithium; anticonvulsants; antimanic agents; antipsychotic agents; antidepressive agents

7.1 Introduction

The pharmacological management of bipolar disorder encompasses the acute treatment of mood episodes, the continuation phase after initial response and the longer term prevention of recurrences. The beginning of the modern era in this field can be dated back to the work of the Australian psychiatrist John Cade, who first described the antimanic properties of lithium in 1949 [1]. Five years later, Mogens Schou and his colleagues [2] noted that Cade's observation of the striking effects of lithium treatment had failed to arouse greater general interest among psychiatrists. Possible reasons included 'difficulties encountered in attempts to convey to others in a quantitative manner the clinical impressions of the effect of a new psychiatric therapy... quantitative assessment of the degree of the psychosis is often difficult... the therapeutic effect and its evaluation are liable to gross distortions due to suggestibility, negative or positive, in the patients as well as in the observers... manias and depressions show spontaneous variations in duration and intensity...' They therefore implemented the first placebo-controlled double-blind trial in psychopharmacology, confirming the antimanic properties of lithium [2].

Subsequent controlled studies in the early 1970s provided evidence that lithium is also able to prevent recurrences of bipolar disorder (for review see [3]). Thereafter, there has been a great evolution in the design of clinical trials across the various phases of bipolar disorder. Controlled trials have investigated drugs administered as monotherapy in comparison with placebo or with other active treatments, as well as combined therapy in comparison with monotherapy.

Current clinical practice is based on different levels of evidence. According to the Evidence Classification System of the US Agency for Healthcare Research and Quality, Class A includes randomized or other controlled studies, Class B well-designed open clinical studies and Class C case series, case reports or retrospective chart reviews with quantitative outcome data. Each class may in turn encompass various examples of sources of evidence (for review see [4]). In addition to individual trials, meta-analyses can be carried out when the number, size and quality of trials is sufficient. Systematic reviews are also available, as are those contained in the Cochrane Database, which are of a high methodological standard and can be continually updated as new primary studies are completed or identified [5]. As controlled trials are generally designed to measure only one main outcome, they may not cover specific issues, such as differences between bipolar I and bipolar II

subgroups, effects of treatments on episodes of different polarity or in the presence of psychotic features. Other characteristics of bipolar disorder, including unpredictable states such as rapid-cycling, dysphoric mania and iatrogenic cycle acceleration, may require specific studies. Therefore, secondary analysis of data from controlled trials may be useful as are results from uncontrolled studies. Another important aspect which is not specifically addressed by controlled trials, also due to ethical reasons, is long-term mortality in bipolar disorder. The latter has been shown to be increased compared to the general population, mostly as the result of naturalistic studies.

In the bipolar disorder field, several large-scale randomized open trials have been implemented in the last decade such as the Bipolar Affective disorder: Lithium/Anticonvulsant Comparative Evaluation (BALANCE) trial [6], the Multicenter Study of Long-term Treatment of Affective and Schizoaffective Psychoses (MAP) study [7], the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP) study [8] or the series of studies from the National Institute of Mental Health (NIMH) Stanley Foundation Bipolar Treatment Outcome Network (SFBN) [9]. In particular, the latter is a multisite international clinical trials network which has been established to address many of the neglected areas of research in bipolar illness.

Clinical practice is often based on guidelines such as those from the American Psychiatric Association [10], the Expert Consensus Guideline Series [11] or the Texas Implementation of Medication Algorithm Project [12].

7.2 Trials in acute mania

The majority of research studies regarding the treatment of bipolar disorder have focused on the management of acute manic episodes. In this case, the efficacy of treatments has been established, replicated and accepted widely; for general reviews see [13, 14].

Several drugs have been approved in different countries for acute mania. The US Food and Drug Administration (FDA) approved lithium in 1970, and the neuroleptic chlorpromazine in 1973. Other medications have long been used in acute mania but not necessarily approved by regulatory authorities. An example is haloperidol which is not FDA-approved but, paradoxically, has been used as a comparison treatment even in the context of recent trials that resulted in approval of second-generation antipsychotics in the US [15, 16].

Another example is clozapine, which has been used as monotherapy or as add-on therapy particularly in the case of treatment-resistant mania, but whose effects were addressed by uncontrolled trials alone [17, 18].

The discrepancies between clinical practice and regulatory approval for bipolar disorder are witnessed by other examples. The anticonvulsant carbamazepine, which has been used in the treatment of the various phases of bipolar disorder in the US since the early 1980s [19], was FDA approved only in 2004 and for acute mania alone. In this case, the development of an extended-release capsule formulation prompted the two randomized placebo-controlled trials required for approval [20, 21].

We experienced a similar story in Italy regarding the anticonvulsant valproate and its analogs, whose antimanic and mood-stabilizing properties had been reported

since the 1960–1970s in France (for review see [22]). Italian psychiatrists had to prescribe valproate ‘off-label’ for many years or use the analog valpromide that had been approved as ‘coadjuvant in depressive states and manic excitement, and in psychomotor agitation’ after the French studies. Eventually, after the introduction of a prolonged-release valproate formulation, the manufacturer applied for and obtained approval for treatment and prevention of mania associated with bipolar disorder in the 2000s.

In the US, valproate semisodium had been approved in 1995 for acute mania and a dramatic change in prescription patterns followed at the expense of lithium, as confirmed by several surveys [23–25].

Thereafter, the interest from pharmaceutical companies in bipolar disorder markedly increased. This was witnessed by their support of the series of randomized placebo-controlled trials that resulted in approval for acute mania, between 2000 and 2004 in the US, of the second-generation antipsychotics olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole [13–16, 26–33].

The primary efficacy measure used in the majority of current protocols is change in the Young Mania Rating Scale from baseline to an endpoint of three weeks. Studies regarding olanzapine, risperidone, ziprasidone, aripiprazole and extended-release carbamazepine included subgroups of patients with mixed mania, resulting in their approval also for this specific indication.

The explosion of controlled trials has prompted a debate as to whether or not the pharmaceutical industry is excessively influencing the clinical practice in bipolar disorder. According to David Healy, we are dealing with a case of ‘disease mongering’ and ‘the latest mania’ is ‘selling bipolar disorder’ [34]. Nassir Ghaemi does not argue in favor of Healy’s hypothesis: he maintains that ‘the newest mania’ is ‘seeing disease mongering everywhere’ [35]. It must be mentioned that, after approval of agents for acute mania, there is the frequent attitude, at least in certain countries, to prescribe them in ‘the real world’ also for the continuation and maintenance phases, even in the absence of specific trials or approval by regulatory authorities for treatment beyond the acute phase. Sometimes, epidemics of off-label prescription follow the mere presentation of case reports. The latter behavior may not necessarily be encouraged by the manufacturers.

In the late 1990s, several reports were published describing improvement in patients with bipolar disorder treated with the anticonvulsant gabapentin, in addition to standard therapies. In a survey of 12 662 patients with bipolar disorder enrolled in the Oregon Medicaid program between 1998 and 2003, divalproex was the most frequently used mood stabilizer (33% of subjects) with gabapentin the next frequently used anticonvulsant (32% of subjects). Lithium was used by 25% of subjects and carbamazepine by 3% [36]. However, a double-blind trial of adjunctive gabapentin in mania, funded by the manufacturer [37], reported in 2000 that the decrease in total Young Mania Rating Scale from baseline to endpoint was significantly greater in the placebo group than the gabapentin group. The Gabapentin study also provided some interesting methodological lessons regarding the choice of the phase of illness to study or the use of add-on treatment design which may be ethically correct but

may hamper the detection of a drug effect when the signal-to-noise ratio is low, as in most psychiatric disorders. In any case, the manufacturer decided to stop further investigation on the potential antimanic properties of gabapentin.

Overall, the above-mentioned examples underline the relevance of issues associated with a drug's remaining patent life and time to marketplace.

Whatever the role of the pharmaceutical industry, published Cochrane reviews supporting the efficacy of treatment of acute mania with the following drugs, alone or in combination, are worth mentioning: valproate [38], olanzapine [39], risperidone [40] and haloperidol [41].

In particular, haloperidol has been shown to be more effective than placebo at reducing manic symptoms, both as monotherapy and as adjunctive treatment to lithium or valproate. It has also been shown to be less effective than aripiprazole but of similar effectiveness as risperidone, olanzapine, carbamazepine or valproate. Haloperidol was associated with less weight gain than olanzapine, but with a higher incidence of tremor and other movement disorders [41].

Valproate was more efficacious than placebo, not different from lithium or carbamazepine and less effective than olanzapine. There were significant differences in the side effect profiles of valproate and olanzapine, with more sedation and weight gain on olanzapine [38].

Risperidone monotherapy was more effective than placebo in reducing manic symptoms and in leading to response, remission and sustained remission. Effect sizes for monotherapy and adjunctive treatment comparisons were similar. Low levels of baseline depression precluded reliable assessment of efficacy for treatment of depressive symptoms. Overall risperidone caused more weight gain, extrapyramidal disorder, sedation and increase in prolactin level than placebo. There was no evidence of a difference in efficacy between risperidone and haloperidol, either as monotherapy or as adjunctive treatment. Overall risperidone caused more weight gain than haloperidol but less extrapyramidal disorder and comparable sedation [40].

Olanzapine was superior to placebo at reducing manic symptoms as monotherapy and in combination with lithium/valproate. Olanzapine monotherapy was superior at reducing psychotic symptoms. Olanzapine was superior to divalproex at reducing manic symptoms. Olanzapine did not lead to a statistically higher rate of clinical response than haloperidol. Olanzapine caused greater weight gain than placebo and somnolence but not more depressive symptoms or movement disorder. Olanzapine caused more prolactin elevation than placebo. Olanzapine caused greater weight gain, somnolence and movement disorders than divalproex but less nausea. Olanzapine caused more weight gain than haloperidol but less movement disorder [39].

With regard to second-generation antipsychotics as a class, a systematic review and meta-analysis of randomized controlled trials [42] concluded that they were significantly more efficacious than placebo and displayed efficacy comparable with that of mood stabilizers. The analysis demonstrated that adding antipsychotic agents to mood-stabilizer treatment was significantly more effective than treatment with mood stabilizers alone.

7.3 Trials in acute bipolar depression

Compared to trials for acute mania, controlled trials for depressive episodes in the frame of bipolar disorder are relatively few. One of the reasons is that the interest from pharmaceutical companies toward this peculiar niche is even more recent. Concerns of antidepressant-induced mania and cycle acceleration, as first suggested in the early 1980s [43], have perhaps contributed to limiting such an interest in the past. One consequence is that antidepressants have been used for many years in bipolar depression in the absence of specific approval from regulatory authorities. Clinical practice has been mostly based on expert guidelines. The majority of guidelines recommend monotherapy with a mood stabilizer or the combination of mood stabilizers with antidepressants.

Double-blind randomized placebo-controlled trials reported the acute antidepressant effect of lithium in the 1970s, and of carbamazepine in the 1980s (for review see [44]). More recently, the effect of carbamazepine was confirmed [45, 46], as was that of the other anticonvulsant divalproex [47, 48]. The anticonvulsant lamotrigine was found to be effective in a first trial [49], but results were not confirmed by four subsequent studies [50].

With regard to the role of antidepressants, alone or in combination with mood stabilizers, the debate is still open. A special issue of the journal *Bipolar Disorders* was published on this matter in December 2003.

In a recent study, the STEP-BD collaborators reported that the use of adjunctive, standard antidepressant medication (paroxetine or bupropion), compared to the use of mood stabilizers (any FDA-approved antimanic agent), was not associated with increased efficacy. Modest trends favoring the group receiving a mood stabilizer plus placebo were even observed across secondary effectiveness outcomes. However, adjunctive antidepressants were not associated with switch to mania or hypomania early in the course of treatment [51].

Paroxetine and bupropion were selected as the standard medication because they represented the antidepressants most commonly prescribed for bipolar depression, at least in the US. Their use had been prompted by controlled trials [52, 53]. In one study [52], both paroxetine and imipramine were found superior to placebo for patients with low serum lithium levels (≤ 0.8 meq/l). Compared to imipramine, paroxetine resulted in a lower incidence of adverse events, most notably emergence of manic symptoms. For patients with high serum lithium levels (> 0.8 meq/l), antidepressant response at endpoint did not significantly differ from placebo. In the other study [53], when bupropion or desipramine was added to an ongoing therapeutic regimen of lithium or an anticonvulsant, no difference was found for acute efficacy between the two drugs. Mania/hypomania was observed in 5 of 10 desipramine-treated patients, but only 1 of 9 bupropion-treated patients.

Based on the hypothesis of reduced dopaminergic neurotransmission in bipolar depression, as suggested by the often prominent psychomotor retardation, bupropion was preferred by some clinical researcher for its peculiar property of inhibiting dopamine reuptake. Whatever the relevance of the latter hypothesis, the bupropion case underlines once again that the pharmacological treatment of bipolar

disorder has been long independent from scientific evidence. Practice may have varied across countries due to commercial strategies, even though the role of pharmaceutical companies has not necessarily been in the expected direction. One example is clomipramine, widely used in Europe as an antidepressant for many years, but approved for obsessive compulsive disorder alone in the US. Similarly, Italian psychiatrists have had to prescribe bupropion off-label for depression for several years because it had been approved for the treatment of nicotine dependence alone. Moreover, its elevated cost has not been paid by the National Health System until the recent introduction, at a lower price, of a modified-release formulation, only approved for depression. On the contrary, other antidepressants with dopaminergic-enhancing properties have long been available in Italy, such as low-dose substituted benzamides. Indeed, we used to treat mild-moderate depressive recurrences in lithium-maintained bipolar patients with short-term treatment with levosulpiride, as also described in a controlled study published in 1993 [54].

According to a recent review,

...randomized, double-blind, placebo-controlled studies have demonstrated that antidepressants exert some efficacy in the treatment of bipolar depression in some populations of patients. Moreover, the risk of manic switch, although not totally countered, appears to be strongly reduced when antidepressants are given in combination with a mood stabilizer and when new-generation antidepressants are preferred over old tricyclic antidepressants. Finally, some studies have proven that the continuous use of antidepressants after the remission of a major depressive episode helps to prevent further depressive relapses without causing a significant increase in manic relapses. [55]

The review concluded that ‘clearly there is a place for antidepressants in bipolar disorder; however, it is important to be cautious and evaluate their use on a case-by-case basis’.

Significant contributions to the study of ‘treatment-emergent mania’ have been provided by the series of reports from the Bipolar Collaborative Network (formerly the SFBN) [56–58]. In a recent paper from the latter network, presence of minimal manic symptoms such as motor activation, pressured speech and racing thoughts coexisting with otherwise full syndromal bipolar depression was associated with antidepressant treatment-emergent mania or hypomania [59], while antidepressants may be effective in some individuals with bipolar disorder, they can precipitate a rapid mood switch from depression to mania. Recent controlled studies using newer agents have reported reduced rates of the latter phenomenon in comparison with the tricyclic antidepressant era, but rates remains clinically significant.

Current interest in the treatment of bipolar depression has been turned toward second-generation antipsychotics alone or in combination with other active treatments. Indeed, based on the results from the required controlled trials, the only FDA approved drugs for bipolar depression are the olanzapine-fluoxetine combination [60] and quetiapine [61, 62].

The primary outcome measure generally used in recent trials is change in the Montgomery–Asberg Depression Rating Scale scores from baseline to an endpoint of

eight weeks. This scale is used frequently in European trials and has been suggested to be superior to the Hamilton Rating Scale for Depression which was more widely used in the US [63].

7.4 Trials in maintenance of bipolar disorder

With regard to prevention of recurrences of bipolar disorder, the number of randomized controlled trials is limited, mostly due to the elevated costs of long-term studies (12–18 months may be necessary to establish prophylactic efficacy). There are some discrepancies in definitions of long-term treatment phases. The term ‘continuation’ should be referred to the first 2–6 months after an acute episode has ended and its objective is to prevent ‘relapse’ of the episode, or ‘switch’ into the opposite pole. The term ‘maintenance’ should be referred to a later phase with the objective of preventing ‘recurrence’, that is new episodes. However, according to the Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder from the European Agency for the Evaluation of Medicinal Products (EMA), maintenance of effect corresponds to the continuation period. Indeed, the terms ‘relapse’ and ‘recurrence’, and the respective treatment phases ‘continuation’ and ‘maintenance’ have been derived from similar definitions in the context of major depression [64], but there is no scientific basis in their distinction. In the context of bipolar disorder, it has been proposed that ‘relapse’ should refer to mood episodes having the same polarity as the index episode and occurring within 90–180 days, whereas ‘recurrence’ should refer to a later new mood episode of any polarity [65]. However, modern trials of long-term treatment of bipolar disorder do not distinguish between prevention of relapse or recurrence, as the primary endpoint generally used is time from randomization to intervention for any mood episode. A possible approach to differentiate between true prophylaxis trials and relapse prevention trials has been proposed, depending on whether patients are euthymic at entry or the study is a continuation of acute treatment [66].

Definitions of treatment phases after the acute episode vary across regulatory authorities from different countries. FDA relies on the term ‘maintenance’.

Lithium, FDA approved for maintenance in 1974, has been the only accepted long-term treatment for three decades (for a review of early controlled studies see [3]).

A seminal double-blind long-term follow-up study, published in 1984, included bipolar patients who received lithium, imipramine or both. Lithium and the combination treatment were superior to imipramine in preventing manic recurrences and were as effective as imipramine in preventing depressive episodes. The combination treatment provided no advantage over lithium carbonate alone. Treatment outcome, which was evaluated primarily in terms of the occurrence of major depression or manic episodes, was significantly related to characteristics of the index episode, i.e. the episode that brought the patient into the study [67].

In the 1990s, the efficacy of lithium was questioned particularly by Joanna Moncrieff who, as commented by Schioldann [68], strongly challenged the validity of the pioneering trials of lithium prophylaxis in bipolar disorder [69–72]. She

rekindled the 'therapeutic myth', suggesting that these trials 'produced spurious results owing to flawed methods' and concluded that 'a close reexamination of these studies' was due. The main criticism was that the results from controlled trials can be explained by lithium withdrawal-induced relapse in the placebo group. Since most maintenance trials switch patients from lithium to placebo, a lithium-placebo difference might be inflated by the withdrawal-induced relapse. Moncrieff's challenge was taken up and a compelling meta-analysis was published in 1999 [73] based on controlled trials world-wide, spanning three decades from 1967 to 1998, and involving approximately 2000 patients. The data showed a highly significant reduction of recurrence with lithium and the authors failed to find sufficient evidence to prove that the lithium-withdrawal relapse phenomenon exists. Subsequently, the efficacy of lithium in maintenance treatment for bipolar disorder was confirmed by systematic reviews [74, 75].

In any case, criticism regarding early trials with lithium prompted a great evolution in methodologies in bipolar disorder maintenance research, especially in areas of enrollment procedures, randomization schemes, specific outcome measures used, statistical analyses and regulatory changes [76].

Evidence of efficacy has been provided for valproate-related compounds resulting in their approval for maintenance of bipolar disorder in several countries other than the US [77–79].

Carbamazepine did not receive industry-sponsored development efforts similar to other treatments, perhaps because its patent life had already expired when there was the explosion of large-scale multicenter studies in bipolar disorder. However, as reviewed by Post and colleagues after 30 years of clinical experience, it

...has an important and still evolving place in the treatment of acute mania and long-term prophylaxis. It may be useful in individuals with symptoms that are not responsive to other treatments and in some subtypes of bipolar disorder that are not typically responsive to a more traditional agent such as lithium. These subtypes might include those patients with bipolar II disorder, dysphoric mania, substance abuse co-morbidity, mood incongruent delusions and a negative family history of bipolar illness in first-degree relatives. In addition, carbamazepine may be useful in patients who do not adequately tolerate other interventions as a result of adverse effects, such as weight gain, tremor, diabetes insipidus or polycystic ovarian syndrome. [19]

Meta-analyses comparing carbamazepine with lithium were published in 1995 [80] and 1999 [73]; the latter included two noteworthy trials. In the first [81], a prospective randomized study of comparative prophylactic efficacy of lithium, carbamazepine and the combination in bipolar disorder, lithium and carbamazepine had a roughly equal but less than adequate prophylactic efficacy in overall bipolar illness. Lithium was superior to carbamazepine in the prophylaxis of mania, whereas the combination was better than either monotherapy, especially in rapid cyclers. In the second [82–84], in a randomized clinical trial with an observation period of 2.5 years, the prophylactic efficacy of lithium versus carbamazepine was compared in bipolar patients. Lithium appeared to be superior to carbamazepine in classical bipolar cases (bipolar I patients without mood-incongruent delusions and without comorbidity) whereas patients with

non-classical features (all other patients) profited more from carbamazepine which was well accepted by the patients. No significant differences between the drugs were found in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified.

The FDA-approved treatments for maintenance do not include carbamazepine but, besides lithium, the anticonvulsant lamotrigine and the second-generation antipsychotics olanzapine and aripiprazole. Controlled trials had found lamotrigine superior to placebo in bipolar patients with recent episodes of either polarity [85, 86], whereas only patients with recent manic episodes were enrolled in trials of olanzapine [87–89] or aripiprazole [90, 91]. Efficacy in maintenance was more evident in patients who had responded to the same drug during the index episode. The latter peculiarity, known as pre-randomization enrichment, is also relevant to lithium as identified by a re-evaluation of randomized monotherapy trials [92].

A more recent trial has reported that maintenance treatment with quetiapine in combination with lithium/divalproex significantly increased time to recurrence of any event (mania, depression or mixed), irrespective of the polarity of the index episode, compared to placebo with lithium/divalproex [93]. The authors suggest that quetiapine with lithium/divalproex can provide an effective long-term treatment option for bipolar I disorder to prevent recurrences not only of mania but also depression.

With regard to newer anticonvulsants, no randomized controlled trials of tiagabine in the maintenance treatment of bipolar disorder were found by a 2006 Cochrane review [94], whereas a 2008 Cochrane Review [95] identified two randomized controlled trials of oxcarbazepine in the maintenance treatment of bipolar disorder that met the methodological criteria for inclusion, but the conclusion was that there is an insufficient methodologically rigorous evidence base to provide guidance on its use.

7.5 What is a mood stabilizer?

As already noted above, there are relevant discrepancies between randomized clinical trials and the ‘real world’, especially in the context of long-term treatment of bipolar disorder. Even the definitions used in clinical practice and pharmacology textbooks differ from those used by regulatory authorities. One example is the term ‘mood stabilizer’ which, despite various definitions [4, 22, 96, 97], is accepted worldwide but is not officially recognized by regulatory authorities including the FDA.

Harris and colleagues [22] depicted an interesting historical picture of the concept of mood stabilization, starting from the serendipitous discovery of the anticonvulsant properties of valproic acid in 1963, describing the first observations of carbamazepine effects in manic-depression in Japan in the 1970s and Post’s hypothesis of kindling as a potential mechanism explaining conditioning and sensitization in the longitudinal course of affective illness proposed in the 1980s [98]. Indeed, Schou had already proposed the term ‘mood-normalizer’ in 1963 [99], but the term ‘mood stabilizer’ in fact only appeared sporadically in the literature until the early to mid-1990s. Thereafter, there was a dramatic growth in the frequency with which the term was included in the title of scientific articles [34]. The impact of the term is also witnessed

by a recent paper that defined the antidepressants as ‘mood destabilizers’, given their propensity to induce rapid cycling [100].

The ideal mood stabilizer is said to have efficacy in the treatment of acute manic and depressive episodes, and also be effective in the prevention of relapse/recurrence. Moreover, it should not induce switch into the opposite polarity. No available agent meets the criteria for a comprehensive mood stabilizer, although lithium comes closest.

The kindling model prompted investigation of several anticonvulsants as potential mood stabilizers, but the results varied. In any case, the notion of mood stabilization replaced the earlier notion of prophylaxis.

7.6 What controlled trials cannot tell us about treatment of bipolar disorder

Harris and colleagues [22] maintained that ‘it has proven all but impossible to demonstrate prophylactic efficacy for agents, other than perhaps lithium, in the case of manic-depressive disorders. A proper trial demonstrating such effects would run for many years’. Grof [101] argued that ‘the methodology has been worked out over many years and proper prophylactic trials are possible, just damned difficult and very expensive’.

The problem of the duration of bipolar illness compared to the duration of a drug in the market has already been discussed above. Long-term outcome can perhaps be studied by naturalistic studies alone. Indeed, several questions have been raised and sometimes answered by clinical investigators from specialized facilities involved in the management of lithium and related therapies.

A very useful instrument in this field is the life chart methodology (LCM). A life chart is a systematic collection of retrospective and prospective data on the course of illness and treatment recorded by a patient and/or clinician on the LCM forms. The NIMH-LCM was developed in the 1980s based on Kraepelin’s principles of charting the course of affective illness [102, 103]. This method was then further developed, codified and computerized [104, 105].

In a series of naturalistic observation studies from Canada, treatment outcome has been evaluated using a scale for retrospective assessment of prophylactic treatment response. The scale rates the degree of improvement in the course of treatment weighted by the likelihood of response being attributable to the treatment. In one of the studies [106], rates of full response to individual mood stabilizers were: lithium 30%, carbamazepine 0%, valproate 13%, lamotrigine 11% and olanzapine 25%. Lithium responders were more likely to be bipolar II, and had a typically episodic course of illness with earlier onset in comparison with non-responders. Responders to valproate had higher rates of psychosis.

In 1994, when the role of lithium prophylaxis began to be questioned, Guscott and Taylor [107] stressed the importance of distinguishing efficacy (the potential of a treatment) from effectiveness (the results obtained under ‘ordinary’ clinical conditions). They noted that

...studies of effectiveness or naturalistic studies show poorer results than efficacy studies in all areas of medicine. The major reason for this discrepancy with lithium prophylaxis is poor compliance. Estimations of the efficiency (cost benefits) of lithium prophylaxis are flawed by the failure to consider such issues'.

Davis and colleagues [73] expressed concern that not only was lithium not taken, but also it was not faithfully prescribed, making reference to so-called 'doctor non-compliance'. One common attitude in non-adherent bipolar patients, especially when psychotic manias were prevalent, was to prescribe long-term treatment with depot neuroleptics, even in the absence of compelling scientific evidence (for review see [108]) and with the risk of inducing depression.

Additional issues associated with long-term treatment of bipolar disorder have been addressed by naturalistic studies, including the following: (i) the potential development of resistance after prolonged treatment or after discontinuation of prophylaxis; (ii) the potential poorer outcome when there is a delay in starting prophylaxis or in the presence of atypical features and (iii) the impact of treatments on costs, quality of life and mortality.

Maj and colleagues reported that a substantial proportion of patients classified as complete responders to lithium after the first two years of treatment experienced recurrences during a further period of five years [109]. A similar observation was reported by Post and colleagues with regard to carbamazepine prophylaxis [110]. We did not observe the same phenomenon in patients treated with the combination lithium-carbamazepine after failure of prophylaxis with lithium alone [111].

Refractoriness after discontinuation of lithium prophylaxis was first described by Post and colleagues in four patients [112], supported by Maj and colleagues [113], but not confirmed by other groups [114, 115].

With regard to outcome when there is a delay in starting prophylaxis, it is noteworthy that Kraepelin, more than a century ago, hypothesized that the predominant natural history of manic-depressive illness is toward progressive cycle acceleration. Accordingly, a greater number of prior episodes of illness, or longer latency of long-term prophylaxis, may lead to inferior treatment response. Kraepelin's hypothesis was not invariably confirmed. Moreover, Baldessarini and colleagues [116] supported the therapeutically favorable conclusion that prior episode counts and treatment delay have little association with morbidity during prophylaxis with mood-stabilizing agents (mostly lithium). Comparisons of morbidity during versus before treatment in episodic disorders are misleading because overall morbidity becomes diluted with longer time-at-risk, whereas therapeutic intervention is typically determined by immediately preceding illness [111, 116].

Calabrese and colleagues [76] hypothesized that the decline in lithium effectiveness reported decades after the early studies was in part attributable to the progressive increase in enrollment of patients with complex, less treatment-responsive illnesses. This hypothesis was not confirmed by subsequent reviews [117, 118], concluding that responses were stable over three decades, benefits of lithium have not been exaggerated in the past or have been lost recently, effectiveness was evidenced in bipolar I and bipolar II and reduced morbidity during treatment was similar in patients with mixed or psychotic episodes or rapid cycling and in less complex cases.

The effectiveness of lithium in bipolar patients with atypical features was supported by a multicenter investigation of patients prospectively followed for approximately 20 years in five centers participating in the International Group for the Study of Lithium-Treated Patients (IGSLI) [119].

An aspect which is not generally addressed by controlled trials is that many patients with bipolar disorder require polypharmacy (for review see [120, 121]). For example, in 2000, Frye and colleagues [122] reported that increasing numbers of medications in more recent NIMH cohorts were required to achieve the same degree of improvement at hospital discharge. The authors concluded that more systematic approaches to the complex regimens required for treatment of patients with refractory mood disorder are clearly needed.

In 2005, Baethge and colleagues [123] commented that, despite wide clinical use of mood-stabilizer combinations for long-term treatment of patients with bipolar disorder, research on risks and benefits of this practice is limited. The small, usually brief, published clinical trials of maintenance treatment with lithium plus carbamazepine suggest added benefit of combination treatment over use of either agent alone, but more adverse effects. In our experience [111], carbamazepine has been safely and effectively added in lithium-refractory bipolar patients. Lithium-related side effects may even be reduced as lower lithium dosage may be effective. We also observed an improved thyroid function after adding carbamazepine to lithium, as witnessed by a decrease in thyrotropin-stimulating hormone. On the contrary, a previous study suggested that the addition of lithium to carbamazepine further decreases thyroid function that is already reduced with carbamazepine monotherapy [124]. The discrepancy can be explained by prior reliance on reduced total thyroxine serum concentrations, which have been shown to be misleading during treatment with carbamazepine. The latter leads to a new balance with a shift toward the free form of the active thyroid hormone triiodothyronine. The observation is not trivial, as thyroid dysfunction has been associated with a poor response to treatment in mood disorders. Recent data have challenged the common view of thyroid dysfunction in bipolar disorder almost entirely as a lithium-related side effect. Indeed, lithium-treated patients are at risk of hypothyroidism, but this risk is significantly associated with the presence of circulating thyroid antibodies [125]. Interestingly, a survey from the SFBN has found excessive prevalence of circulating thyroid antibodies in bipolar patients, irrespective of lithium exposure [126].

With regards to costs-effectiveness of treatments in bipolar disorder, Reifman and Wyatt [127] had already evidenced its relevance in 1980. They computed the economic impact of lithium in the US by estimating the cost of care before and after its introduction. Economic gains in production were also calculated. The use of lithium as a treatment for manic-depression had saved \$2.88 billion in 10 years and resulted in a \$1.28 billion gain in production, or a conservative total of over \$4 billion.

More recently, the World Health Organization (WHO) has ranked bipolar disorder seventh among the worldwide causes of non-fatal disease burden. In a 2006 review, Fleurence and colleagues [128] evaluated costs and benefits of the atypical antipsychotics approved for the treatment of bipolar disorder. They concluded that this area

remains under-researched. Based on the limited available studies, there appears to be no significant difference in healthcare resource use between olanzapine, quetiapine, risperidone and valproate semisodium. While a cost-effectiveness study for the UK found haloperidol to be more cost effective than atypical antipsychotics, these results must be considered with caution because of the non-inclusion of adverse effects in the model. No economic data were available for aripiprazole, clozapine or ziprasidone in bipolar disorder. According to the review, future economic studies evaluating atypical antipsychotics should address the issue of long-term costs and effectiveness to reflect the chronic nature of bipolar disorder, the variety of health states that patients may experience and the range of treatments they may receive. A better understanding of the complex interplay between effectiveness, safety, quality of life, adherence and resource use should ultimately contribute to improving treatment.

Another review [129] concluded that, notwithstanding the substantial evidence that bipolar disorder is associated with significant impairment to functioning and well-being, few clinical trials comparing treatments for bipolar disorder have incorporated health-related quality-of-life assessments.

The problem of psychosocial functioning had been addressed by a secondary analysis of the data from a randomized, double-blind, prospective trial of two different doses of lithium for maintenance therapy [130]: the 'standard' dose, adjusted to achieve a serum lithium concentration of 0.8–1.0 mmol/l and a 'low' dose, resulting in a serum concentration of 0.4–0.6 mmol/l. Risk of relapse was higher among patients in the low-range group than among those in the standard-range group. Side effects were more frequent in the standard-range group. In the secondary analysis [131], patients receiving lithium doses that achieved standard serum levels were found to have better psychosocial functioning in areas of work, interpersonal relationships and global functioning, than those receiving doses that achieved low serum levels. This effect was partially but not wholly mediated through relapse prevention.

According to Mohr [132], second-generation antipsychotics consistently showed their superiority over placebo in effects on quality of life of patients with bipolar disorder. The most studied in this field is olanzapine [133]. More long-term controlled double-blind trials are needed to definitively uphold superiority and different effects of individual second-generation antipsychotic. Zhang [134] underlined that promoters of new medications often argue that using newer drugs can reduce use of non-drug medical services and therefore reduce total healthcare spending. In his study, the drug-offset hypothesis for bipolar disorder was examined by comparing olanzapine and lithium from private sector insurance claims data collected from a nationally representative sample of US health plans between 1998 and 2001. Compared to similar lithium users, olanzapine users spent more on non-drug medical services during the first year after initiation of drug treatment, due to both higher rates of re-hospitalization and more outpatient visits. Including the direct cost of the drugs (olanzapine, \$153 per month; lithium, \$16 per month), patients taking olanzapine spent \$5600 more annually on health care services compared to similar patients taking lithium. Zhang concluded that new drugs do not 'pay for themselves' by

reducing the need for other health care services, at least in the case of olanzapine for bipolar disorder. This does not mean that the new drug is not ‘cost-effective’, because increased ‘benefits’ associated with the drug in terms of the improved quality of life may be worth the increased costs. However, the findings do indicate that ‘cost-offsets’ must be measured and not taken for granted.

A WHO study [135] estimated the cost-effectiveness of interventions for reducing the global burden of bipolar disorder. Hospital- and community-based delivery of lithium and valproic acid, alone and in combination with psychosocial treatment, were modeled for 14 sub-regions of the world. A population model was employed to estimate the impact of different strategies, relative to no intervention. Total costs and effectiveness (disability-adjusted life years averted) were combined to form cost-effectiveness ratios. Lithium was estimated to be no more costly yet more effective than valproic acid, assuming its potential antisuicidal effect (see below). Community-based treatment with lithium and psychosocial care were estimated to be more efficient than hospital-based services, each disability-adjusted life year averted costing between one and three times average gross national income.

The potential protective effect of lithium against mortality has been suggested by naturalistic studies. For example, overall mortality among lithium patients followed for years in centers participating in the IGSLI [136] was similar to that observed in the general population, whereas it was found twofold higher in a meta-analysis including studies from the pre-lithium era [137]. The protective effect of lithium would be visible only after prolonged treatment [136]. We reported similar data in a 20-year follow-up of a cohort of 1411 patients registered at our lithium clinic. Treatment with lithium for more than five years appeared to normalize the otherwise twofold excessive mortality of patients from the overall cohort [138]. In particular, survival analysis revealed that patients who had not attended the clinic regularly after admission had an increased subsequent mortality from external causes (mostly suicides) compared to the subgroup who had attended for at least two years [139]. The relevance of treatment duration was also observed in a study of patients who purchased lithium at least once in Denmark. Mortality from suicide decreased with the number of lithium purchases, an indirect measure of prolonged treatment [140]. It appears that prolonged attendance at a specialized facility is crucial for the protective effect, and that there is a negative effect of abandoning regular prophylaxis. Indeed, 10 suicides occurred among patients from our cohort who had proven compliant for several years, although only one while continuing attendance. Differences in suicide risk according to period on or off lithium therapy have been consistently reported. A meta-analytic review yielded a pooled suicide rate of 0.155×100 patient-years on lithium versus 1.30×100 patient-years off lithium [141]. The possibility of confounding by selecting patients who both stay on long-term treatment and are at lower mortality risk is not easily resolved given the implausible and potentially unethical randomization in this field. It may be difficult to interpret whether the reduction in risk of suicide associated with prolonged attendance at a specialized facility is drug-specific. However, no similar evidence is available regarding currently prescribed alternatives to lithium, including carbamazepine [142], valproate [25] and gabapentin [36]. Moreover, even a systematic review of data from randomized trials,

that necessarily focused on shorter-term treatment periods, confirmed that lithium is effective in the prevention of suicide, deliberate self-harm and death from all causes in patients with mood disorders, compared to placebo and other active treatments [143].

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8

Special Issues of Research Methodology in Bipolar Disorder Clinical Treatment Trials

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Abstract

Treatment approaches to bipolar disorder are understudied relative to other serious mental disorders, largely because of controversies over optimal clinical trial methodology and design. The extraordinary heterogeneity of presentations and phases of bipolar disorder and its comorbidities make it a poor fit for most of the requirements of the traditional RCT with a parallel placebo group design. Other approaches that might be more efficient and provide more clinically useful information are discussed and include crossover and intensive N-of-1 designs. Assets and liabilities of these differential approaches are discussed, and methods for circumventing problems and analyzing N-of-1 and crossover studies are presented. The contradictory requirements of clinical homogeneity for efficacy studies and registration of a drug compared to greater inclusiveness for effectiveness studies and examination of mediator and moderator variables are also highlighted. Without new allocations and sources of funding for treatment research in bipolar illness, the inherent difficulties of studying it are likely to prevail over consensus about the most optimal range of elegant to practical clinical trial methods for the illness.

Key Words

randomized controlled clinical trials (RCTs); intensive designs; mania; depression; rapid cycling; efficacy; effectiveness; lithium; mood stabilizers; treatment resistance; power

8.1 Introduction

A number of characteristics of bipolar illness make it particularly difficult to study. It is not only extremely pleomorphic, but is complicated by more psychiatric comorbidities than virtually any other major psychiatric illness. This vast heterogeneity of illness presentation stands in absolute contradiction to the ideal requirements (for homogeneity) in the traditional randomized controlled clinical trial (RCT) [1]. The episodes of bipolar disorder are characterized by psychomotor behaviors of essentially opposite poles of manic over-activity and depressive slowness, lethargy, lack of motivation and social withdrawal [2]. Each type of episode can further vary in terms of severity and duration, yielding patterns ranging from isolated intermittent episodes, to more rapid cycling, biphasic and triphasic mood alterations, and continuous cycling without a well interval. In our recently collected outpatient series, 40% of patients had a pattern of rapid cycling (four or more episodes in the year prior to Network entry), a substantial group of these had ultra-rapid cycling (four or more episodes/month) and a surprising 20% had ultradian cycling (mood switches within a single 24 hour period on four days/week) [3–5].

Further complicating this picture are episodes which present admixtures of mania and depression, yielding multiple types of mixed states. One is dysphoric mania with substantial degrees of anxiousness, irritability, agitation and an unpleasant sense of being overdriven, as opposed to the more classic concept of a happy, elated, euphoric picture [6]. The Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis of mixed states also includes patients with ultradian cycling and extreme switching between depressions and either euphoric or dysphoric hypomanias or manias [7].

More recently, an admixture of several minor manic symptoms has been observed in otherwise classic depressive patients and this has been labeled as a depressive mixed state. This is a depression that has only a few manic components, such as racing thoughts and increased energy. This latter state is noteworthy because it appears to be a predictor of increased rate of switching into hypomania and mania upon treatment with classic unimodal antidepressants [8].

Either phase of illness can present with or without classic psychotic elements of hallucinations and delusions or extremes of irritability, and anger attacks are not uncommon in either phase of illness. Superimposed on these extremely diverse presentations are a very high incidence of comorbidities; 40% or more have an anxiety disorder or substance abuse disorder [9, 10]. The comorbid anxiety disorders can run the full gamut from social phobia to outright panic attacks to obsessive-compulsive disorder and post-traumatic stress disorder.

Substance abuse complications often begin early in adolescents; those with bipolar disorder are nine times more likely to adopt substance abuse compared to non-bipolar groups of adolescents [11]. Rates of marijuana use are also high. Alcohol use and abuse appears to be extremely high and over-represented in women with bipolar illness and is particularly associated with increases in depression and anxiety, suggesting attempts at self-medication [12].

8.2 Efficacy–effectiveness gap

While the presence of each type of comorbidity – alcohol abuse, substance abuse or a comorbid anxiety disorder – can yield a more difficult-to-treat bipolar disorder with a less favorable prognosis than in those without these comorbidities, the complexity of illness presentations and the designs required to deal with them has led to a virtual absence of study of these comorbid states in those with bipolar illness. Thus, attempts to generate highly homogeneous patient populations for clinical trial studies has led to a loss of generalizability because, in many instances, 80–90% of the potential subject population is excluded from a given study for a variety of reasons [13].

Data on efficacy are therefore derived from highly selective subject populations and often highly overestimate the degree of effectiveness in real-world treatment situations – the so-called ‘efficacy–effectiveness gap’. This has very major implications for treatment and clinical decision making, with many studies directed toward demonstrating efficacy for approval by the FDA or some other regulatory body being of little assistance to patients and clinicians in choosing the most appropriate and useful treatment options and, especially in the face of non-response, choosing and sequencing alternatives [1, 14].

The problem is particularly pressing when one considers the typical 50% rule that applies to a great many clinical trials in the treatment of acute mania or acute depression. That is, usually about 50% of the patients on active drug respond to a criterion of 50% improvement on a rating scale after more than 50% of typical patients are eliminated from the trial. This leaves the 50% of patients who are improved in need of further pharmacology therapy, the other 50% (non-responders) as ill as previously and all of the other patients who were on placebo in complete therapeutic limbo.

8.3 Trials for drug registration versus those that are most clinically informative

If a patient does meet the 50% response criterion, no information is provided about what treatment options may be required in order to achieve a more complete response or the ideal goal of remission. This is increasingly an important goal because considerable data indicate that residual manic or depressive symptomatology is a poor prognosis factor and augurs for the increased likelihood of a full-blown syndromal breakthrough episode at some point in the near future [15, 16].

Moreover, while there is wide recognition that the use of multiple drugs in combination is the norm for children and adult bipolar outpatients, the drugs are almost invariably initially studied for regulatory approval as monotherapy and, more recently but still rarely, dual drug combinations. Clinical trial designs have not yet included those needed to help elucidate the best sequences of drugs to be tried and the combinations most likely to be effective [1, 17].

Additionally, since real-world complex patients with anxiety and substance abuse comorbidity are typically excluded even from the monotherapy and combination therapy trials, the clinician is without a substantial clinical trials database for these more complex presenting subjects. In addition, trials in acute mania and acute depression are often extremely short-term, ranging from three to eight weeks, which does not allow sufficient time to assess the true magnitude of initial drug effect or requirement for more complex augmentation strategies. If rapid cycling patients are being studied, for example, there may be substantial confounding of the results of acute clinical trials by high spontaneous remission rates when clinicians are, in fact, more interested in sustained rather than transient responses.

8.4 The need for designs that more optimally inform clinical practice

For these and a multitude of other reasons, many have strongly advocated for funding of more practical clinical trials, particularly for patients with bipolar disorder. These studies are more typical of what has been considered services research and categorized more as effectiveness trials [17–19]. These are particularly helpful in increasing generalizability and including patients with more complex and multiple comorbidities in their presentations. Initial effectiveness and tolerability data can be rapidly acquired in a much less expensive open fashion with, for example, patients exposed to one or another active treatment arm. These could be performed following an open randomization or in a purely observational comparative study with a relatively large N [20, 21]. Approaches and statistical analyses are available for ascertaining the likelihood that a non-randomized subject would ordinarily have likely been exposed to either treatment X or treatment Y [22]. If the particular characteristics of a given subject violate this assumption, that subject would be excluded from the observational analysis.

Another approach to clinical utility and observational clinical trials would be to cross over non-responsive patients to the other agent in a comparison. One could also cross over partial responders in order to achieve within-subjects comparability of the two treatments for both efficacy effectiveness and tolerability, particularly when both treatments are generally considered at equipoise.

The Systematic Treatment Enhancement Program for Bipolar Disorders (STEP-BD) network has utilized a series of nested trials similar to those employed in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which a given patient continues in the program being exposed to additional options to either switch treatment or augment treatment in multiple sequences with the goal of bringing as many patients as possible into remission [17, 23, 24].

Examining the effectiveness of complex combination treatments employed in observational studies using naturalistic treatments may provide a variety of preliminary and exploratory data and hypotheses about what might be the most optimal sequences to explore in more systematic sequential clinical trials such as those utilized in STAR*D. For example, in our outpatient network, we examined what

medications were required to obtain a sustained improvement or remission for at least six months in those who were ill at network entry. This took an average of 18 months of prospective treatment and follow up with an average of three medications (after two others had been tried and discontinued). The addition of lithium or valproate were the most likely changes associated with a sustained response (R.M. Post *et al.*, 2008, unpublished data). Comparing and contrasting the effectiveness of one three-drug regime (such as lithium, lamotrigine and carbamazepine) to others (such as valproate, gabapentin and aripiprazole or such as carbamazepine, nimodipine and ziprasidone) might provide preliminary views on the relative utility of combinations of two mood stabilizers and an atypical antipsychotic agent.

Other options include playing the winner strategies, mirror images and a variety of other approaches used in cardiology, oncology and infectious diseases [24–27]. In fact, in these areas clinicians often have data from randomized clinical trials examining the effectiveness of one combination of three or four drugs compared to another combination of agents. These types of studies have provided information about optimal combination treatment for congestive heart failure, lymphomas and AIDS, to give just a few examples. The authors are not aware of any such systematic explorations of multiple drugs used in combination in bipolar disorder, although use of complex combination therapy appears to be the norm in most academic and clinical practice settings.

One of the reasons such clinical trials have not yet been used is the vast over-estimation of the efficacy of single treatment agents based highly selective populations, short-term clinical trials and 50% response rates. These are appropriate for FDA registration, in which a drug only has to beat placebo, but are otherwise not optimal for informing clinical therapeutics aimed at achieving and maintaining clinical remission.

8.5 'Hidden' high degrees of treatment resistance

The gross over-estimation of effectiveness of single agents in bipolar illness has further unintended negative spin-offs. The degree of treatment resistance in the general population of patients with bipolar disorder is grossly underestimated [4, 5, 28–30]. Lithium is still touted in many text books as being efficacious in some 50–80% of bipolar patients based on inferences from the selective acute clinical trials, while response rates (much or very much improved on the Clinical Global Impressions for Bipolar Disorder or CGI-BP [31]) in long-term prophylaxis are closer to 25% using 'lithium monotherapy'. However, in reality, such a designation often also allows antidepressants, benzodiazepines and antipsychotics as necessary [32, 33]. Another example of this derives from the data of Calabrese and associates [34] in rapid cycling bipolar patients, a not uncommon variant. In these instances, patients experienced only short-term mood stabilization to the combination of lithium and valproate in 25% of the observed cases and in only 17% of the intent-to-treat population. Of those who did acutely stabilize and were then randomized either to lithium or valproate monotherapy, approximately 50% relapsed on either maintenance treatment,

suggesting that only some 10–12% of rapid cycling patients may be responsive to monotherapy.

The perception of the high degree of efficacy of lithium and related anticonvulsant mood stabilizers has been cited as one of the reasons that clinical trials of psychopharmacological agents in bipolar illness have been so consistently under-funded in the past 40 years compared to other serious mental illnesses such as schizophrenia [35, 36]. Other reasons for the vastly under-funded clinical treatment research in bipolar illness are particularly pertinent to the topic of this chapter. In addition to the complexities of presentations of the illness and its great variability, the lack of agreed-upon designs and outcome measures for long-term assessment of the illness have also been identified as major reasons for the lack of funding.

8.6 Controversy about optimal designs and rating instruments

Review panels readily accept the appropriateness of the Hamilton Depression Rating (HAM-D) scale for depression, the Yale-Brown Obsessive Compulsive (Y-BOCS) scale for obsessive-compulsive disorder and the Positive and Negative Syndrome (PANSS) or Brief Psychiatric Rating (BPRS) scales for studies in schizophrenia, but there is little agreement on the most appropriate instruments for assessing the longitudinal course of bipolar illness. Repeated cross-sectional measures with the Young Mania Rating scale (YMRS) and the Montgomery Asberg Depression Rating scale (MADRS) or HAM-D scales for depression are often inadequate for accurate assessment of the course in rapidly fluctuating patients.

In this regard, the National Institute of Mental Health Life Chart Method™ (NIMH-LCM™) is a clinician-rated instrument that also has a self-rated version for assessing severity of mania and depression on a daily basis [37, 38]. It can also track ultradian cycling or number of switches within a single day, the presence of dysphoric mania and comorbid symptoms. In addition, it has a running tally of medications and a space for rating side effects or mild, moderate or severe impact. Reliability is excellent, as severity of mania and depression is rated on the degree of functional impairment with which each phase is associated, making recall of severity relatively easy even at intervals of several weeks to a month between rating sessions [39, 40]. Patients are able to recall whether they had little, some, much or extreme difficulty in their usual social, educational and employment roles based on depressive symptomatology, yielding rating of mild, low moderate, high moderate and severe. Parallel ratings are used for mania. In this instance, mild may be associated with little or no functional impact or an actual increase in functioning, while low and high moderate involve some or much impairment in ability to stay organized and attend to tasks that need to be completed.

The scale has been validated against other measures and used productively in a number of studies including long-term comparisons of lithium vs. carbamazepine vs. the combination for one year of prophylaxis for each phase [32], comparisons of lamotrigine, gabapentin and placebo [41, 42] and, most recently, detailed analysis of

lamotrigine's long-term effects on mood stability [43]. Related longitudinal ratings have been performed by the STEP-BD program [17] and a detailed description of the precise course of illness is particularly important in instances of ultra-rapid and ultradian cycling, which can occur in a substantial proportion of bipolar outpatients.

These recommendations for a daily longitudinal measurement device are also consistent with data from a variety of prospective follow-up studies, indicating that patients with bipolar illness are ill an average of some 50% of the time, with three times more days depressed than days manic [44, 45]. Moreover, mild or subsyndromal symptomatology is highly prominent; patients may fluctuate into and out of full-blown episodes from either a well or dysthymic baseline. Given the repeated observations that minor increases in symptomatology are often precursors to the occurrence of a more major episode, such fine-grained assessments are of great clinical importance as well as necessary for capturing the nuances of mood fluctuations during clinical trials.

One of the major assets of such detailed longitudinal ratings is the ability to simultaneously assess and evaluate different thresholds for what one might consider a mild, moderate or severe relapse, as well as employ modal measures such as that of area under the curve, signifying the magnitude and duration of mania and depression. Such a measure of area under the curve allows for precise intra-individual comparisons of the degree of symptomatology, observed prior to and after a given experimental manipulation as a continuous variable, which should vastly increase the power to detect treatment difference compared to a single endpoint of percentage of relapse into a new episode [46].

Traditional designs in assessment of the efficacy of a prophylactic treatment have typically required patients to achieve substantial improvement or remission for a given period of time and they are then randomized and followed up until the occurrence of a new episode or need for clinical intervention [47, 48]. While this has merits in some circumstances, particularly in patient populations in whom this degree of wellness is readily achieved, it is far from ideal for those with highly treatment-resistant illness.

In the epilepsies, for example, one does not require patients to be seizure-free in order to assess a single or adjunctive therapy, but one looks rather to the reduction in seizure frequency from a baseline [49]. Similarly, assessing the reduction in area under the curve of manic and depressive symptomatology would appear to have considerable merit in those with high degrees of treatment resistance. This is typically the case when one is attempting to ascertain which treatments, adjuncts or combinations are in fact most likely to stabilize the patient, rather than asking the question of how long a patient, once stabilized, can maintain this degree of improvement.

Using this strategy, one can begin to make statements about prevention of mania and depression based on relatively short timeframes of observations [50, 51]. In fact, it has been pointed out by Ilo Lepik, M.D. [52] that in the epilepsies, the higher the seizure frequency at baseline, the shorter the duration of the clinical trial that is needed in order to demonstrate prophylactic efficacy of a given treatment agent. As the degree of treatment resistance in bipolar illness has been vastly underestimated, and the field begins to attempt to develop new treatments for those difficult-to-treat

patients with relatively high percentages of rapid cycling, ultra-rapid cycling and ultradian cycling, such rating and design strategies (making use of the most highly recurrent patients rather than excluding them) are all the more useful.

Another example of the utility of the Life Chart Method is derived from the study of Langosch *et al.* [53] who conducted an open-label, randomized, parallel group monotherapy study comparing valproate with quetiapine in rapid cycling bipolar disorder. The Life Chart Method revealed that there were significantly fewer days of moderate and severe depression on quetiapine (11.7 ± 16.9 days) compared to valproate (27.7 ± 24.9 days, $p = 0.04$). However, upon using the two most widely used cross-sectional rating scales (the HAM-D and MADRS) no significant differences were revealed. This is likely based on the fact that in rapid cycling patients, performing these cross-sectional ratings at a given clinic visit may or may not coincide with a time of illness exacerbation. Such a problem obviously does not occur when using daily prospective ratings.

Highly sophisticated methods of analyzing such rapidly changing state data are discussed by Geller *et al.* [54]. Since last observation carried forward (LOCF) analysis has many liabilities, especially when there is missing data, there is much to recommend the use of linear mixed models [55] and related models [56].

8.7 The traditional RCT is expensive, cumbersome and prone to failure

Klein [57], Kraemer [58] and Brouwer and Mohr [59] emphasized that one of the reasons traditional placebo parallel group RCT studies fail is that not enough preliminary work is done in advance of these large, extremely expensive trials [58, 60, 61]. They suggest that there should be adequate testing of effective doses and preliminary assessment of whether a given group is likely to be responsive. In these instances, initial pilot studies can be invaluable in avoiding potential negative outcomes in RCTs [59, 62–65].

However, too often one considers pilot studies only from the perspective of a small RCT with placebo parallel group design as the ideal way to preliminarily assess whether a large multi-center RCT should be conducted. This has very significant liabilities related to the issues of pleomorphy and heterogeneity so inherent in bipolar illness. The risks of both type 1 and 2 errors are enormous. There are a variety of alternative strategies, however, that may be considered in this light.

8.8 Alternative designs for pilot and proof of principle efficacy studies

We suggest the utility of considering the usefulness of on-off-on designs and N-of-1 trials to more efficiently make preliminary assessments of potential drug efficacy [1]. These may be particularly useful in clinical research involving treatment refractory patients and examination of potential neurobiological mechanisms and predictors of

clinical response to a given drug. In these intensive designs, all of the patients in the clinical trial are started on placebo (off) and then assigned to the active agent (on). Responders can be confirmed in a second off trial and then reconfirmed by re-responsiveness during the second on trial, that is, the utilization of a B-A-B-A design.

This type of design allows for the assessment of clinical responsivity in all of the patients studied rather than just half the population in the traditional placebo parallel group design without a crossover. It also deals with illness heterogeneity well, as patients are used as their own baseline as a control from which to assess responsivity. Moreover, in traditional RCTs, there is no way of assessing whether an individual patient has or has not responded to a drug [64–66], particularly in instances where there are relatively high placebo response rates. The confirmation of responsivity during the second off and on phases mitigates this problem and essentially, if the response and re-response is robust enough, proves that a given patient is actually a responder [50, 67]. This then reduces the variance in the assessment of clinical and neurobiological predictors of response to a given agent because true responders and non-responders can be identified and fewer patients are required in the study as all are exposed to the active treatment [57, 58]. The utility of N-of-1 design has also been endorsed in the general medical literature as having many advantages, particularly in longitudinal studies, over exclusive RCTs [68].

In addition, this design is particularly applicable for studies of patients with treatment-resistant illness. If, for example, a patient has been showing ultradian cycling for several years despite multiple medication trials, one is not interested in examining the response to a given new active potential monotherapy compared to placebo. Placebo response rates are inordinately low in this subgroup, and substantial periods of exposure of severely ill patients to conventional monotherapies or to no treatment at all begins to raise ethical dilemmas [69]. In the B-A-B-A design, after the initial placebo run-in phase (which is now no longer recommended in the traditional RCT [26]), non-responsive patients would not be further exposed to placebo. Moreover, in the responsive patients assessed in this design, the second off phase of placebo treatment could be minimized as a function of utilization of relatively low threshold for declaring a relapse and then restarting the patient on the active treatment. Once it has been established that a drug is effective in a series of N-of-1 trials, one could then move to more observational and comparative clinical trials in order to assess the wider percent likelihood of response in different subgroups of patients and, at the same time, gain more robust tolerability data.

The relative assets and liabilities of the traditional placebo parallel group RCT and that of the B-A-B-A designs are outlined in Table 8.1. One sees immediately that there are multiple liabilities for the traditional RCT as it applies to bipolar illness, with many requirements of the RCT particularly ill fitting to the characteristics of the illness as noted above. On the other hand, there are multiple assets of the B-A-B-A design as enumerated. Moreover, the relatively few liabilities to the utilization of this approach can usually be surmounted. One liability is that these designs are not traditionally FDA-acceptable, but as the FDA has already made clear in the testing and approval of multiple adjunctive agents for those in the refractory epilepsies, and

Table 8.1 Assets and liabilities of the traditional RCT and off-on-off-on (B-A-B-A) trial designs in bipolar illness.

The traditional parallel group, randomized clinical trial (RCT) in bipolar illness		Off-on-off-on (B-A-B-A) designs	
Assets	Liabilities	Assets	Liabilities
+ Meets FDA requirements	– Cumbersome, inflexible	+ Flexible, suitable for pilot studies	– Traditionally not FDA acceptable
+ Standard in literature	– Not appropriate for initial phases of drug discovery	+ Dose exploration possible	– Statistics not agreed upon
+ Minimizes time commitment for patients	– Requires large N; typically multiple centers	+ Smaller N possible to demonstrate efficacy	– Possible sequence or carry over effects
+ Standard statistics readily available	– Placebo exposure mandated for a portion of subjects	+ Placebo periods can be dropped in non-responders	– Uncertain number of N-of-1 studies sufficient to demonstrate efficacy
+ Controls for group-oriented confounds	– Focus on overall group response	+ Less prone to type II errors	– Extended time commitment required of patients
+ Relatively easy interpretation of results	– Confounds individual & placebo response assessment	+ Less expensive	– ‘Off’ trials risk illness exacerbation
+ Potential for demonstrating assay sensitivity	– Only half of patient population available for biological and predictor studies	+ Can be conducted at one site	– Ethical issues about giving placebo
+ Less prone to type I errors	– Focused entry criteria and homogeneous samples	+ Patient as own control	– Group-oriented effects more difficult to examine
+ Ability to stratify samples	– Dose schedule usually predetermined	+ Wider entry criteria feasible	– Potential for unplanned crossover effects
	– Costly and difficult to manage	+ Trial length can be individualized in individuals	
	– No guarantee of active medication exposure for all patients	+ Response can be confirmed in individuals	
	– Ethical issues about giving placebo	+ All patients available for biological and predictor studies	
	– No comparative information for clinicians	+ Causality of side effects may be established and confirmed	
		+ Comparison of response to multiple medications possible	
		+ Suitable for high risk populations with refractory illness	

now more recently for adjunctive treatment in bipolar depression, one would hope that other innovative designs would also increasingly be acceptable to the FDA.

Another potential liability of the B-A-B-A design is that the statistics for analyzing such data are not widely agreed upon, although there are multiple approaches to this problem, several of which we will list and illustrate below. A further liability is not only the possibility of sequence and carryover effects being a problem, but it is also possible that a patient who has a bona fide response to a given active agent will not show a relapse during the off phase, either because the episode is over, the illness cycles are not rapid enough, or the unusual instance in which the drug has a much more long-term therapeutic effect than its actual duration of time in the body at appropriate pharmacokinetic levels.

In the face of a series of positive N-of-1 studies, one may also be at a loss to decide the appropriate threshold for the number of such positive individual responders observed in order to consider a drug efficacious enough to promote the development of a large RCT or, in some instances, directly win FDA approval. Busk and Serlin [70] suggest N-of-1 trials can be aggregated to provide evidence of an overall drug effect even in special populations such as those with treatment resistance.

Lastly, such a design is only feasible in the face of chronic treatment-resistant phases of illness when attempting to show appropriate degrees of clinical improvement and exacerbation during the B-A-B-A design, or in instances when the illness is extraordinarily rapid cycling in such a manner that clear-cut off-on-off-on differences can be readily assessed.

8.9 Statistical analysis of N-of-1 trials

Statistical approaches to analyzing off-on-off-on data are made easier with such ultra-rapid fluctuations. Gentile *et al.* [71] and others have made the argument that treating these within-subjects data on extreme mood fluctuations as emanating from the individual as ‘a random events generator’ can lead to the appropriate application of analyses originally intended for completely independent events. Issues of autocorrelation can also be addressed at the beginning of the statistical analysis [72].

Many of these approaches have been illustrated in some detail in McDermut *et al.* [67] and overviewed in our paper on unique design issues in clinical trials for patients with bipolar affective disorder [1].

- 1 In the simplest iteration for a patient with extremely rapidly fluctuating moods, one could use the chi square technique and look for a percentage of days euthymic while on placebo versus on active drug. If the drug appears to be effective, one could then proceed to a second placebo and active phase in days euthymic aggregated for placebo versus active treatment and subject to straightforward chi square analysis.
- 2 Another method was described by Gentile *et al.* [71] and also involves aggregating all of the data from each on-drug phase and each off or placebo phase and then performing between group t-tests on whatever rating scales are being used.

This approach is obviously less useful when there are major time trends in the data and one is examining a patient who is gradually improving or deteriorating during the repeated on-off phases.

- 3 When there are substantial time trends in the data, however, one might consider Winer's Z approach which calculates a mean symptomatology score for each separate phase and compares it sequentially to the next phase with a t value [73]. In a $B_1-A_1-B_2-A_2-B_3-A_3$ design there would be five different t values at each off-on or on-off transition point for any given rating. Similar to a meta-analysis, each of the five t values could then be summed in an overall Z score computed that represents the overall efficacy of a drug for that patient. Any changes that ran contrary to the hypothesized direction of improvement for a drug would result in a lower total Z score.
- 4 An alternative approach to Winer's Z when there are major time trends in the data was suggested by Chassan [72]. A regression line should be determined with the mood ratings as a dependent variable and time as the independent variable. Then the mean of the residuals (the difference between the actual score and the time-trend line) from the intervention phases can be compared to the mean of the residuals from the baseline and placebo phases using a t -test.
- 5 Multiple other approaches can be used and analyzed with these types of data. Krishef [74] discussed the use of the Mann-Whitney U , the R_n statistic, the W statistic, celeration line, Stewart chart procedure and the C statistic. Richards *et al.* [75] discussed time series and randomization tests, while Zucker *et al.* [76] demonstrated a Bayesian approach.

8.10 Statistical approaches to estimating necessary trial durations in individual patients

Further potential liabilities of the B-A-B-A trials in individual patients relate to questions of how long a trial phase should last. If this can be estimated mathematically, it would help mitigate the problem that the clinician may be biased in shortening or lengthening the trial in order to optimize an expected effect. These kinds of approaches may also be particularly helpful when there is extreme variability in cycle frequencies between patients to be entered in the trial, such that slower cycling patients may require longer on-drug trials than those who are showing ultra-rapid or ultradian cycling. Again, all of these techniques make use of the patients' baseline as their own control, so that even large degrees of variability across patients can be dealt with accordingly. Some of the methods are relatively easy to use and apply [77]. They are also equally appropriate for making decisions on the necessary duration of the inactive or off phase estimates, and can also be utilized to help minimize the length of the off or placebo phases. Examples of these include the following:

- 1 One can utilize the ratio of number of episodes observed over a previous baseline period to generate an expected number of episodes during the treatment

period. Using a chi square, minimum trial duration can be determined based on comparisons of likelihood of no or N numbers of episodes versus the expected number in that given time period. This method can also be used to evaluate a trial after it has been completed [78].

- 2 Similarly, one can examine the ratio of euthymic to non-euthymic days over a baseline period and the period over a drug trial, again using the chi square statistic to predict the number of days needed to see a significant effect for a pre-specified degree of reduction, such as 50%, in non-euthymic days.
- 3 The standard deviation of episode duration or of the previous euthymic intervals can also be used. In this fashion, any decrease in episode duration or increase in euthymic interval that is likely to occur less than 5% ($\alpha = 0.05$) of the time (which is just under two standard deviations) can be considered as a significant deviation from the baseline distribution.
- 4 The sequential probability ratio test (SPRT) can be used to create a confidence interval using baseline means and variances, expected changes from the mean and desired alpha and power levels (see examples in [77]). If the cumulative sum of the observations deviates outside of the confidence interval the trial can be halted [79, 80].

Much more complicated mathematical approaches to estimating necessary trial lengths are available and discussed elsewhere. These might include Markov chain analyses, predictions from chaos theory [81] or computer simulations.

8.11 Crossover trials for enhancing clinical informatics and statistical power

March *et al.* [18] and many others have advocated for greater use of practical clinical trials in order to generate data more pertinent to clinical decision making, as well as facilitate data acquisition with easier to perform and less expensive clinical trials. One of these approaches would be a randomization to two active agents for an initial examination of effectiveness and tolerability. Then, non-responders to either treatment could be crossed over to the other treatment. In a potential third phase, non-responders to either monotherapy could then be randomized to a combination of the two initially-studied drugs compared to a third new intervention. These kinds of practical clinical trial approaches that not only more closely follow clinical decision making, but would help inform it, have been widely used in the STAR-D, STEP-BD, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Stanley Foundation Bipolar Network attempts to study real patients more longitudinally and begin to ascertain what might be the most effective treatment approaches for eventually achieving sustained responses and remissions.

Another more formal alternative is to systematically crossover all patients to a given set of treatments. These kinds of designs have often been met with global

statements that they are discredited, partially based on the critique of Brown [82]. However, many statisticians have made the opposite argument and favor the more clinician- and patient-friendly characteristics of the crossover design compared to the traditional RCT. Laska *et al.* [64] make the point that ‘the increased power of crossover designs and the ability to study all patients on an active agent for generating clinical and neurobiological markers and correlates of clinical response, together outweigh any of the potential liabilities of crossover designs such as sequence or carryover effects’.

An illustration of an even more complex example of such a study is that of Frye *et al.* [41] and Obrocea *et al.* [42]. In these instances, all patients were exposed in a randomized double-blind fashion to three different phases of treatment for an intended six weeks. This included exposure to a placebo, lamotrigine and gabapentin. There was a two-week interval between each phase for taper and upward titration of each agent, and each intended six-week phase could be attenuated if there was substantial clinical worsening (which did, in fact, occur in several instances). Later, when the blind was broken, these exacerbations typically occurred in the placebo phase. In this design, one could then examine moderate to marked response rates on different CGI improvement scales for those who finished all three phases of the crossover study. In this instance, there was a 53% (19/36) overall response for lamotrigine, 28% (10/36) for gabapentin and 22% (8/36) for placebo, which was significantly different by Cochran’s Q ($p = 0.014$). Post hoc analysis revealed that lamotrigine was superior to both gabapentin and placebo.

The cross-over studies also demonstrate the increased statistical power derived from exposing all patients to each drug or phase, as opposed to the traditional RCT. In the case of the study described above, if one examined only the patients randomized to the first phase, that is, a potential traditional parallel three group comparison study of lamotrigine vs. gabapentin vs. placebo, the same general clinical response trends would have been revealed, but they would not even approach the statistical significance demonstrated in the crossover design in this relatively small one-center study.

Figure 8.1 illustrates the differences in minimal sample size required for a given effect size. If one has a large effect size, for example where d equals about 0.80, only 15 subjects would be required in a one-sample crossover design study in order to achieve a two-tailed $\alpha = 0.05$ and power = 0.80. However, in the traditional parallel group, two-sample design, 26 subjects/group (i.e. a total of 52, or more than three times that required in the crossover sample), would be required. With a medium effect size of 0.5, a one-sample design would require 34 subjects, but the two-sample design would require a total of 126 subjects, or 63 patients per group. The figure illustrates that the crossover trials only need about 25% of the number of patients that are needed in the parallel design trial [83].

This increased power, as well as having all of the subjects exposed to each treatment in an intensive neurobiological investigation, may be invaluable. In this fashion one could efficiently study a variety of measures that may be associated with prediction of clinical response or examine neuropathological effects of the illness interacting with drug effects.

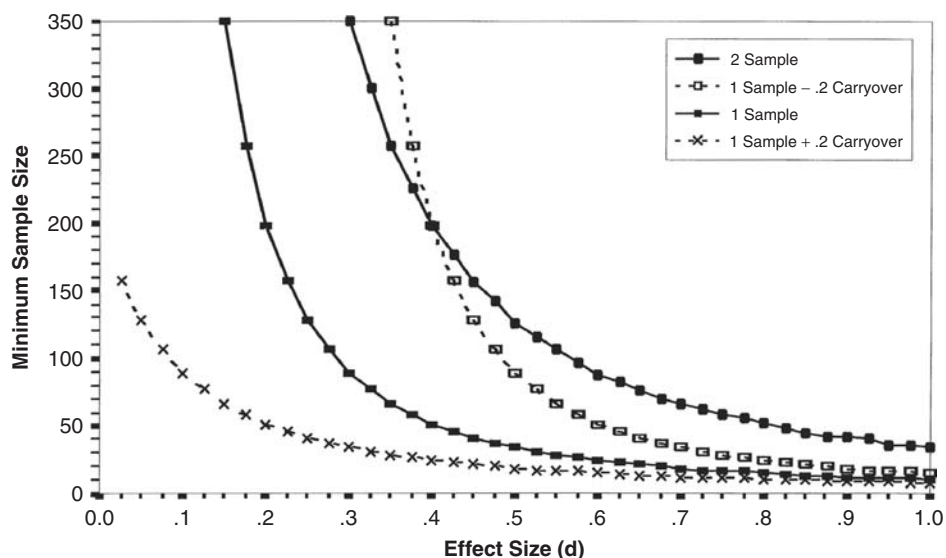


Figure 8.1 Graph depicting minimum sample size for one vs. two sample studies.

For example, in the above-mentioned study on lamotrigine, Obrocea *et al.* [42] were able to identify a variety of clinical predictors of who might respond to lamotrigine, which was significantly more effective than either gabapentin or placebo on the CGI improvement scale for depression. In this instance, even though lamotrigine was more effective than the other agents in this highly treatment-resistant subgroup of patients, the analysis with all patients exposed to lamotrigine revealed that those with the greatest number of prior clinical trials and hospitalizations for depression were significantly less likely to respond to lamotrigine. Several correlates of response to gabapentin were of interest and deserve further investigation, including more positive responses in those with younger ages of onset. Interestingly, the only correlate of placebo responsiveness was those with lower levels of baseline anxiety.

Such exposure of all subjects to each agent also allowed the concurrent assessment of a variety of potential neurobiological correlates of the pharmacological effect of a drug or of treatment response, using studies of cerebrospinal fluid (CSF) and functional brain imaging with positron emission tomography (PET) imaging conducted in each of the three phases. None of these preliminary assessments of potential moderators or mediators of response (see discussion below) would have been possible without a design allowing all patients enrolled in the study to be exposed to each treatment.

In addition to the statistical and research benefits of this unusual crossover design on a tertiary clinical research unit, one other novel design component was utilized in this clinical trial which illustrates the potential utility of additional longitudinal examination of individual patients in order to help ascertain and confirm clinical responsivity to a given agent. After all three of the six-week crossover trials had been accomplished, there was a fourth phase called 'response confirmation' in which

the patient and clinician who were blind to treatment assignment returned to the phase that appeared to be the most effective for that patient. If the patient again showed substantial improvement as he/she had in the first exposure to that phase, one would have much greater confidence in that individual's responsivity to that agent employed. The magnitude of the improvement assessed during each exposure could then be incorporated into an overall CGI-BP rating.

A fifth phase iteration was also included in this study design [41, 42] where, if the patient did not show substantial improvement or remission upon re-exposure to the best of the three previous phases in the phase four response confirmation, one could add the other active agent, that is, lamotrigine to gabapentin or vice-versa. Since all patients, investigators and nursing personnel on the unit were blind to which phase involved which treatment, at this point a non-blind clinical trial pharmacist was consulted in order to confirm that the adjunctive trial was one of the two potentially active pharmacological agents and not exposure to a placebo augmentation trial. In this fashion, using the combination of lamotrigine and gabapentin in phase five, we were able to show that a substantial number of partial monotherapy responses such as minimally improved (a C) or much improved (a B) on the CGI-BP, could be converted to more complete responses or a very much improved rating (an A or essential remission) on the CGI-BP.

This last phase was the first part of a response optimization phase of the research hospitalization during which every attempt was made to help patients (who had just made major contributions to the research effort in formal clinical trials) reach an improved or remitted state prior to their discharge from the hospital [51]. In the case of partial to excellent responders to gabapentin and/or lamotrigine, this could naturally evolve from their formal double-blind clinical trial, but could also involve alternative agents for the non-responders (thus making clinical use of even a lack of clinical response to a given agent to further inform a patient's subsequent individual clinical therapeutics). Trials containing a combination of traditional experimental designs and observational studies have also been endorsed elsewhere [84, 85].

8.12 Carryover effects

The complicated multiple crossover trial discussed above, as well as more simple single crossovers, bring about concerns regarding the effect of carryover on response rates and the greater potential for drop-out with a longer study period, as emphasized by Brown [86]. However, there are some additional advantages of the crossover design. In contrast to the parallel group trials, an investigator need not assume and demonstrate that the two randomized groups are not different on the basis of demographics, illness severity course or pattern of presentation at baseline, since patients act as their own control throughout the study.

While carryover effects are clearly a potential problem in the crossover trial, it is also noteworthy that unintended carryover effects can still occur in parallel group studies in which treatment responsivity or non-responsivity to previous drug exposures is rarely considered in the RCT. The study of Gelenberg *et al.* [87] originally

concluded that higher doses of lithium were more effective than lower doses (albeit at the cost of three times greater side effects burden). However, Perlis *et al.* [88] found that prior lithium status was the major determinant of the outcome. Those who were (originally unknowingly) switched from high to low lithium assignment with the randomization fared poorly, while those who had been on low lithium prior to the study and were randomized to the low lithium group showed very good responses.

In the lamotrigine/gabapentin/placebo crossover trial, we had attempted to minimize carryover effects with a two-week washout period between phases. In addition, statistical approaches can be used to take the carryover effects into account [89]. If we factor the possibility of small to moderate carryover effects into the calculation of the required sample size for a study, however, the crossover design still tends to require a smaller sample as illustrated in Figure 8.1. When the carryover effect accounts for the equivalent of a small effect size, the crossover design still continues to require many fewer participants than the two-sample study until the total sample required reaches about 200. It is only when there is a substantial amount of carryover effect that the parallel group design begins to require a smaller sample size than the two-sample design.

8.13 Long-term trend in studies of bipolar disorder compared to other major mental disorders

In 1989 and 1994 the NIMH sponsored meetings in an attempt to elucidate the reasons for the relative deficit in the clinical trials portfolio in bipolar illness that had been long recognized, and to develop potential solutions [35, 36]. The McArthur Foundation sponsored a similar meeting in 1992, and at all of these meetings one of the more prominent reasons enumerated for the deficit in clinical trials was lack of agreement about optimal clinical trial design and rating instruments. In the 1994 meeting, John Rush MD summarized some of the recommendations from the two prior meetings, nicknamed ‘Rush’s Rules’ for easy recognition.

Among the recommendations was the inclusion of BP-I, BP-II and BP-NOS subtypes in treatment studies. Since BP II and BP-NOS are debilitating and are as (or more) prevalent than the estimated 1% incidence of BP-I in the general population, they should not be excluded from study. Despite these recommendations, there have been extraordinarily few studies targeting these highly prevalent populations with BP-II and BP-NOS subtypes. The same recommendation for inclusion was for patients with substance abuse, anxiety and other comorbidities which are extremely common in the illness, as noted in the introduction. Rush also recommended including patients with varying cycle frequencies, a theme on which we have frequently commented on in this manuscript. He also advocated the development of a standardized outcome assessment package and a development of consensus on choices of acceptable longitudinal rating instruments. A general recommendation was that the list of acceptable design strategies be broadened so that other approaches besides the traditional parallel group RCT could be more widely used. These include crossover,

mirror image and equipoise stratified designs, head to head comparisons, adaptive and the many other designs alluded to here and elsewhere that would provide more clinically useful information to treating physicians [27, 90].

Most of these recommendations were endorsed by many others [1, 18, 91]. Recently, Gelenberg *et al.* [26] recommended new design approaches in studies of unipolar depression, including the use of adaptive clinical trial designs in which clinical decisions and adjustments in clinical care are based on threshold-dependent algorithms that reflect individual patient's needs, as well as the mechanism of action of the drug being tested and the expected response times. They suggested that benchmarks be established in advance, such that timeframes and symptomatic criteria for clinical decision making (such as when to raise or lower a dose, augment or switch treatment strategies) are clearly delineated.

In spite of these multiply-iterated consensus recommendations summarized above under the rubric of Rush's Rules, there has been very little progress in any of these areas. Indeed, it is sad that at this juncture of more than 50 years after the beginning of the psychopharmacological revolution that we do not know, for example, what are the best treatment approaches to acute bipolar depression. Comparative trials of mood stabilizers, atypical antipsychotics or adjunctive antidepressants have rarely been conducted. This lack of progress is not only reflected in the continued undersized pharmacological-trials portfolio for bipolar illness compared to other major illnesses such as schizophrenia or depression, but this problem has now carried over in an even more disturbing fashion into the area of clinical treatment trials for childhood-onset bipolar illness.

8.14 Parallel and pressing design issues for childhood-onset bipolar illness

There is increasing recognition that this illness now exists in very young children [92], is highly disabling over 8 years of follow up [93], difficult to treat, requires long periods of time to achieve mood stabilization [94], and often requires complex treatment combinations [95, 96]. However, there is an extraordinarily sparse clinical-trials portfolio and few systematic comparative clinical trials to assess relative effectiveness and tolerability of even widely used agents to assist in clinical decision making.

Many of the difficulties that have enumerated in studying adult-onset bipolar illness are mirrored, if not multiplied, in young children. Both their youth and the diagnostic controversies continuing around the precise thresholds for a bipolar diagnosis (particularly for the most controversial BP-NOS presentations) have, again, contributed to this shortfall. The pharmaceutical industry has recently conducted RCTs of essentially all of the atypicals and found efficacy in children generally ranging from ages 10 to 18, such that some of these agents are now FDA approved [97].

However, how these agents should be deployed and sequenced in relationship to other widely used mood stabilizers (such as lithium and the anticonvulsants, valproate, carbamazepine and lamotrigine) has not been studied. Developing an easier

to conduct series of practical clinical trial designs would appear to have much merit for this particular population, especially when parents may have some reluctance to enter children into RCTs involving a placebo arm [2]. Practical clinical trials have been endorsed by March *et al.* [18], Post and Kowatch [91] and by the American Academy of Child and Adolescent Psychiatry (AACAP) 2006 research forum entitled: ‘Advancing research in early onset bipolar illness: barriers and suggestions’, as summarized by Carlson *et al.* [98].

8.15 Contradictory balance between inclusiveness (for generalizability) and homogeneity (for efficacy)

One of the reasons that few of the recommendations of prior NIMH and McArthur conferences on design strategies in bipolar illness have been carried out is that there is an apparent incompatibility between the use of designs and populations that are most clinically informative and the statistical and analytic requirements for a successful study. How one deals with the inclusion of BP-I, BP-II and BP-NOS patients (and their comorbidities) in the same study feasibly and statistically is not readily apparent.

In a recent NIMH-convened meeting (the Bipolar Statistical Summit: Methodologies to Advance Long-Term Intervention Trials chaired by Charles L. Bowden MD at the National Library of Medicine in Bethesda, 29 October 2008), Joseph Calabrese MD raised the question of how one could deal statistically with the inclusion of more representative patients with one or more comorbidities into clinical trials without sacrificing clinical power. Distressingly, this question was never clearly answered at the statistical summit. While one approach might be to stratify for bipolar patients with and without a given comorbidity, this conflicts with the general recommendations to stratify for as few variables as possible in order to limit loss of power in a given study.

8.16 Assessing moderators and mediators

Kraemer *et al.* [99, 100], Hinshaw [101] and Gelenberg *et al.* [26] discuss the importance of delineating moderators and mediators in efficacy studies. Problematically, however, is the concomitant need for extremely large N in order to accomplish this clinically critical task. Moreover, treating a comorbidity as a potential moderator variable requires a second study to definitely demonstrate the effect, that is, that patients with a given comorbidity would be less likely to respond to a given treatment than those without. A moderator variable is thus something identified and measured prior to randomization as a pretreatment variable that might have an effect on the treatment outcome. This could include age, gender, psychiatric or medical comorbidity and so on.

In contrast, a mediator variable is one that would be observed over the course of the treatment trial that may influence the outcome. For example, the effectiveness of treatment of a mother’s depression could influence the response of a child entered into a clinical trial of the efficacy of an agent for an externalizing disorder, such as

attention-deficit hyperactivity disorder (ADHD) or an internalizing disorder such as anxiety or depression. While substance abuse comorbidity might be a presumed moderator variable in clinical treatment trials of those with bipolar illness, it is also possible that the degree of clinical improvement observed during the trial could be a mediator variable for whether or not a primary substance abuse outcome is improved. In the case of comorbidities, separating moderator and mediator variables would appear to be of considerable import and begin to allow better delineation of most appropriate treatments.

In any of these instances, including more representative patients in the clinical trial does appear to increase design complexity and potentially reduce statistical power for assessing the main efficacy outcome. These design attributes and difficulties perhaps reflect the pharmaceutical industry’s almost universal choice to deal with highly selective and more homogeneous patient populations in classical RCTs in their attempts to register a new drug. However, while this is most appropriate from a registration perspective, it stands in marked contrast to designs to generate information to better inform clinical decision making. Leon [102] and Kraemer and Kupfer [103] also make the point that the increasing use of effect sizes and number needed to treat (NNT) or number needed to harm (NNH), as illustrated in Table 8.2, are highly dependent upon the population studied, and that NNT and NNH may be virtually useless without appropriate weighing of these variables and the severity of the consequences of non-treatment. To these ends, alternatives to the RCT should be supported by the NIMH and other funding sources, as pharma is relatively unlikely to proceed in this direction.

Table 8.2 Summary of effect size and related bench marks [104].

	Cohen’s D	AVC	SRD	NNT
Small	0.20	0.56	0.11	8.89
Medium	0.50	0.64	0.28	3.62
Large	0.80	0.71	0.43	2.33

A problem with this highly recommended approach, however, is that many internal NIMH review committees and those from other outside funding agencies continue to view the traditional RCT as the platinum standard for the field, and view many of the more clinically informative trial designs as unworthy or inferior. These alternatives are therefore rarely supported. We have also seen this occur repeatedly in intermediate investigator awards from National Alliance for Research on Schizophrenia and Depression (NARSAD), one of the largest funding alternatives to the NIMH. In these instances, reviewers tend to reject more informative and practical clinical trial designs and are more likely to support RCTs with a traditional placebo parallel group as more sophisticated, orthodox and elegant.

Hinshaw [101] concluded that: ‘Treatment research in the future should explicitly consider the exploration of moderator and mediator variables, which can greatly aid the explanatory power of clinical trials and specify the critical next steps for

intervention research'. This is particularly important in bipolar illness clinical trials in which potential moderator and mediator variables are all too plentiful. When establishing a moderator variable (which requires that there is a statistical interaction between the moderator variable and the predictor variable), this also immediately raises the issue of how to better deal with that given moderator in subsequent clinical trials. That is, if the presence of an anxiety disorder comorbidity is found to be an important mediator of a less good response (to lithium for example, as the bulk of the evidence would now suggest), the next obvious pressing clinical question is to what sets of treatments such patients may, in fact, respond.

Similarly, moderator variables have now been extended to include genotypes and single nucleotide polymorphism (SNP) profiles, which are expected to help with the prediction of differential responsiveness of individuals to individual medication interventions. Once more, we are faced with the need for rather large N clinical trials in order to begin to ascertain what is likely to be the first fruits of the molecular genetics revolution in the form of personalized medicine.

Both moderator and mediator tests are explanatory, exploratory and comprise secondary analyses to generate hypotheses for the next set of potential series. Hinshaw quotes Kraemer *et al.* [100] in indicating that, all too often, such analyses are viewed pejoratively as 'fishing expeditions' and are looked at askance by both granting and manuscript review bodies. Instead, Hinshaw [101] and Kraemer *et al.* [100] stress the necessity of probing for subgroups for which treatments optimally work (moderator variables) and examining the processes by which treatments exert effects (mediators). In this fashion, it is stressed that these types of examination help bridge the large gap between theory and practice. Hinshaw states

There is often a balance between the typical goal of an efficacy study – to generate internally valid conclusions regarding the precise effects of treatments on relative outcomes, which suggest narrow homogeneous samples – and the more ecologically valid objectives of effectiveness studies related to having diverse samples that yield (a) external validity and generalizability of findings and (b) tests of key moderator-defined subgroups. . . [101]

8.17 Conclusions and implications

From the foregoing discussion we can readily see that bipolar illness is a poor match for the traditional RCT, providing little of the needed clinical information about responsive subgroups and best sequences of treatment, and what to do if a given treatment fails. The fact that the design strategies require large numbers of children or adults with bipolar illness to provide effectiveness data is generally viewed unfavorably by grant review bodies. A third liability is that even in a well-designed efficacy study that includes latitude for exploring moderator and mediator variables, there is a need for a follow-up study in order to further validate the variables identified, as well as (of critical, but usually unstated, importance) a second or third set of follow-up studies in order to begin to address what might be more successful treatments for those subgroups who have been identified as unresponsive.

Altogether, these problems indicate both the contradictory nature of the design issues differentially required for efficacy versus effectiveness studies, but also yield the unfortunate conclusion that there is also a huge political/administrative/funding gap that so far has proved to be unbridgeable. That is, even if we were to design ideal studies, they would likely not be funded in the current environment and, if they were funded, the necessary follow-up studies would likely not occur.

Clinicians, academicians and statisticians can continue to recommend what might be more ideal clinical design and analytic strategies, but without a resolve to systematically address these problems, which are particularly pressing for adults and children with bipolar disorder, little progress is likely to be made (as has been demonstrated by the last quarter century of understudy of adult-onset bipolar illness).

What are some of the potential solutions to this deficit of clinical treatment trials in the bipolar disorder impasse? One solution is to provide a certain amount of money that is mandated to be spent directly on bipolar illness in children and adults so that the endless disagreements about the most ideal study designs do not preclude the conduct of almost any study in the extramural grants program. A related solution is to mandate the Substance Abuse and Mental Health Services Administration (SAMSHA) to spend a certain amount of its money targeted toward treatment of bipolar illness *per se* and specifically effectiveness trials. A third possibility is to have an entire new national initiative for research in bipolar illness similar to that initiated some 30 years ago for schizophrenia, with much success. Based on the results of that initiative, there are now multitudes of comparative clinical trials of virtually every antipsychotic treatment against every other one. Because of this, the exploration and understanding of the neurobiology of schizophrenia has also proceeded at an extraordinarily rapid pace.

Fourth, establishing a clinical trials network for children with early-onset bipolar disorder would do much to meet many of the recommendations of the AACAP working group [98] for children, parents and clinicians to have a modicum of systematic treatment outcome data from which to base their clinical decision making. Re-establishing the adult STEP-BP network would also be a step in the right direction because, despite some of its pitfalls, it has produced important new findings and identified areas of great need for further research. A new network could be further enhanced by the experience of the original.

Finally, and reluctantly, one must consider direct lobbying of Congress to provide the monies for such types of studies, particularly given the paucity of treatment efficacy and effectiveness studies for childhood-onset bipolar disorder. Hinshaw [101] designed, carried out and published the near ideal 'multimodal treatment study of children with ADHD' only after an intensive lobbying effort in Congress was successful. The study included some 579 children who were randomized to one of four groups with sufficient N to examine a variety of moderator and mediator variables. Briefly, the study found for the outcome of improved ADHD symptomatology that the (i) medication management and (ii) combined medication and psychosocial treatment groups proved superior to either (iii) behavioral treatment or (iv) community treated controls. For virtually all the other five outcome domains, the most consistent finding was that the (ii) combined treatment group yielded significantly more improvement

than (iv) community controls, that is, delivered naturalistically in the community. Since we now also know that naturalistic treatment of childhood-onset bipolar illness in the community yields extraordinarily poor short-term (and apparently long-term) outcome [93], defining more optimal treatment strategies is imperative. Interestingly, Hinshaw [101] found that the subgroup of children with ADHD and comorbid anxiety disorders had a preferential response to behavioral treatments.

We raise the issue of this groundbreaking study for ADHD in this context because Congress had to be lobbied directly in order to make the funds available. It apparently took the persistent efforts of Peter Jensen MD in order to acquire the funding for this classic study. Jensen is no longer at the NIMH and no-one with the motivation or political connections to make such a needed lobbying effort for treatment research in bipolar disorder appears to be available. Therefore, it is likely to take the lobbying efforts of some outside set of forces in order to bring to fruition even a modicum of the necessary studies to guide clinical treatment of childhood- and adult-onset bipolar illness.

Some might argue that the inclusion of these types of statements about funding recommendations and potential strategies to achieve such an end is not appropriate in a chapter on clinical trial designs for bipolar disorder. However, as we have seen, the recommendations for what one might consider an ideal clinical trial design for a given study are not only extremely varied and controversial but, in many instances, contradictory. Without adequate recognition of these conundrums and concerted action to resolve or circumvent them, very little of the data needed to drive clinical therapeutics of adult- and childhood-onset bipolar illness in a more ideal direction will likely be forthcoming in the near future. We endorse the general principles and guidance offered in 'Rushes rules' summarized above, and hope some of the unique design issues for bipolar illness that have been reviewed and discussed will help facilitate a wider range of studies of this difficult-to-study disorder.

After this manuscript was completed, a series of important papers were published in the December 2009 issue of *Psychiatric Annals* (Volume 38(12)) on 'Design and Analysis of Longitudinal Studies' (guest editor Robert D. Gibbons PhD), which are highly recommended. The articles include topics such as sample size [105]; intent to treat and non-adherence [106]; missing data [107]; analytic issues [108] and balancing treatment comparisons [109].

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9

The Utility of Low-dose Antidepressants

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Abstract

In recent years, there has been increasing evidence that antidepressants are effective even in doses that are lower than those suggested for their chief indications (depressive and anxiety disorders). Besides being effective, low doses are associated with lesser side effects than standard dosage. In addition, low doses of antidepressants may produce effects that go beyond those associated with the remission of the clinical conditions for what they are usually prescribed. In this chapter, we review evidence surrounding the use of low doses of antidepressants for insomnia, gastrointestinal problems, chronic pain, hormonal-related issues, premature ejaculation, movement disorders, attention and memory deficits and emotional instability. Additionally, aspects related to emotion regulation by low doses of antidepressants in healthy individuals are highlighted.

Key Words

antidepressants; low doses; extra-therapeutic effects

9.1 Introduction

Antidepressants are prescribed extensively around the world and there is undeniable evidence of their efficacy in many conditions as well as their classical prescription for depressive, obsessive-compulsive and anxiety disorders. In this chapter, we review the usefulness of antidepressants in low doses for their chief indications and their utility for a number of other conditions and discuss the potential for low doses of antidepressants to enhance emotional regulation in healthy individuals.

9.2 Low dose antidepressants for chief indications

There is renewed evidence for the use of antidepressants in doses that are lower than shown in their labels or text books for their chief indications. Low doses may not only be effective for many patients but produce less side effects than standard doses. A systematic review and meta-analysis of 35 studies that enrolled 2013 participants compared low doses of tricyclic antidepressants (75–100 mg/day) with placebo and six studies compared low doses with standard doses of tricyclics for depressive disorders. In low doses, tricyclics were significantly more likely than placebo to elicit response at both 4 and 6–8 weeks, whereas in standard doses tricyclics produced more dropouts due to side effects but were not more effective than low dose tricyclics [1]. Critics of this meta-analysis pointed out several potential flaws including the poor methodological quality of some of the studies, as many of the trials took place when diagnostic and outcome criteria were not sufficiently standardized. There was concern that its conclusions could be misinterpreted, deterring the prescription of recommended doses of tricyclics and leading to failure to adequately treat depression.

Similar results have also been reported for panic disorder [2]. High and low doses of clomipramine were compared to placebo in 180 patients with panic disorder, with or without agoraphobia. The doses were equally effective and the lower dose elicited fewer side effects [3]. A low dose of venlafaxine (47 mg/day) was proven effective in panic disorder [4].

One possible explanation for the effectiveness of low doses of antidepressants is pharmacokinetic differences, such as a higher inclusion of slow (or poor) metabolizers in some studies. Most antidepressants are metabolized by CYP2D6. The variant allele CYP2D6*4 is the main polymorphism resulting in reduced enzyme activity in Caucasians. It is suggested that these individuals may need lower doses than subjects without this allele [5]. This hypothesis, however, has not been tested.

9.3 Antidepressant use for other indications

Insomnia

Approximately one-third of adults report sleep problems and half of them rate their insomnia as severe, impairing the quality of their lives. Acute (transient or intermittent) insomnia tends to be self-limited and is associated with acute illnesses, travel and stress. Sleep hygiene techniques are frequently all that is required to solve acute insomnia. Yet chronic insomnia is more complex symptom, and may require specific treatment. Sedative-hypnotics may worsen sleep apnea or are associated with abuse/dependence. Therefore, it is sometimes preferable to use a low dose of a sedating antidepressant, such as trazodone, mianserin or mirtazapine, as (differently from traditional hypnotics) they do not depress respiration and have low abuse potential. Although uncommon, one serious adverse effect of trazodone is priapism [6–9]. Another option in geriatric populations is the use of doxepin, a tricyclic antidepressant, in low doses (1–6 mg/day) due to its antihistaminic (H1) properties [10].

Gastrointestinal problems

Pain associated with functional gastrointestinal problems such as those originated in the esophagus (functional chest pain), the stomach (functional dyspepsia) and the colorectum (irritable bowel syndrome) is often treated with low doses of antidepressants. Patients suffering from these disorders may or may not have concomitant depressive and anxiety symptoms. The mechanism of action of antidepressants in these functional disorders is unclear but seems to be independent of their 'antidepressive' effects.

Functional chest pain of unknown origin represents an important medical problem that may affect over 13% of people, leading to a high number of cardiac catheterizations performed. Tricyclic antidepressants and trazodone are good options for acute chest pain [11].

Chronic nausea and/or vomiting are frequent symptoms that are related to a functional gastrointestinal disorder (also called functional nausea and vomiting). Often no definable organic cause is found. Symptoms may be severe at times and usually respond to low doses of tricyclic antidepressants independently of the concomitant presence of depression [12, 13]. The mechanism of action whereby tricyclics ameliorate nausea and vomiting is not entirely clear. It probably involves histaminic, anticholinergic and serotonergic actions that are at the basis of the vomiting process. Also, an increased tolerance to aversive visceral sensations might be involved [14].

Mirtazapine, an antidepressant that selectively blocks the 5-hydroxytryptamine₃ (5-HT₃) receptor, promotes antiemetic effects that have been successfully used in nausea associated with chemotherapy and pregnancy, as well as post-operative nausea. Doses as low as 7.5 mg/day have proven to be effective within a few days of its introduction [15].

Irritable bowel syndrome is characterized by symptoms of altered bowel motility and abdominal discomfort or pain. Symptoms are related to hypersensitivity to stimulation and central pain regulation is involved. Studies have shown that amitriptyline reduces brain activation during rectal distension in patients with irritable bowel syndrome, particularly in cortical regions associated with affective and cognitive components of pain. Hence, the analgesic effect of amitriptyline is centrally exerted by a reduction of the affective component of pain [16]. Low-dose amitriptyline (20 mg/day) has also been used successfully in patients suffering with idiopathic fecal incontinence, probably due to its antimuscarinic actions that improve the anal sphincter function in these patients [17].

Chronic pain

The analgesic properties of tricyclic antidepressants in low doses have been recognized for several decades. The efficacy of amitriptyline 25 mg/day appears early after its introduction in cases of chronic pain and the mechanism of action is independent of its antidepressive action [18]. It was previously the only drug with proven efficacy for the prophylactic treatment of chronic headache, and its analgesic efficacy involves both serotonin reuptake and increased noradrenergic neurotransmission. Amitriptyline (25–50 mg/day) has also proven effective in relieving postoperative neuropathic

pain in women with breast cancer [19] and in chronic generalized musculoskeletal pain often diagnosed as fibromyalgia [20, 21].

Low-dose antidepressants such as trazodone (50 mg/day) have been extensively used in painful polyneuropathic diabetic patients [22]. Animal studies and case series suggest that mirtazapine with its serotonergic and noradrenergic properties may be useful in chronic pain conditions such as migraine and tension-type headaches [23, 24].

Hormonal-related issues

Hot flashes are frequent and bothersome among menopausal women and even more so among breast and prostate cancer survivors. They are associated with negative mood, fatigue and sleep problems, compromising overall quality of life. Selective serotonin reuptake inhibitors (SSRIs) and/or serotonin and noradrenergic reuptake inhibitors (SNRIs) are widely used in the treatment of hot flashes. Controlled studies suggest that venlafaxine and paroxetine are more effective than placebo in decreasing frequency and severity of hot flashes. Paroxetine at 10 mg daily dose is particularly useful for menopausal women with no history of breast cancer [25]. Because paroxetine is a powerful inhibitor of CYP2D6, which metabolizes tamoxifen, a selective estrogen receptor modulator frequently used to treat breast cancer in women and men, venlafaxine (which is a weak inhibitor of CYP2D6) is preferable to paroxetine in breast cancer survivors. In low doses (such as 10 mg daily), it has been used successfully for prostate cancer men undergoing androgen-deprivation therapy [26]. Compared to placebo, venlafaxine reduces physiological and self-reported hot flashes at both 37.5 and 75 mg doses. Interestingly, the reduction in hot flashes seems to be greater at low doses compared to high doses. At 37.5 mg daily dose, effects on physiological hot flashes appear earlier in treatment (week 1), as compared to the 75 mg dose (greatest effect at week 5). This is not consistent with antidepressant effects which can take several weeks, indicating that the low-dose mechanism of action on hot flashes, although not clear, may be different from the antidepressant mechanism [27]. In other studies, doses as low as 12.5 mg orally twice daily rendered similar reductions in hot flashes in both breast cancer and prostate cancer patients [28, 29]. Similar results regarding reduction in frequency and intensity of hot flashes after breast cancer treatment were obtained with fluoxetine 10 mg daily dose [30, 31].

Approximately 5% of women of reproductive age experience premenstrual symptoms that substantially impact their social functioning. Evidence from numerous controlled trials has clearly demonstrated that low-dose SSRIs, used intermittently or continuously, are effective for both premenstrual dysphoric disorder as well as premenstrual syndrome [32]. For instance, low-dose sertraline (25 mg daily) has been tested in three different ways: intermittent luteal-phase across two cycles, continuous luteal-phase across two cycles and symptom-onset dosing. All three strategies were effective in treating premenstrual symptoms (and better than placebo). Compared to a 50 mg dosage, the lower dose was more effective. The mechanism by which SSRIs/SNRIs work to alleviate premenstrual dysphoric disorder is independent of the antidepressant mechanism and involves allopregnanolone and gamma-aminobutyric acid [33].

Premature ejaculation

Premature ejaculation is the most common male sexual dysfunction seen in clinical practice and it has been successfully treated with antidepressants for years. SSRIs are well-known for side effects such as anorgasmia and delayed ejaculation and their use in low doses has demonstrated their usefulness in treating this bothersome condition with fewer side effects [34]. A double-blind placebo-controlled study of clomipramine showed an increase in penetration time of 6 and 8.5 minutes on 25 and 50 mg of clomipramine, respectively, compared to placebo [35].

Movement disorders

Akathisia is a common neuroleptic-induced movement disorder. Although this side effect is less frequent with the use of novel antipsychotics, acute akathisia remains a common finding among psychiatric patients treated by both conventional and atypical neuroleptics. Unfortunately, many patients fail to respond to standard therapeutic modalities. Recently, it has been shown that 5-HT_{2A} antagonists (such as ritanserin, cyproheptadine and mianserin) may effectively treat akathisia. Both open and double-blind, placebo-controlled trials of the tetracyclic antidepressant mianserin at low doses (15 mg) have demonstrated its usefulness in the treatment of acute akathisia in schizophrenic and schizoaffective patients [36]. Mirtazapine at 15 mg has also demonstrated to be efficacious in ameliorating akathisia compared to placebo and propranolol. Mirtazapine is structurally and pharmacologically similar to mianserin and also exhibits marked 5-HT_{2A} antagonism, the mechanism by which its anti-akathisia effect is produced [37, 38].

Restless legs syndrome is a common disorder for which agents that enhance dopaminergic activity, including dopamine agonists and levodopa, are the treatment of choice. Case series have highlighted the usefulness of low doses of bupropion, an antidepressant that inhibits dopamine and noradrenalin reuptake in improving symptoms of restless legs syndrome [39].

Attention and memory deficits

A recent review performed with the aim of establishing biomarkers for Phase 1 studies of antidepressants showed that attention (as measured by neuropsychological tests) improves after SSRIs administration, particularly at low doses. The same was observed regarding tests measuring memory, with an inverted dose-response relationship (e.g. at low doses the improvement of memory was greater compared to increasing doses) [40].

Harmer and colleagues [41] demonstrated that the SSRI citalopram facilitates memory consolidation in healthy volunteers. Furthermore, pre-clinical studies suggest that citalopram at very low doses reversed tetrahydrocannabinol-induced impairments of spatial memory by reversing the decrease of acetylcholine release in the dorsal hippocampus that tetrahydrocannabinol triggers [42]. Although promising, more studies are needed to determine the effectiveness of citalopram and other SSRIs in ameliorating memory deficits.

Emotional instability

The use of low doses of SSRIs such as sertraline (25–50 mg), paroxetine, fluoxetine and citalopram has been reported in the treatment of aggression in children and adolescents with autism and conduct disorders. Higher doses, however, may actually increase irritability. Additionally, small case series suggest that venlafaxine, in low doses (18.75 mg/day), could also be beneficial in adolescents and young adults with autism, particularly for self-aggressive features. Such low doses may be considered too low to recruit noradrenergic activity. However, animal studies suggest that, even at low doses, venlafaxine is able to increase both serotonin and noradrenaline activities [43].

Emotional lability is a common, distressing complication in patients with stroke and in its most severe form is referred to as pathological laughing and crying. This condition is characterized by episodes of uncontrollable laughing and/or crying that are not appropriate to the behavioral context. Basal ganglia, pons, cerebral cortex and cerebellum have been reported to be involved and the circuitry connecting the frontal/temporal lobe, basal ganglia and ventral brainstem might influence its development. The mechanism underlying pathological laughing and crying seems to involve serotonergic dysfunction after partial destruction of the raphe nuclei or their projections to the hemispheres. Controlled studies have established the efficacy of tricyclic antidepressants (e.g. amitriptyline and nortriptyline) and low-doses of various SSRIs (e.g. citalopram, sertraline, fluoxetine and paroxetine) in the treatment of pathological laughing and crying. For cases unresponsive or that cannot tolerate SSRIs, bupropion and mirtazapine may be options [44]. Response to low doses of SSRIs usually appears within 1–7 days after initiation of treatment. This response rate is much faster than that observed in major depression. The difference in response times suggests that pathological crying and major depression, despite being comorbid at occasions, are independent disorders [45].

9.4 Emotion regulation in healthy individuals

A number of studies found that low-to-regular doses of antidepressants can enhance emotional regulation in patients and in normal individuals, independently of the presence of anxiety or depression [46–48].

Decreased irritability and increased cognitive efficiency, self-confidence and general well-being in patients with panic disorder treated with low doses of antidepressants were interpreted as improvements beyond pre-morbid functioning [2]. Increases in perceived interpersonal tolerance and cognitive efficiency reported by healthy volunteers under low doses of clomipramine (e.g. 10–40 mg/day) or regular doses of citalopram (20 mg/day) suggest that these drugs can improve normal mood in some individuals [49, 50]. Noteworthy, these changes toward positive affect and a 'care-less' attitude were not due to sedation, psychostimulation or disinhibition.

Pharmacodynamic effects of antidepressants in low doses have been documented. For instance, positron emission tomography (PET) studies of receptor occupancy show that doses as low as 10 mg of clomipramine result in nearly 80% occupancy of

5-hydroxytryptamine transporter (5-HTT) [51], which is the minimum threshold of receptor occupancy needed before a change in transmission in the monoamine system can occur, as evidenced in different studies [52]. Another line of investigation demonstrated that a distinct electroencephalogram theta rhythm from the frontal midline area named frontal midline (Fm) theta displays individual differences and is more frequent in less anxious persons evaluated by personality questionnaires. Moreover, there is a correlation between the frequency of Fm theta rhythm and decreases in anxiety after administration of benzodiazepines. Thus, its appearance reflects relief from anxiety in humans. Among healthy university students, those more anxious exhibit decreased amount of Fm theta rhythm when acutely administered low doses of clomipramine (10 mg, [53]).

9.5 Conclusion

In this chapter we reviewed the evidence surrounding the usefulness of low doses of antidepressants in several distinct clinical conditions, besides their traditional antidepressive and anti-anxiety effects. We also summarized their action as enhancers of emotion regulation in both patients and healthy individuals. In many of these situations, effects appear a few days following medication introduction, which is different from antidepressant action that may take several weeks. This is suggestive that low-dose mechanisms of action are different from the antidepressant mechanism. Further research is needed to elucidate the mechanisms of action of low doses of these medications for different disorders, as well as for emotion regulation enhancing.

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SECTION III

Clinical Trials in Anxiety and Other Disorders

10

Clinical Trials for Anxiety Disorders

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Abstract

The most widely used treatments for anxiety disorders are drug therapies (i.e. antidepressants and high-potency benzodiazepines) and cognitive behavioral therapies. However, a number of meta-analyses have led to contradictory results regarding their efficacy, the main reasons being related to the inclusion of heterogeneous studies and influences of selection bias. Randomized controlled trials are the building blocks on which physicians and therapists rely for sound information about the safety and effectiveness of treatments. Nevertheless, a number of methodological considerations have arisen over the past decade suggesting that the field of treatment research for anxiety disorders continues to suffer from less than ideal methodologies and designs. This chapter aims to discuss methodological issues in treatment research of anxiety disorders in adult patients, and presents available evidence-based treatment strategies.

Key Words

panic disorder; generalized anxiety disorder; social anxiety disorder; post-traumatic stress disorder; randomized controlled trials; evidence-based medicine; antidepressant drugs; antiepileptic drugs

10.1 Introduction

It is now established that anxiety disorders are chronic conditions with a relapsing remitting time course [1, 2]. The evidence comes mostly from cross-sectional and retrospective assessments of duration of illness and, much less frequently, from prospective studies. This has been clearly demonstrated, for example, for panic

disorder [3, 4] and generalized anxiety disorder (GAD) [5] while much less information is available about the course of illness of social phobia, although both community and patient samples suggest an age of onset in mid to late teens with a chronicity that is equal to or greater than that of panic disorder [1, 6]. Moreover, it has to be acknowledged that the natural history of anxiety disorders is frequently complicated by Axis I and Axis II comorbid diagnoses. Comorbidity is significantly higher for patients seeking treatment than for persons not in treatment in the community [1]. For example, the Epidemiologic Catchment Area (ECA) survey [1], as well as the Zurich cohort of Angst [6], found that 73% of patients with panic disorder had other comorbid conditions ranging from major depression to substance abuse until Axis II disorders, mostly cluster C type. It is, therefore, evident that any long-term anxiolytic treatment strategy must take account of these high rates of comorbidity that appear to develop during the longitudinal phase of the disease.

Randomized controlled trials (RCTs) are the building blocks on which physicians and therapists rely for sound information about the safety and effectiveness of treatments. However, a number of methodological considerations have arisen over the past decades suggesting that the field of treatment research for anxiety disorders in general continues to suffer from less than ideal methodologies and designs [7]. A number of meta-analyses have led to contradictory results regarding the efficacy of the psychological and pharmacological treatment of anxiety disorders, the main reasons being related to the inclusion of heterogeneous studies and influences of selection bias. This chapter is aimed at discussing methodological issues in treatment research for anxiety disorders, emphasizing the need for evidence-based treatment strategies. All major anxiety disorders are discussed apart from obsessive compulsive disorder, which is the main object of Chapter 15. Available evidence for the treatment of major anxiety disorders is reviewed briefly.

A search of MEDLINE/PubMed back to January 1980 was conducted for randomized controlled trials in each anxiety disorder, using the limiting terms 'humans', 'randomized controlled trials' and 'English'. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded. The reference list of relevant articles were hand-searched for additional publications (e.g. book chapters or review papers) if relevant to the discussion.

10.2 Methodological issues in treatment research for anxiety disorders

The methodological and design difficulties faced by researchers in the field of psychiatric disorders in general, and anxiety disorders in particular, include (i) procedures, (ii) assessment of symptoms and (iii) measurement of treatment-produced change [7] (Table 10.1).

Table 10.1 Methodological issues in treatment research for anxiety disorders.

Procedural issues	Study design
	Ethnicity
	Gender
	Age
	Concomitant treatments
Assessment of symptoms	Classification of disorders (DSM-based vs. dimensional approaches)
	Selection of symptoms (anxiety vs. disorder-specific symptoms)
	Self-rating scales vs. structured interviews
Measurement of treatment-produced changes	Outcome analyses
	Comorbidity of symptoms and diagnoses
	Outcomes and moderators

Procedural issues

Several procedural issues need to be considered in the development, design and evaluation of treatment procedures for anxiety disorders. Among them the study design, presence of ethnic, gender or age diversities of participants, treatment comparisons and medication status need to be examined as potential factors moderating treatment outcome.

There are a number of specific concerns that need to be addressed when designing clinical trials of psychotropic drugs. Some of the most salient issues include dose finding, efficacy vs. placebo, efficacy vs. standard reference compound, continuation and maintenance treatment efficacy and acute vs. long-term adverse effects. In this regard, it is not always possible to have sound information on dose-finding tolerability studies because it is difficult ethically to justify administering psychotropic drugs to healthy volunteers for more than a week or two. It is not always possible to predict clinical dosage requirements accurately from preclinical studies. Dosage recommendations may change after a drug is marketed.

A variety of characteristics related to the subject, such as ethnicity, gender or age, should be considered in terms of inclusion or exclusion criteria. Age can affect pharmacokinetics of drugs. Elderly patients are more likely to have comorbid medical conditions or to be more sensitive to some adverse effects. On the contrary, younger people may metabolize drugs in different ways [8]. The issue of adverse effects during long-term treatment should be carefully considered in young individuals. Ethnicity may also have implications for drug metabolism and disposition [9, 10]. As pharmacogenetic strategies are developed to extend clinical trial data, more accurate documentation of race will be critical. Gender is an important variable, mainly in anxiety disorders where women are over-represented. Paradoxically, women are often under-represented in preclinical studies and clinical trials. Finally,

a number of patient-related issues should be taken into account as potential biases affecting study results, such as marital status (this can be a proxy for psychosocial adjustment and illness course), premorbid social adjustment, comorbid psychiatric disorders, previous treatment strategies and duration of the trial. In general terms, it would be preferable for RCTs to include a non-treatment control condition of equal duration. This design generally ensures that treatment gains are neither due to the mere passage of time nor regression to the mean. However, the longer the duration, the more difficult is it to justify the retention of patients on placebo. In addition, the higher the dropout rate, the less useful are the data.

Medication status and treatment comparison need to be carefully considered. Ideally, a compelling investigation would require that, unless it is a specific feature of the research design, participants cannot take prescribed or non-prescribed medications that can influence the main dependent variables. These drugs may be psychotropic medications for comorbid conditions but also a number of other medications for medical conditions.

The issue of treatment comparison is linked with that of the elimination of placebo responders or drug non-responders from the trial. In fact, this can produce a biased evaluation of medication effects because this practice would be comparable to the removal of clients who are non-responsive to the psychosocial treatment.

Assessment of symptoms

The assessment of anxiety symptoms is directed to both selection and classification of symptoms and/or disorder and treatment evaluation.

A number of instruments are used in the assessment of anxiety in RCTs for anxiety disorders (Table 10.2). The development of clinical instruments for the assessment of anxiety symptoms followed the development of RCTs and DSM. Thus, it became less relevant to identify masked symptoms, or 'atypical' symptoms belonging to psychodynamic theories. Rather, focus upon objectively identifiable symptom patterns that could be treated with psychotropic medications turned out to be of primary importance. Sensitivity to change became the most important criterion for the assessment of symptoms. Also, the point of view of clinicians shifted from trait anxiety to state anxiety.

Test-retest reliability may be the most important psychometric parameter from which to choose a clinical instrument for RCTs. Split-half reliability is another important parameter especially for chronic patients or 'stable' disorders, such as obsessive compulsive disorder, where the detection of minimum changes is fundamental. In fact, split-half methods eliminate the need for two administrations of a test, hence eliminating the difficulties of developing another form or changes in a person over time.

Structured clinical interviews are generally thought to provide accuracy, reliability and reproducibility, also taking into account a number of clinician-based biases such as the criterion-drift which, in some cases, might affect RCTs. Moreover, such instruments investigate a number of symptoms that are not often mentioned by patients with anxiety disorders because they may feel them to be considered 'crazy'. These

Table 10.2 Clinical instruments for the assessment of anxiety.

Rating scale	Citation	Exploring area	Evaluation	No. items	Score range
Manifest Anxiety Scale (MAS)	[11]	Anxiety-trait	Self	50/20	–
Hamilton Rating Scale for Anxiety (HRSA or HAM-A)	[12]	Anxiety-state	Interview	14	0–56
State-trait anxiety inventory (STAI) (Form Y) T-Anxiety Scale	[13, 14]	Anxiety-trait	Self	20	20–80
STAI (Form Y) S-Anxiety Scale	[13, 14]	Anxiety-state	Self	20	20–80
Self-rating Anxiety Scale (SAS)	[15]	Anxiety-state	Self	20	35–65
Anxiety Status Inventory (ASI)	[15]	Anxiety-state	Interview	20	20–80
Schalling Anxiety Rating Scale (SARS)	[16]	Anxiety-state	Interview	10	10–50
Wang Anxiety Scale (WAS)	[17]	Anxiety-state	Interview	12	12–48
Cognitive-Somatic Anxiety Questionnaire (CSAQ)	[18]	Anxiety-trait	Self	14	14–70
Clinical Anxiety Scale (CAS)	[19]	Anxiety-state	Interview	6 (+1)	0–24
Somatic, Cognitive, Behavioral Anxiety Inventory (SCBAI)	[20]	Anxiety-state	Self	36	0–288
Sheehan Patient Rated Anxiety Scale (SPRAS)	[21]	Anxiety-state	Self	35 + 11	0–140 + 0–44
Sheehan Clinician Rated Anxiety Scale (SCRAS)	[21]	Anxiety-state	Interview	35	0–140
Covi Anxiety Rating Scale (CARS)	[22]	Anxiety-state	Self	3	3–15
Beck Anxiety Inventory (BAI)	[23]	Anxiety-state	Self	21	0–63
Clinical Anxiety Scale (CAS)	[24]	Anxiety-state	Self	25	0–100

include depersonalization or derealization symptoms. The recollection of an event can trigger anxiety, as happens in phobic patients.

Self-report rating scales represent another option. However, the structure of these instruments is fixed and, because of this inflexibility, the situation-specific and individual aspects of disturbing anxiety may be lost.

Although a number of instruments have been developed for the assessment of anxiety symptoms (Table 10.3), we are still far away from a standardized evaluation of such symptoms for the purpose of psychopharmacology research. Mostly, because anxiety symptoms are heterogeneous, they can often display an asynchronous pattern of occurrence and severity. For example, the extent of the avoidance behavior does not always correlate with the degree of phobic symptoms. Finally, the large overlap between anxiety symptoms and depressive symptoms needs to be acknowledged. In psychopharmacology research, a multidimensional assessment of patients is the most helpful.

Table 10.3 Clinical instruments for the assessment of panic attack disorder and phobic disorders.

Scales	Citation	Exploring area	Evaluation	No. items
Fear Survey Schedule-II (FSS-II)	[25]	Simple phobia	Self	51
Fear Questionnaire (FQ)	[26]	Simple phobia	Self	24
Marks-Sheehan Phobia Scale (MSPS)	[21]	Simple phobia	Self	16
Social Avoidance and Distress Scale (SAD)	[27]	Social phobia	Self	28
Fear of Negative Evaluation Scale (FNE)	[27]	Social phobia	Self	30
Social Interaction Self-Statement Test (SISST)	[28]	Social phobia	Self	30
Interaction Anxiousness Scale (IAS)	[29]	Social phobia	Self	15
Audience Anxiousness Scale (AAS)	[30]	Social phobia	Self	12
Liebowitz Social Phobia Scale (LSPS)	[31]	Social phobia	Interview	24
Brief Social Phobia Scale (BSPS)	[32]	Social phobia	Interview	11
Agoraphobic Cognitions Questionnaire (ACQ)	[33]	Agoraphobia	Self	15
Body Sensations Questionnaire (BSQ)	[33]	Agoraphobia	Self	18
Mobility Inventory for Agoraphobia (MIA)	[34]	Agoraphobia	Self	27
Agoraphobia Rating Scale (ARS)	[35]	Agoraphobia	Interview	12
Panic Attack and Anticipatory Anxiety Scale (PAAAS)	[21]	Panic attack	Interview	18
Anxiety Sensitivity Index (ASI)	[36]	Panic attack	Self	16
Panic Attack Cognitions Questionnaire (PACQ)	[37]	Panic attack	Self	23
Panic Attack Symptoms Questionnaire (PASQ)	[37]	Panic attack	Self	33

Measurement of treatment-produced change

Issues deserving attention in the measurement of change across time include: the breadth of the symptoms assessed; attrition and outcome analyses; and comorbidity of symptoms and/or diagnoses. In general terms, multiple dependent variables with a unitary focus, namely anxiety, are necessary for an optimal assessment of that singular construct. A singular focus is not sufficient to reflect accurately the full picture of the problem. High estimates of comorbidity among patients with anxiety disorders and the relationship between comorbidity and treatment outcome emphasize the importance of the measurement of multiple constructs. A comprehensive evaluation of the outcome requires multiple measures of anxiety symptoms. However, what is gained in sensitivity may be lost in specificity. It is well established that anxiety disorders are frequently comorbid, thus necessitating the assessment of problems beyond anxiety. Also, without a broad assessment, there is no opportunity to examine response covariation. Assessments addressing an issue other than the primary focus are necessary to determine the presence of favorable changes in other symptoms and diagnoses and/or the emergence of new disorders. For example, when assessing anxious distress, measures of anxiety can be administered to assess whether changes in anxiety alone, or anxiety in conjunction with other emotional states, are the outcomes of treatment. Researchers may employ a diagnostic procedure that permits the identification of disorders in addition to anxiety disorders.

In clinical outcome studies there is a loss of research participants prior to post-treatment and follow-up data collection. Attrition is problematic for the analysis of outcomes; different strategies have been used such as the analyses of treatment completers and analyses of intent-to-treat samples.

10.3 Panic disorder with/without agoraphobia

The most widely used treatments for panic disorder are drug therapies and cognitive behavioral therapies.

Drug-treatments depend largely upon antidepressants and high-potency benzodiazepines. Several meta-analyses have been published demonstrating that antidepressants have at least equal efficacy compared to benzodiazepines [38–41]. By contrast, benzodiazepines are not superior to antidepressants in reducing depressive symptoms that may accompany panic disorder [40]. A meta-analysis comparing short-term efficacy of selective serotonin reuptake inhibitors (SSRIs) vs. tricyclic antidepressants (TCAs) showed no difference between the two drug classes in terms of efficacy, but concluded that SSRIs are usually better tolerated than TCAs [41].

The issue of psychotherapy in panic disorder has been reviewed in a Cochrane meta-analysis [42]. The authors reviewed evidence concerning short- and long-term advantages and disadvantages of combined psychotherapy plus antidepressant treatment in comparison with either drug therapy alone or psychotherapy alone. In the acute phase treatment, the combined therapy was superior to antidepressants alone (RR 1.24; 95% CI 1.02–1.51) or psychotherapy alone (RR 1.17; 95% CI 1.05–1.31).

However, the combined therapy produced more dropouts due to side effects than psychotherapy alone (Number Needed to Harm around 26). After the acute phase treatment, as long as the drug was continued, the combined therapy appeared to be superior to monotherapy. Interestingly, the combined therapy was more effective than pharmacotherapy alone (RR 1.61 95% CI 1.23–2.11) and was as effective as psychotherapy alone (RR 0.96 95% CI 0.79–1.16) during the continuation phase. This suggests that either combined therapy or psychotherapy alone may be chosen as first line maintenance treatment for panic disorder with or without agoraphobia, depending upon patient preference. Bandelow *et al.* [43] observed that panic disorder is the only anxiety disorder where the combination of pharmacological and psychological treatment was superior to either treatment alone.

Controlled data on treatment resistant panic disorder are scant. Medication augmentation can be an effective and well-tolerated short-term treatment strategy for non-responders to first-line pharmacotherapy. However, any conclusion is often tentative in view of the methodological and clinical heterogeneity of available literature. A meta-analysis of pharmacotherapeutic augmentation strategies in treatment-resistant anxiety disorders [44] identified only one trial for panic disorder to include in the analyses. In this study, the beta-blocker pindolol was effective in reducing symptom severity (standard mean difference or SMD -3.73 95% CI -5.1 to -2.36) in patients with treatment-resistant panic disorder [45].

10.4 Generalized anxiety disorder

GAD is a common mental disorder affecting approximately 5% of the general population in the United States. [46]. It is an impairing disorder, usually characterized by a chronic course and often associated with extensive psychiatric and medical comorbidity. Finally, GAD may often contribute to shape the final phenomenology of a comorbid mood or anxiety disorder, further complicating the clinical picture. Evidence-based implemented treatment strategies may be useful for research on GAD.

The most widely used treatments for GAD are drug therapies and cognitive behavioral treatments. Among different drugs, SSRIs, SNRIs, benzodiazepines, azapirones (e.g. buspirone), antihistamines (e.g. hydroxyzine) and the anticonvulsant pregabalin have been used. At a clinical level, benzodiazepines have, until very recently, been the most widely used anxiolytic drugs [47]. Earlier trial results coupled with the very short-term effect upon anxiety [48] converted benzodiazepines to the gold standard [49]. Subsequently, and mainly due to the adverse effects generated by these compounds such as dependency, low long-term tolerance or cognitive disorders [50], research into the treatment of GAD shifted toward safer and more effective compounds such as, for example, buspirone or SSRIs [51]. A systematic review of 23 RCTs of benzodiazepines in GAD showed that, based on total withdrawals from clinical studies, benzodiazepines are not proven to be definitely better than placebo in the short-term treatment [52]. This is clearly an incongruity with the general assumption that benzodiazepines are useful in GAD. A possible reason for such a

contradiction could reside in a number of biases, such as publication bias, quality of the trial literature and a non-differential response to the placebo effect [52].

A systematic review of antidepressant drugs confirmed their efficacy in GAD especially for imipramine, venlafaxine and paroxetine [53]. Imipramine showed a smaller number-needed-to-treat (NNT) (NNT 4.07 – 95% CI 2.39–13.74) than venlafaxine (NNT 5.06 – 95% CI 3.6–8.6) and paroxetine (NNT 6.6 – 95% CI 3.9–24.7). However, as pointed out by Schmitt and collaborators [53], this does not allow for the conclusion that the effect size of imipramine is larger. Moreover, if the high rates of comorbidity in GAD patients, especially major depression and dysthymia, are taken into account, caution is required in translating these findings as an anti-anxiety effect *per se*. Further research clarifying this issue is warranted.

Finally, among other drug classes, a number of studies have established the role of the anticonvulsant pregabalin in the short-term treatment of GAD [54, 55]. Recent data are now supporting the efficacy of this compound in the long-term treatment [56] and in the amelioration of comorbid depressive symptoms [57].

The efficacy of cognitive behavioral therapy (CBT) for GAD was investigated and compared to the efficacy of pharmacological therapy in a meta-analysis [58]. The results indicated that CBT is effective in reducing not only the main symptoms of anxiety, but also the associated depressive symptoms, subsequently improving quality of life. However, as noted by the author, the effect sizes found may significantly overestimate the real effect of CBT in GAD. Two-thirds of the studies included in the analysis did not use structured interviews to diagnose GAD and findings for CBT vs. drug therapy varied depending upon method of analysis (random vs. fixed effects) [59].

A more recent meta-analysis of RCTs of psychopharmacological and psychological treatments pointed out that the number of published studies is too small to draw final conclusions in GAD [43]. The small set of data indicates a superiority of CBT over drug treatment; the combination of CBT and pharmacotherapy is, on the one hand, better than CBT and placebo but, on the other, inferior to CBT alone. Further studies are needed to clarify whether a combined approach, psychological and pharmacological, can be useful for long-term treatment and the specific subpopulation for who it can be successfully used.

Controlled data on treatment resistant GAD are worse than scant. The only available studies are those on the atypical antipsychotic drugs olanzapine and risperidone [60], showing promising results in terms of reduction of Hamilton Anxiety scores [44].

10.5 Social anxiety disorder

The growing interest in the development of treatment strategies for social anxiety disorder reflects an increasing awareness on the prevalence and clinical significance of this condition, along with the growing availability of new psychological and pharmacological treatments. The most widely used treatments for social anxiety disorder are drug therapies and cognitive behavioral therapies.

A large review of RCTs for a range of medications, from antidepressants to anticonvulsants, demonstrated short-term superiority of all medication groups over placebo [61]. However, SSRIs were significantly more effective than both moclobemide and, to a lesser extent, brofaromine. In particular, SSRIs reduced not only social anxiety disorder symptom clusters, but also comorbid depressive symptoms and associated disability. These data have been confirmed by a subsequent meta-analysis [62], which highlighted the need for a careful evaluation of long-term maintenance of treatment gains.

Comparative evidence from 15 RCTs on second generation antidepressants showed that escitalopram (RR 1.3; 95% CI 1.2–1.5), paroxetine (RR 1.9; 95% CI 1.5–2.3), sertraline (RR 1.8; 95% CI 1.5–2.2) and venlafaxine (RR 1.7; 95% CI 1.5–1.9) all produce significantly more responders than placebo in terms of anxiety severity and functional impairment [63]. Fluvoxamine did not demonstrate statistical significance (RR 1.5; 95% CI 0.9–2.4). Aside from documented differences in the incidence of specific adverse events, existing evidence does not suggest differences in efficacy of these drugs.

Although CBT is useful in a number of anxiety disorders [64], results from studies in social anxiety are less clear. Only two studies had a combined treatment arm [65, 66]. Data from these studies showed higher effect sizes for the combination drug plus CBT, than for placebo plus CBT. In other words, all direct comparisons between different treatments for social anxiety disorder showed no clear superiority of one treatment over another and do not support the use of combined treatment [43].

No meta-analysis or systematic reviews of RCTs have been published about treatment resistant social anxiety disorder. A 12-week cross-over study of paroxetine potentiation with pindolol showed no substantial difference when compared to placebo [67]. It is clearly evident that we are still some distance from an evidence-based approach to the treatment of social anxiety disorder. Further studies are needed as well as strong evidence of specific treatment approaches.

10.6 Post-traumatic stress disorder

For post-traumatic stress disorder (PTSD) the situation is even more cloudy. There is limited information, especially compared to other anxiety disorders.

Many authors have focused on antidepressant drugs. However, current evidence is unable to demonstrate superior efficacy or acceptability for any particular medication class, despite suggestions that the SSRIs are more effective and tolerable than older antidepressants [68, 69]. Nevertheless, the fact that the SSRI trials constitute the bulk of the evidence for the efficacy of medication in treating PTSD suggests that it is reasonable to consider SSRIs as first choice at the moment. Among SSRIs, it is unlikely that all compounds are equally effective in treating PTSD. There is some evidence favoring paroxetine and sertraline in reducing the severity of PTSD symptoms while, to the contrary, trials of alprazolam, brofaromine, desipramine, lamotrigine and olanzapine showed no efficacy in terms of treatment response or symptom reduction [69].

In general terms, treatment response to medications has been generally described as modest in PTSD patients and several open studies have been published regarding augmentation strategies to antidepressant drugs. However, controlled data are still limited.

A 20-week, double-blind, placebo-controlled, cross-over study showed significant reduction in Clinician Administered PTSD Scale (CAPS) scores during treatment with prazosin [70]. A recent meta-analysis analyzed RCTs of atypical antipsychotics involving a total of 192 PTSD patients [71]. The results showed that these compounds may have a beneficial effect in the treatment of PTSD, as indicated by the changes from baseline in CAPS total scores ($SMD = -0.45$; $95\%CI = -0.75 -0.14$). In particular, the symptom of ‘intrusion’ was mainly responsible for this significant improvement. The atypical antipsychotic risperidone failed to demonstrate greater efficacy than placebo over a period of five weeks on the total CAPS scores in a sample of 37 PTSD patients with comorbid psychosis [72]. RCTs of the anticonvulsant drug topiramate in PTSD failed to demonstrate a significant effect over placebo as either monotherapy or adjunctive therapy [73, 74]. High dropout rate in the treatment group prohibits definitive conclusions at the present time.

Data on psychotherapy in PTSD are limited. A large meta-analysis of RCT on CBT in anxiety disorders showed the strongest effect size for acute stress disorder while RCTs in PTSD patients are still controversial [64]. Mueser *et al.* [75] published data on a RCT of a CBT program developed for PTSD in severe psychiatric conditions. Their findings suggest that CBT may be of value in severe patients with PTSD and psychosis or suicidal ideation. However, further studies are needed to support the use of specific psychotherapeutic programs in PTSD and to identify populations of patients that may benefit from such a treatment.

10.7 Conclusions

We are still some distance from a solid evidence-based approach to the problem (Table 10.4). Controlled data are not available for all disorders. Even in the instances

Table 10.4 Available evidence on treatment of anxiety disorders.

Disorder	Drug therapy	Psychotherapy
Panic attack disorder	SSRIs = TCAs	Combined with drug therapy during acute phase Alone or in combination with drug therapy during continuation phase
Generalized anxiety disorder	Venlafaxine, Paroxetine, Imipramine, Pregabalin	Controversial
Social anxiety disorder	Sertraline, Venlafaxine, Paroxetine, Escitalopram	Not enough evidence for combined treatment
Post-traumatic stress disorder	Not enough evidence (sertraline and paroxetine are promising)	Not enough evidence

of those with a solid literature (i.e. panic attack disorder), a number of methodological problems make these results problematic.

Potential ameliorative strategies may result in greater attention to the methodologies of treatment research in psychiatry. Study designs need to take into account the use of multiple-method measurements with diverse samples; consideration of and control for participants' psychopharmacological status; and outcome measures that go beyond the Diagnostic and Statistical Manual (DSM) categorical system and carefully address patients' needs.

Further research is warranted in order to derive standardized and evidence-based guidelines for treatment of anxiety disorders.

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11

Pharmacological Trials for the Treatment of Substance Use Disorders

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Abstract

Pharmacotherapy for substance use disorders (SUDs) may include interventions to assist with recovery from overdose, detoxification and relapse prevention. Multiple medications have been identified as potential treatments to help patients who suffer from an SUD. As a result, much research has been conducted to test the efficacy of these interventions. Unfortunately, many factors create burdens for researchers attempting to conduct pharmacotherapy trials with this population. For example, researchers may experience challenges in recruiting appropriate participants, achieving randomized double-blind conditions, limiting treatment non-adherence and drop-out, selecting adequate outcome measures and preventing safety concerns. These difficulties can negatively affect the reliability, validity and generalizability of study results. As a result, many contradictory findings have been published, and the field still awaits the discovery of medications that will assist individuals recovering from various substances of abuse. However, advances in pharmacological treatment have revolutionized clinical care for patients with SUDs, and many individuals are able to achieve stable recovery and lead productive lives.

Key Words

addiction; substance use disorders; alcohol; drugs; pharmacotherapy; clinical trials

11.1 Psychopharmacological trials for the treatment of substance use disorders

Definitions of ‘addiction’ have changed significantly in the past decades. For example, in 1952 the World Health Organization’s Expert Committee defined alcoholics as ‘those excessive drinkers whose dependence on alcohol has attained such a degree that it shows in a noticeable mental disturbance or an interference with their bodily and mental health, interpersonal relations and their smooth social and economic functioning’ [1]. Since then, advances in the understanding of addiction (i.e. the development and acceptance of the disease concept) have changed perceptions of individuals who suffer from addiction disorders. These advances have also resulted in new methods for studying the prevention and treatment of substance use disorders (SUDs). For example, identification of the roles of dopamine, serotonin, glutamate and other neurotransmitters in the development of substance abuse and dependence set the stage for the use of psychopharmacological interventions with these patients. Researchers around the globe have conducted trials to examine the efficacy and effectiveness of numerous pharmacological interventions for SUDs, with varying degrees of success. The present chapter will review the importance of psychopharmacological trials for the treatment of SUDs and various factors that make such trials challenging.

11.2 Definitions of substance use disorders

Despite the expansion of the term ‘addiction’ to include a wide assortment of substances (including food) and even behaviors (such as gambling, sex, etc.), most current definitions of substance abuse and dependence classify the phenomenon of addiction in behavioral terms. The SUDs have been established as chronic relapsing disorders, characterized by compulsive use, loss of control and associated withdrawal syndromes subsequent to cessation of long-term use of the drug. For diagnostic purposes, substance abuse is described as a maladaptive pattern of behavior that leads to clinically significant impairment or distress associated with the repeated use of the substance despite negative consequences [2]. To meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for substance abuse, an individual must display at least one of the following symptoms within a 12-month period: (i) failure to fulfill major role obligations due to substance use, (ii) repeated use of the substance when it is dangerous to do so, (iii) multiple legal problems related to substance use or (iv) sustained use of the substance despite social or interpersonal consequences [2].

A diagnosis of substance dependence is indicated when the persistent use of the substance, despite consequences, is characterized by both physical effects (e.g. tolerance, medical consequences) and socio-emotional consequences occurring within the same 12-month period. Specifically, to meet criteria for substance dependence, an individual must display at least three of the following symptoms over the course of one year: (i) physical tolerance to the substance, (ii) withdrawal symptoms, (iii)

using more of the substance than intended, (iv) repeated attempts to control substance use, (v) significant time spent in activities related to substance use, (vi) reduction of important activities due to substance use or (vii) continued use of the substance despite significant physical or psychological consequences [2].

The diagnostic criteria for substance abuse and substance dependence rely on specific symptomatology; however, the underlying mechanisms (whether biological, psychological or social) by which a person transitions from substance use to abuse and dependence are not yet fully understood. Factors that contribute to the development of SUDs may include availability, genetics, history of drug use, stress and life events. Neurobiological models point to the dysregulation of reward systems in the brain that may be the driving force which transitions an individual from an impulsive to a compulsive disorder [3]. Regardless, the consequences of untreated SUDs can be devastating. In addition to psychosocial problems created by addiction (e.g. unemployment, divorce, bankruptcy, etc.), substance use frequently results in illness, injury and even death. Indeed, many hospital admissions are related to SUDs, and 10–26% of patients in general practice settings may suffer from an SUD. Given the prevalence of SUDs (i.e. almost 10% of Americans meet criteria for an SUD during any given year [4]), the development of effective interventions for SUDs has great implications for public health.

11.3 Introduction to psychopharmacotherapy for SUDs

In general, the aims of most pharmacological interventions fall into one of two categories: alleviating uncomfortable and possibly dangerous withdrawal symptoms (for a review see [5]) and preventing relapse (for a review see [6]). Other medications are also available to treat acute intoxication and to provide ‘maintenance’ therapy for individuals who experience severe withdrawal symptoms that prevent them from achieving abstinence. Pharmacotherapies for SUDs with significant empirical support are listed in Table 11.1.

Until recently, much of the research on addiction and substance abuse has focused on the treatment and relapse prevention of alcohol abuse. Despite a relative paucity of research when compared to studies on alcohol, pharmacotherapies for the treatment of withdrawal from other substances (e.g. stimulants, opiates, cannabis, nicotine, etc.) are widely utilized. However, more research is needed to evaluate pharmacotherapies that decrease craving and relapse for these substances of abuse [6]. As improved theoretical models of substance abuse and addiction have been developed, new modes of treatment have emerged. For example, the discovery of the neurophysiological adaptation that occurs pursuant to stimulant abuse resulted in the exploration of anticonvulsants, antidepressants and dopaminergic medications for the treatment of cocaine (and other stimulant) dependence [7].

Goals of pharmacotherapy for SUDs

As indicated previously, pharmacotherapy for SUDs may target various consequences of addiction (e.g. overdose, withdrawal, craving/relapse). In addition, the medications

Table 11.1 Pharmacotherapies recommended for specific substance use disorder treatments.

	Alcohol	Opiates	Sedative-hypnotics	Cocaine and other stimulants	Cannabis
Overdose		Naloxone	Flumazenil	Diazepam	
Acute withdrawal	Benzodiazepines, barbiturates, carbamazepine	Methadone, buprenorphine	Benzodiazepines, barbiturates		
Mild symptoms (e.g. sleep disturbance, physical discomfort)	Thiamine, folate	Methadone, clonidine, lofexidine, buprenorphine			
Relapse prevention	Disulfiram, naltrexone, acamprosate, topiramate, SSRIs ^a , carbamazepine ^a	Methadone, naltrexone buprenorphine ± naloxone		Cocaine vaccine ^a , stimulant therapy (e.g. modafinil, cocaine tea, pemoline) ^a , disulfiram ^a , naltrexone ^a , topiramate ^a , baclofen ^a	Lofexidine ^a
Cravings	Acamprosate, naltrexone, atenolol ^a	Methadone, buprenorphine		Baclofen ^a , modafinil ^a	Oral THC substitution (esp. first day) ^a

^aMore studies needed or inconclusive evidence of efficacy.

typically target specific drugs of abuse. As a result, many trials have been conducted to examine the efficacy of psychopharmacological treatments for SUDs. Table 11.2 includes representative studies for various substances of abuse and key characteristics of the trials. A brief explanation of the types of treatments being evaluated is included below.

Reversal of acute overdose

Pharmacotherapy has traditionally played a significant role in the emergency treatment of either accidental or purposeful overdose. For example, naloxone, a non-specific and fast-acting opioid antagonist, has long been used for the reversal of opiate overdose [33]. By binding to delta, mu and kappa opioid receptors, naloxone can reverse the effects of overdose (e.g. respiratory depression, cardiac effects and coma) in 1–2 minutes [34]. Nalmefene is another option for pharmacologically reversing opiate overdose, often chosen because its effects are much longer lasting than naloxone with a half-life of approximately 11 hours (compared to 1–1.5 hours in naloxone) [35]. This longer half-life usually eliminates the need for multiple doses; however, it can also lead to extended withdrawal symptoms [35]. In addition to opiate overdose, pharmacological interventions are available for benzodiazepine overdose (using treatment with flumazenil) and gamma-hydroxybutyrate overdose (using treatment with physostigmine) [36, 38].

Recently the use of pharmacological interventions to reverse overdose has also been applied as a preventive measure. Because naloxone has no abuse potential and can readily reverse opioid overdose, researchers have investigated the utility of prescribing it to known heroin users for use in the event of an accidental overdose [39]. One Chicago study found that introduction of such a program (i.e. providing prescriptions for naloxone along with overdose education) resulted in a reversal of the trend related to deaths by heroin overdose. Specifically, the rates of death changed from rapidly increasing each year to decreasing by 20% the first year the program was implemented, and decreasing by an additional 10% in the second and third years after the program was implemented [39].

Unfortunately, this practice has since come under criticism due to ethical issues. Results of one study examining the attitudes of heroin users regarding such easy access to naloxone found that 62% of users believed they would be less likely to seek emergency help; 35% reported they might feel comfortable using greater amounts of heroin; 30% believed they would leave an overdose victim after administering naloxone and 46% felt they would be unable to dissuade overdose victims from using heroin again in order to alleviate the withdrawal symptoms induced by the naloxone [40]. These findings were particularly troubling given that one dose of naloxone is typically not sufficient, and that patients frequently need cardiopulmonary resuscitation (CPR) or experience side effects that require medical attention [41]. As a result, more work is needed in this area to determine the most effective way to decrease heroin-related deaths.

Table 11.2 Recent examples of pharmacotherapy trials for various substance use disorders.

Authors	Drug	Pharmacotherapy	Study type	N	Type of groups	Outcome measures	Results
<i>Stimulants</i>							
De La Garza <i>et al.</i> [8]	Methamphetamine	Rivastigmine	Double-blind, placebo-controlled laboratory study	22	(a) 1.5 mg rivastigmine	1°: Choice of methamphetamine vs. money	No effect of rivastigmine on overall choice
					(b) 3.0 mg rivastigmine		
					(c) Placebo		
Pettinati <i>et al.</i> [9]	Co-occurring cocaine/alcohol	Disulfiram/ Naltrexone combo	Double-blind, placebo-controlled trial	208	(a) Disulfiram (250 mg/d)	1°: In-trial abstinence from cocaine and/or alcohol	Subjects taking disulfiram were most likely to achieve abstinence from cocaine <i>and</i> alcohol
					(b) Naltrexone (100 mg/d)		
					(c) Combo (same doses)		
					(d) Placebo		
Johnson <i>et al.</i> [10]	Methamphetamine	Ondansetron	Preliminary randomized, double-blind, placebo-controlled study	150	(a) Ondansetron 0.25 mg BID	1°: Methamphetamine use (verified by urine testing) 2°: Craving, withdrawal	Ondansetron doses equal to placebo for reducing use, withdrawal, craving, severity dependence
					(b) Ondansetron 1.0 mg		
					(c) Ondansetron 4.0 mg BID		
					(d) Placebo/CBT3 ×/wk for all groups		
Meredith <i>et al.</i> [11]	Methamphetamine	Risperidone	Open-label pilot	11	Average risperidone dose: 3.6 mg/d	1°: Abstinence from methamphetamine 2°: Neuro-psychological functioning	Well-tolerated, associated with decreased METH use

Elkashef <i>et al.</i> [12]	Methamphetamine	Bupropion	Double-blind, placebo- controlled trial	151	(a) Bupropion 150 mg BID (b) Placebo	1°: Number of weeks of abstinence from METH 2°: Use of METH, craving, HIV risk behaviors, other substance use	Bupropion plus behavioral group therapy effective for increasing number of weeks abstinent from METH
<i>Alcohol</i>							
Sarid-Segal <i>et al.</i> [13]	Alcohol	Levetiracetam	Open label trial	20	Subjects received 200 mg/d for 10 wk	1°: Alcohol intake	Alcohol intake decreased from 5.3 to 1.7 drinks/d
Florez <i>et al.</i> [14]	Alcohol	Topiramate, Naltrexone	Naturalistic, randomized, open-label trial	102	(a) Naltrexone (b) TopiramateBoth groups received relapse preven- tion therapy ^a	1°: Alcohol intake, cravings, changes in biomarkers of alcohol consumption 2°: Disability, quality of life	Both groups showed reduced alcohol intake; topiramate group had greater reduction in cravings
Soyka <i>et al.</i> [15]	Alcohol	Rimonabant	Placebo- controlled, double-blind proof-of-concept study	260	(a) Rimonabant	1°: Alcohol consumption 2°: Weight changes	Rimonabant group showed lower relapse and greater weight loss
Martinotti <i>et al.</i> [16]	Alcohol (in dually diagnosed patients)	Quetiapine	Open-label trial	28	(b) Placebo Subjects received flexible doses of quetiapine for 16 wk	1°: Alcohol craving and consumption 2°: Psychiatric symptoms	Decreased alcohol consumption, craving and psychiatric symptoms

(continued overleaf)

Table 11.2 (continued)

Authors	Drug	Pharmacotherapy	Study type	N	Type of groups	Outcome measures	Results
<i>Alcohol</i>							
Wilens <i>et al.</i> [17]	Alcohol (in patients with comorbid ADHD)	Atomoxetine	Three-month, double-blind, placebo-controlled trial	80	(a) Atomoxetine (b) Placebo	1°: ADHD symptoms 2°: Time to relapse to heavy alcohol use	Atomoxetine improved ADHD symptoms; no difference in relapse
Weinberg <i>et al.</i> [18]	Alcohol	Ethanol (IV), Diazepam	Randomized trial	50	(a) Ethanol (b) Diazepam	1°: Alcohol withdrawal symptoms	Ethanol showed no advantage over diazepam in treating withdrawal
McKee <i>et al.</i> [19]	Alcohol	Transdermal nicotine replacement	Within-subject, double-blind study	19	(a) 0 mg/d(b) 21 mg/d	1°: Subjective intoxication 2°: Self-administration of alcohol	Nicotine patch attenuated response and delayed drinking
Karhuvaara <i>et al.</i> [20]	Alcohol	Nalmefene	Randomized, double-blind, placebo-controlled multicenter study	403	(a) Nalmefene (10–40 mg) (b) Placebo	1°: Heavy drinking days 2°: Biochemical indicators of alcohol consumption	Nalmefene group showed greater reduction in heavy drinking
Martinotti <i>et al.</i> [21]	Alcohol	Oxcarbazepine, Naltrexone	Randomized, open-label trial	84	(a) Naltrexone (50 mg) (b) Oxcarbazepine (1500–1800 mg) (c) Oxcarbazepine (600–900 mg)	1°: Relapse 2°: Craving, psychiatric symptoms	High oxcarbazepine group had more abstinence & fewer symptoms; less craving with nalmefene

Ooteman <i>et al.</i> [22]	Alcohol	Naltrexone, Acamprosate	Randomized, double-blind experiment	131 (a) (b) (c)	Acamprosate Naltrexone Placebo	1° : Cue-induced craving 2° : Autonomic nervous system response to alcohol-related cues	Naltrexone had reduced craving; acamprosate had reduced autonomic response
Myrick <i>et al.</i> [23]	Alcohol	Gabapentin	Double-blind trial within clinical lab paradigm	35 (a) (b)	Gabapentin (up to 1200 mg) Placebo	1° : Tolerability/safety of anticonvulsant drugs 2° : Alcohol consumption, craving or craving	Gabapentin well-tolerated; demonstrated no effect on drinking or craving
Koethe <i>et al.</i> [24]	Alcohol	Oxcarbazepine	Double-blind, randomized, placebo- controlled, multi-center pilot study	50 (a) (b)	Oxcarbazepine Placebo	1° : Need for rescue medication clomethiazole 2° : Withdrawal symptoms and craving	No significant difference between groups on any measure; no adverse effects
Opiates							
Kastelic <i>et al.</i> [25]	Various opiates	Methadone, slow-release oral morphine	Prospective, open, non- comparative multi-center study.	72	Subjects received doses of oral morphine equivalent to their methadone maintenance dose	1° : Adverse effects 2° : Withdrawal symptoms and craving	Morphine well-tolerated; withdrawal symptoms and craving were significantly reduced

(continued overleaf)

Table 11.2 (continued)

Authors	Drug	Pharmacotherapy	Study type	N	Type of groups	Outcome measures	Results
Opiates							
Woody <i>et al.</i> [26]	Various opiates	Buprenorphine/ naloxone, detoxification taper	Multi-site, randomized clinical trial	154	(a) Buprenorphine/ naloxone (up to 24 mg/d) for 12 wk	1°: Opioid-positive urine test	Buprenorphine- naloxone had less opioid use and injecting; both groups had high opioid use at follow-up
					(b) Buprenorphine (up to 14 mg/d) for 2 wk, followed by taper		
Kovas <i>et al.</i> [27]	Heroin	Buprenorphine, Clonidine	Retrospective chart review	200	(a) Clonidine	1°: Reduction in severity of withdrawal symptoms	Buprenorphine associated with increased length of stay and treatment completion
					(b) Buprenorphine		
Threlkeld <i>et al.</i> [28]	Heroin	Buprenorphine, Tramadol	Retrospective matched cohort controlled study	115	(a) Buprenorphine	1°: Reduction in severity of withdrawal symptoms	Few clinical differences
					(b) Tramadol		
Sedative-Hypnotics							
Peles <i>et al.</i> [29]	Benzodiazepines	Melatonin	Double-blind, crossover study	80	(a) Melatonin (5 mg/d)	1°: Abstinence from benzodiazepines (verified by urine)	Melatonin does not enhance benzodiazepine discontinuation, improves sleep
					(b) Placebo	2°: Self-reported sleep, depression	

Nakao <i>et al.</i> [30]	Benzodiazepines	Paroxetine	Randomized controlled trial	66	(a) Paroxetine (10–20 mg paroxetine) (b) Placebo (c) Reference group (no benzodiazepine reduction)	1°: Abstinence from benzodiazepines	SSRI group had 45.5% rate of abstinence compared to 17.4% of taper group
<i>Cannabis</i>							
Van Nimwegen <i>et al.</i> [31]	Cannabis (in patients with comorbid psychotic disorders)	Olanzapine, Risperidone	Double-blind, randomized controlled trial	128	(a) Olanzapine (b) Risperidone	1°: Subjective well-being scores 2°: Cannabis craving	Both olanzapine and risperidone improve subjective well-being and decrease craving
Huestis <i>et al.</i> [32]	Cannabis	Rimonabant	Randomized, double-blind, parallel group design	42	(a) Rimonabant (40 mg/d) for 15 d (b) Placebo (14 d), then rimonabant (90 mg) on day 15 (c) Placebo (15 d)Subjects received cannabis or placebo on days 8 and 15 ^a	1°: Subjective effects of cannabis 2°: Physiological effects of cannabis	Rimonabant associated with decreased cannabis-induced tachycardia and peak subjective effects after 8 d but not after 15 d

Detoxification/maintenance

In addition to providing life-saving treatment, psychopharmacological interventions can aid significantly in the detoxification process for individuals with substance dependence. For some users, detoxification is the most difficult component of addiction treatment, due to the highly aversive physical or psychological symptoms associated with withdrawal from the substance of abuse. Effects caused by sudden detoxification can range from discomfort to fatality. In the case of alcohol detoxification, results of pharmacological trials have demonstrated benzodiazepines to be the safest and most efficient medications for treatment of withdrawal symptoms by chemically ‘imitating’ alcohol’s effects on the brain’s gamma-aminobutyric acid (GABA-A) receptors [42]. In addition to benzodiazepines, one study has shown that treatment with clomethiazole during alcohol detoxification may reduce risks of premature discharge among inpatients [43].

Opiate detoxification is an especially difficult process, and pharmacotherapy is used in the majority of inpatient cases. Results of pharmacotherapy trials have shown the most effective treatment to be substituting and tapering methadone or buprenorphine [44]. In addition, for patients with poly-substance dependence, research has demonstrated that a combination of buprenorphine and valproate is a safe and effective option for the treatment of a variety of withdrawal symptoms [45]. One study found that during opiate detoxification, the combination of psychosocial treatments and pharmacotherapy significantly aided long-term treatment effectiveness [46]. For some patients, long-term treatment (i.e. maintenance therapy) with methadone, buprenorphine or other medications may allow them to avoid withdrawal symptoms while abstaining from the drug of abuse.

Relapse prevention

Relapse occurs in a very high percentage of individuals who receive treatment for an SUD. For example, prevalence of relapse for those recovering from alcohol dependence or nicotine dependence is approximately 75% one year after treatment [47, 48]. As a result, identifying ways to decrease rates of relapse has been an important area of focus among researchers studying psychopharmacological treatments for SUDs. For many patients, pharmacological interventions are viewed as a vital component of their long-term treatment. By blocking the positive effects associated with drug use, reducing craving for the drug or inducing negative consequences of drug use, pharmacological interventions have been a key factor in assisting many drug users to maintain drug abstinence [49]. Pharmacotherapy can be an important addition to long-term psychosocial treatment of SUDs, and may also assist with treatment of comorbid psychiatric symptoms. This may further prevent risk of relapse due to psychiatric illness and may help to increase compliance in addiction treatment [50]. For example, studies have shown that treatment with selective serotonin reuptake inhibitors enhance relapse prevention in alcoholics with comorbid depression [51, 52]. In their 12-week placebo-controlled study, Moak and colleagues found treatment with sertraline and cognitive behavioral therapy to reduce both depression

and alcohol use in subjects, compared to control groups. Kranzler's multi-site study replicated these findings.

11.4 Considerations in pharmacotherapy trials for SUDs

Given the prevalence of SUDs and the relatively low rates of success for substance use treatment (i.e. approximately 90% of outpatients experience relapse within one year [53, 54]), it is clear that improved treatment options could have tremendous public health implications. As a result, research continues in the area of both psychosocial treatments and pharmacological treatments for SUDs. Unfortunately, many factors complicate this research, which has slowed the progression of the field. General issues, which plague all pharmacotherapy trials but may require additional consideration with SUD patients, as well as special problems specific to this population, are reviewed below.

General issues to consider

Recruitment

As in any clinical trial, selection of appropriate participants is vital to the quality of the data that are collected. Recruitment of participants for trials evaluating pharmacological treatments of SUDs can be particularly challenging for a number of reasons. First, identification of a sufficient number of participants has remained problematic within the field. Indeed, a significant number of the published studies include few participants, which limits power for the analyses and may limit generalizability of the results. For example, Mitchell and colleagues [55] conducted an elegant study of Australian methadone maintenance patients, which compared the efficacy of slow-release oral morphine to methadone as a maintenance pharmacotherapy option for patients with opioid dependence. Although they were able to demonstrate favorable results of slow-release oral morphine pharmacotherapy, they only recruited 18 patients to participate, and only 15 patients completed the study. Such data are not sufficient to warrant drastic changes in clinical care, so more work is needed to replicate these findings and extend them to patients from different environments.

Second, results of the study may be affected by the population from which the participants are selected. The decision to use 'treatment-seeking volunteers' versus a random sampling of substance abusers in general may influence interpretation of the results. Given that motivation for treatment is generally low among individuals with SUDs, inclusion of only treatment seekers may artificially inflate the success rates for the trial, compared to what would be expected in the clinical setting. On the other hand, recruitment of individuals who are not interested in treatment might not provide an accurate view of the efficacy of the intervention among individuals who are motivated for treatment. An exception to this problem is when the purpose of the trial is to determine participants' physiological or psychological response to the medication, without attempting to change their behavior. For example, Wachtel and de Wit [56]

conducted a laboratory study assessing the physiological and subjective effects of pre-treatment with naltrexone, prior to administration of tetrahydrocannabinol (THC). Using a placebo-controlled, double-blind, within-subject cross-over design, they were able to demonstrate that naltrexone did not alter the effects of THC among regular marijuana users.

Third, determination of appropriate compensation for study participation can be challenging in this population, due to the ethical challenge of providing monetary compensation or other items of value which might be sold or exchanged for drugs. This can be particularly problematic if close supervision of the participants is not possible. As a result, some researchers have attempted to utilize rewards that are consistent with treatment goals. For example, in one study [57] assessing the feasibility of every-fifth-day dosing of buprenorphine (as compared to daily dosing or every-third-day dosing), participants were compensated \$50 if they reported to the clinic for each dosing and remained abstinent from opioids (as confirmed by urine screenings). Obviously, this creates additional problems for the interpretation of the study results, because the investigators introduced a behavioral treatment (i.e. contingency management) into the study protocol as ‘compensation’ for participating in the pharmacological trial. Because they did not include a ‘no compensation’ control group, it is impossible to determine whether abstinence rates were affected by buprenorphine dosing, motivation to receive the \$50 compensation or both.

Finally, participation in a pharmacotherapy trial for treatment of SUDs frequently requires making multiple visits to the study site each week. This may be overly burdensome for individuals with family or work responsibilities, and can be particularly challenging to individuals who do not have reliable transportation. Some investigators have attempted to manage this problem by providing transportation (i.e. fare cards, taxi service to appointments, etc.), but this can add significantly to the cost of the trial and limits generalizability of the results to individuals who have transportation available to them.

Comorbidity

Once potential participants are identified, most published studies delineate fairly stringent inclusion/exclusion criteria to improve the internal validity of the study. For example, many studies exclude participants who meet criteria for an additional Axis I diagnosis (e.g. depression, anxiety, psychosis, eating disorders, etc.). Given the extremely high prevalence of psychiatric comorbidity among patients with SUDs [58, 59], this can be particularly problematic. Pharmacotherapy for SUDs is often challenging, and individuals with comorbid psychiatric conditions may not have the resources (financial or otherwise) to maintain their pharmacological regimen. For example, they may have limited transportation options to get to the clinic for methadone dosing. They may not be able to afford prescriptions for their medications. In addition, they may have increased difficulty remembering to take their medications or following the regimen as prescribed. Patients with comorbid psychosis may also be suspicious of the doctor or medication and may be unwilling to take the medication as directed. As a result, studies that exclude these individuals may have artificially-inflated success rates.

On the other hand, many patients with psychiatric conditions may also be receiving treatment for that disorder, which could influence their drug use behavior. For example, noradrenergic antidepressant medications have been targeted as potential treatments for individuals who abuse stimulants. Szerman and colleagues [60] conducted a small study in Madrid, Spain in which reboxetine demonstrated some efficacy in the treatment of cocaine dependence. In addition, patients who are undergoing psychotherapy for a psychiatric condition may learn coping skills that also help them to manage their drug use. This may contribute to any positive outcomes they demonstrate while participating in the pharmacotherapy trial. Similarly, inclusion/exclusion of patients with comorbid medical conditions can also be problematic. Some medications are contraindicated for patients with certain medical disorders due to side effects or negative interactions with other medications. Some conditions may also affect the way that medications are metabolized, thereby reducing their efficacy for those patients.

Random assignment

Given that random assignment is generally considered a critical component of clinical trials, this aspect of study design cannot be overemphasized. Unfortunately, random assignment is not always possible in pharmacotherapy trials for patients with SUDs due to issues of both safety and convenience. For example, Vigezzi and colleagues [61] conducted a field study in Milan, Italy comparing use of methadone and buprenorphine for individuals who were dependent on both heroin and cocaine. Although random assignment to the methadone condition or the buprenorphine condition would have been preferable, some patients were not eligible for treatment with methadone due to a history of severe respiratory failure, colelithiasis, pancreatic disease or methadone intolerance, and some patients were not eligible for buprenorphine treatment due to ongoing methadone maintenance treatment, hepatic/renal failure, comorbid alcohol or benzodiazepine abuse or comorbid DSM-IV Axis I disorder. As a result, patients in this study were informed of their options and selected which treatment they would receive. When the data were analyzed, it became apparent that the group of individuals who selected buprenorphine treatment had higher baseline DSM-IV Global Assessment of Functioning (GAF) scores than the group who selected methadone treatment. In general, higher baseline GAF scores are associated with improved treatment outcome for patients with an Axis I diagnosis [62, 63]. Although the buprenorphine group demonstrated better outcomes than the methadone group, it is likely that the results were confounded by the higher baseline GAF scores in this group.

Double-blind procedures

Much like randomization, use of a double-blind procedure is important to the conduct of clinical trials. This allows investigators to interpret the findings with more certainty, because they can account for the ‘placebo effect’ and minimize expectancy effects of the study participants. Unfortunately, use of double-blind procedures can be very difficult to implement with this population. Elaborate procedures may need

to be undertaken in order to adequately mask whether the active or inert substance is being consumed (or what dose is being administered). Even under these conditions, blinding may not be successful. For example, Ray and Hutchinson [64] conducted a study examining genetic moderators of the effects of naltrexone on alcohol sensitivity using a placebo-controlled, within-subjects double-blind laboratory trial. They found that 79% of participants guessed correctly when administered the placebo and 72% guessed correctly when administered naltrexone. Given the significant expectancy effects that have been demonstrated in alcohol sensitivity [65], the subjects' beliefs may have influenced the results of the trial.

Treatment drop-out

As in all clinical trials, treatment drop-out is a significant problem plaguing pharmacotherapy trials for the treatment of SUDs. In fact, attrition rates for this population are typically much higher than those seen in clinical trials for patients with other psychiatric disorders [66].

There are many ramifications of treatment attrition. First, differential treatment attrition between groups may reflect actual problems that need to be addressed. For example, participants in one arm of the study may drop out due to significant difficulty following the regimen or side effects of the medication. However, if they do not return to complete the study assessments, the investigators will not obtain this information. Second, non-completers result in a great deal of missing data.

As a result, investigators must rely on intent-to-treat (ITT) analyses and/or completer analyses to evaluate the data. Both methods have flaws that negatively impact interpretation of findings. ITT analyses may provide the best measure of the overall efficacy of the intervention, when taking into account the fact that many clinic patients will also drop out of treatment prematurely [67]. However, due to the lack of follow-up data, ITT analyses utilizing the 'last observation forward' results may be considered insensitive if a large number of patients drop out [68]. In this case, the analyses may fail to account for any treatment success that was achieved (if the participant responded well to treatment but did not return for follow-up) or overestimate any treatment success (if the participant was initially responding favorably to treatment for a short time but failed to return for any follow-up assessments after relapsing to drug use). In addition, the lack of success demonstrated by the treatment drop-outs may mask significant improvement among the treatment completers. On the other hand, completer analyses may overestimate the effectiveness of the treatment in the 'real world', where patients are typically not monitored as closely as research participants, and rates of treatment attrition may be even higher than in the study.

On a related note, some investigators adopt fairly extreme measures in order to retain the participants in the study. For example, study participants may be provided with transportation, free medication, food, counseling and/or monetary compensation for treatment participation. Although this approach generally results in the collection of more usable data, the study will have limited external validity because community clinics will not have the resources to entice their patients to come for treatment with these same rewards. Other investigators have combined pharmacotherapy with psychological and/or behavioral interventions, as this has demonstrated efficacy in

reducing attrition (for a review see [69]). However, this approach also results in difficulties interpreting the study results, as it is difficult to separate the effects of the two interventions.

Treatment non-adherence/non-compliance

Much like treatment drop-out, treatment non-adherence/non-compliance negatively affects the outcome of pharmacotherapy trials for addiction. Non-adherence may increase participants' experience of side effects and promote treatment drop-out. In addition, lack of adherence will minimize the efficacy of the intervention, resulting in less-robust findings. Study participants' perception of their disease can influence compliance with the therapy. For example, some individuals may be in denial about their SUD, leading them to refuse treatment or underestimate the importance of adherence to the prescribed regimen. In other cases, the individuals may actively choose not to take the medication as prescribed, in order to retain the ability to experience the euphoric effects of their drug of choice. Still others may show poor adherence/compliance due to ignorance. As a result, psychoeducation regarding the appropriate use of the medication is a necessary component to any pharmacotherapy trial. Adherence may also be improved by simplifying the treatment regimen, minimizing unpleasant tasks and helping patients learn convenient ways to adhere. For instance, in their study of naltrexone vs. acamprosate for treatment of alcohol dependence in Australia, Morley and colleagues [70] provided four to six sessions of 'compliance therapy' to assist patients with the regimen.

Researchers may attempt to track treatment adherence using various strategies. For example, Morley *et al.* [70] asked participants to return the pill container at the end of the study in order to count the remaining pills. Others utilize electronic monitoring devices to assess when the pill container was opened. Others utilize even more 'high-tech' procedures. For example, in their study assessing the use of naltrexone and fluoxetine to treat heroin addiction in St Petersburg, Russia, Krupitsky and colleagues [71] infused the pills with a riboflavin biomarker. They were then able to perform urine tests on the study participants to assess for the presence of riboflavin, in order to ensure medication adherence. Unfortunately, none of these methods is fail-safe, and treatment adherence remains a significant concern in this area of research.

Concurrent therapy

Research has demonstrated that combining pharmacotherapy with psychosocial interventions (e.g. cognitive-behavioral therapy, participation in a 12-step program etc.) can improve outcome for patients with SUDs [69]. As mentioned previously, participation in psychosocial treatment may actually improve adherence to the medication, thereby improving the data that are collected. Unfortunately, this introduces an additional difficulty to the conduct of pharmacotherapy trials. Assuming that participation in psychosocial treatment does improve outcome, there are ethical concerns related to withholding psychosocial treatment from individuals while they participate in a pharmacotherapy trial. However, providing a concurrent therapy

may minimize between-group variance, decreasing the strength of the findings. In addition, it is difficult to standardize exposures to psychosocial treatments. For example, the skill of the therapists can vary, the quality of rapport between the patients and therapists may differ and the patients' level of investment in the treatment program (i.e. adherence to the 12-step philosophy) can influence the efficacy of the psychosocial intervention.

Special problems in pharmacotherapy trials for SUDs

In addition to the many factors that must be considered by researchers conducting pharmacotherapy trials for patients with other disorders, researchers working with patients who have SUDs face additional challenges. The nature of addiction and its associated consequences complicate the clinical and research picture, resulting in increased problems for investigators. Some of the specific challenges are highlighted below.

Safety concerns

One of the most important considerations when conducting a pharmacotherapy trial for patients with SUDs is maintaining patient safety. To begin with, some medications utilized for treatment of SUDs may have abuse potential themselves. As a result, strict monitoring and/or dispensation of the medication by study personnel may be necessary. In other cases, the medication may interact with the patient's drug of choice. In this situation, any relapse to drug use would be dangerous to the research participant. For example, patients who are receiving methadone maintenance treatment can experience an opiate overdose if they use additional opiates while taking methadone. In addition, some medications are contraindicated in patients who have specific medical concerns (e.g. decreased liver function), which is more common among individuals with a long history of drug and/or alcohol abuse. As a result, many patients who might otherwise benefit from the medication under study may be excluded from the trial. Similarly, individuals with a significant history of drug or alcohol use may metabolize certain substances differently, resulting in the potential for over- or under-dosing. Researchers must therefore evaluate the health status of potential research participants prior to enrollment. Finally, many pharmacotherapy trials for patients with SUDs include studies of 'off-label' use of FDA-approved medications. For example, Szman *et al.* [60] evaluated the use of reboxetine to treat cocaine dependence among patients in Spain. Krupitsky and colleagues [71] examined whether fluoxetine might assist with relapse prevention for patients with heroin dependence in Russia. Off-label use of medication always presents additional risks, so investigators must work with supervising clinicians and be vigilant to adverse effects.

Drug of choice/polysubstance abuse

Typically, individuals must report a certain frequency, duration, stability and severity of substance use to qualify for the study. This helps to ensure that any changes in substance use are related to study interventions. However, it may limit conclusions

about the efficacy of the pharmacotherapy to patients with severe SUDs, as opposed to problematic users who may not meet abuse or dependence criteria. In addition, many studies limit participation to individuals who do not abuse other drugs. For example, studies of a pharmacological intervention for opiate dependence may exclude individuals who also use cocaine, marijuana or other drugs. Although many individuals with SUDs report a preferred drug, the majority will also abuse other substances [72]. As a result, conducting the study with only mono-drug users can severely impact the interpretation of the findings and the generalizability of the results. Decreases in use of one substance may lead to increased use of other substances. In addition, drug interactions may negatively impact the effectiveness of the pharmacological intervention or lead to additional side effects. Polysubstance abuse may also be related to decreased adherence to the regimen and/or increased treatment drop-out.

Measurement of treatment outcome

Many clinicians who work with patients with SUDs would assert that the goal of treatment is to promote ‘recovery’ within the patient. However, there is disagreement within the field regarding what constitutes recovery, and the perceived efficacy of a pharmacological intervention may depend on what type of outcome is measured. For example, recent meta-analyses comparing pharmacological trials of acamprosate and naltrexone for the treatment of alcohol disorders have suggested that acamprosate may assist patients to achieve abstinence from alcohol whereas naltrexone may be more effective for reducing heavy drinking [73, 74]. Efforts supported by the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse have resulted in major improvements to the measurement of treatment outcome [75–77]. For example, many studies now assess for number of drinks on drinking days, number of drinking (or drug use) days, time to first drink (or drug use) following the intervention, success with controlled drinking, alcohol/drug craving, withdrawal symptoms and affective or psychiatric symptoms.

However, even these extensive outcomes may not fully assess the individual’s recovery status. Indeed, the Betty Ford Institute Consensus Panel has recently suggested a more comprehensive definition of ‘recovery’ that includes (i) sobriety, (ii) personal health and (iii) citizenship [78]. Although having a standard definition represents an important advance in this area, those components are extremely difficult to measure. For example, sobriety – seemingly the most straightforward of the criteria – can be difficult to monitor. Use of self-report is the most cost-effective, but may not provide accurate data. Individuals may not recall or be able to report their usage accurately, particularly if using drugs or alcohol in large amounts. In addition, individuals are not always honest regarding reporting drug and alcohol use. Frequent drug screening via urine, blood, breath or hair samples may provide more accurate and reliable results. However, these methods are expensive and can be invasive and/or burdensome, particularly if patients are being treated on an outpatient basis. The drug screening itself may sometimes become a contingency management treatment [79]. Sometimes other biomedical measures (e.g. liver function tests) are utilized to estimate exposure to drugs of abuse, although these procedures share

many of the same problems as drug screening. Yet another difficulty relates to polysubstance abuse. Many medications were developed to treat abuse of specific drugs, but SUD patients often use multiple drugs. As a result, the medication may help the patient abstain from one drug of abuse while s/he continues to use other drugs. Does this constitute 'abstinence?' Is this a 'successful' treatment? These issues necessitate further study. Finally, the personal health and citizenship components of recovery cannot easily be operationally defined, making them very difficult to assess across treatment and follow-up. More research is needed to determine how to evaluate these important areas of outcome.

An additional concern related to measurement of treatment outcome is the length of the follow-up period. Although many studies assess individuals' ability to achieve abstinence, their likelihood of achieving long-term maintenance of sobriety frequently remains unknown. As relapse is common among individuals with SUDs, this information is vital to the advancement of clinical care. Many studies follow the participants for only a short period of time. For example, Baltieri and colleagues [80] compared topiramate to naltrexone in the treatment of alcohol dependence among patients in Brazil. Although they utilized stringent research methodology (i.e. a double-blind, placebo-controlled study with a relatively large sample), they only followed the study participants for a period of 12 weeks. Obviously, this period of study was insufficient to determine the effectiveness of these medications. Follow-up assessments at 12 months or longer are needed to assess accurately the efficacy of the medications in preventing relapse.

Measurement of associated symptoms

Along with measurements of primary outcome (i.e. abstinence from drugs), many researchers and clinicians are interested in secondary outcomes such as intensity and frequency of cravings, experience of withdrawal symptoms, general mental health, quality of primary relationships, return to work, lack of criminal activity and overall daily functioning. Although some of these data can be obtained via public record (e.g. arrests and incarcerations), others can be difficult to assess. Again, most researchers rely on self-report or collateral report to provide data in these important areas. More work is needed to identify improved methods for evaluating important secondary treatment outcomes, in order to more fully understand the potential benefits of pharmacotherapy for SUDs.

Prevalence of relapse

As most clinicians are aware, relapse is the rule rather than the exception for patients with SUDs. In general, more than half of patients treated for an SUD will experience relapse, generally within the first year following discharge. Originally defined as failure of treatment or catastrophic loss of 'recovery status', relapse is now considered an expected part of the addiction cycle. Unfortunately, this high rate of failure makes the conduct of pharmacotherapy trials for SUDs particularly challenging. Assessment of long-term outcomes following cessation of the treatment will likely mask any short-term efficacy of the medication, due to the high rates of relapse that are typical

to this population. As discussed earlier, relapse negatively affects the results of pharmacotherapy trials, because it frequently results in treatment drop-out just at the time when increased clinical attention is needed.

Treatment setting

The choice of treatment setting for the study (e.g. laboratory, inpatient, outpatient or partial hospitalization) may be determined by cost, convenience or other parameters of the study. Appropriate choice of setting may help to alleviate many of the problems listed above, such as safety concerns, issues of compliance, assessment of treatment outcome and participation in concurrent psychosocial therapies. For example, conducting the trial within an inpatient hospital setting may minimize safety concerns related to manipulating doses, overdose or withdrawal, drug interactions, severe side effects or other medical complications. It may also assist with adherence to the treatment protocol, as staff members will be available to monitor medication dispensation. Observer ratings can be collected as an additional assessment of treatment outcome, and patients can be assigned to participate in standard psychosocial treatments within the hospital setting.

However, the majority of patients do not receive inpatient treatment for SUDs, so results of such studies may not generalize to community-based clinical care. Outpatient settings are generally most similar to community-based clinical care, but they present a number of challenges (e.g. transportation problems, inconvenience to participants, difficulty monitoring treatment adherence, difficulty monitoring drug/alcohol use, etc.). Laboratory-based studies may be most appropriate when evaluating short-term effects of a medication under controlled conditions. For example, Parasrampur and colleagues [81] conducted a laboratory-based study examining the abuse liability of methylphenidate in various formulations. This allowed them to complete a double-blind crossover study while monitoring safety, side effects, participant ratings and blood samples from the participants at predetermined intervals pre- and post-medication. Such analyses would have been impossible in an outpatient setting.

11.5 Conclusions and future directions

Pharmacotherapy for SUDs is clearly an important area of study. Millions of people worldwide suffer from drug and alcohol use disorders, and more effective treatments are needed to decrease rates of relapse among this population. Unfortunately, many factors impede the development of new interventions and create barriers to evaluating their efficacy. Psychopharmacological trials for SUDs are fraught with limitations, but investigators continue to attempt to find more reliable, valid and generalizable methods for assessing these medications. Future research will need to extend the results of tightly-controlled randomized trials to community-based settings in order to identify the barriers faced by 'real patients'. In addition, more trials are needed to replicate promising findings from newly-discovered potential interventions. Results of this research could have tremendous impact on public health.

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12

Clinical Psychopharmacology of Patients with Eating Disorders

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Abstract

In this chapter we will review the current knowledge concerning both the design and conduct of trials examining the efficacy of pharmacotherapy for patients with eating disorders. One of the first issues that needs to be considered is what diagnostic criteria to use, since many patients seen clinically for eating disorders do not meet full syndromal criteria. Various assessment strategies have been developed including both self-report and interview-based measures. There are also a number of methodological and statistical issues to consider, some common to pharmacotherapy trials in general and some specific to eating disorder trials. Consideration also needs to be given to combined trials which involve both pharmacotherapy and psychotherapy components. In general, trials in eating disorder patients have been modest in size and relatively brief. Both of these variables are at least partly attributable to the lack of interest in eating disorders on the part of the pharmaceutical industry.

Key Words

psychopharmacology; anorexia nervosa; bulimia nervosa; binge eating disorder; eating disorders; clinical trial

12.1 Introduction

The purpose of this chapter is to review our current knowledge concerning the design and execution of trials that examine the efficacy of psychopharmacological

interventions in patients with eating disorders. We will focus on bulimia nervosa (BN), anorexia nervosa (AN) and binge eating disorder (BED). We will begin by discussing various diagnostic issues related to subject selection. In particular, we will focus on the growing awareness that many individuals who are seen for evaluation and treatment of an eating disorder do not meet full diagnostic criteria. Indeed, in many clinical samples eating disorders not otherwise specified (EDNOS) constitutes the most common diagnosis. Therefore, we need to make decisions regarding the possible inclusion of both full and subsyndromal patients. Also, issues related to comorbidity should be considered, since the prevalence of comorbidity is quite high among these patients.

We will then turn to a discussion of assessment strategies, including self-report measures, interview-based measures and the use of some of the new emerging strategies including the use of human feeding laboratory research.

Next, we will discuss a number of methodological and statistical issues including stratification, randomization procedures, adherence assessment and inter-rater reliability determination and data analytic techniques. We will then turn to a discussion of pharmacotherapy trials including their design, duration, target population and treatment setting and the proper selection of controls or contrasting treatments. We will then briefly discuss combined trials where both psychopharmacology and pharmacotherapy are used.

12.2 Diagnostic issues

An important initial consideration in designing trials for patients with eating disorders is the choice of diagnostic criteria to use. Traditionally the most straightforward option has been to include full Diagnostic and Statistical Manual, 4th edition (DSM-IV) diagnostic criteria for the standard eating disorder diagnoses: AN and BN. However, research has fairly consistently shown that the majority of patients seen in most outpatient clinics for eating disorder do not meet full diagnostic criteria for either AN or BN. Using standard DSM-IV criteria, the majority would parsimoniously be diagnosed as EDNOS [1]. However, since the definition of EDNOS is unfortunately fluid (with only a few examples offered) and can be interpreted very broadly to include any disordered eating, using such a diagnosis as a criterion for inclusion in a trial would result in a very heterogeneous patient mix.

One consideration is the possible inclusion of subsyndromal patients. This can be accomplished in several ways, and there is no standardized format for doing so. For example, for subjects with BN, frequency criteria can be altered (e.g. requiring binge eating and compensatory behaviors present only once a week). For patients with AN, the weight criteria can be liberalized to include patients at a low body weight who do not meet full criteria (e.g. those <90% of ideal body weight for height and age), and the criterion for amenorrhea can be omitted. It seems fairly well established at this point that amenorrhea does not improve diagnostic

specificity for AN [2]. The problem with including subsyndromal patients is the lack of standardization.

Subgroups of EDNOS can be included. The number of possible permutations here is enormous. The most obvious and common example would be to study BED as defined in the appendix of the DSM-IV. Generally these criteria have been used in treatments for BED, despite the fact that these criteria were included as criteria for further study [3]. Therefore, there is a paucity of data using alternative diagnostic models.

EDNOS can also be broken down beyond the obvious categories of subsyndromal AN and BN cases, as well as BED. One additional possible subtype which has received some attention in recent research (although not in controlled treatment studies) is 'purging disorder' where patients purge, but do not engage in objective binge eating episodes. This pattern apparently is not uncommon [4]. Other subgroups are also possible.

If we examine the recent literature and current opinions in the field, the following general guidelines can be suggested.

- 1 When studying subjects with BN, the inclusion of subsyndromal patients, particularly those who engage in the targeted abnormal eating behavior at less than the required frequency, is probably highly desirable. A cutoff in the neighborhood of once per week rather than twice per week for binge eating is reasonable. Most studies also include both purging and non-purging disorder subgroups, although the percentage of non-purging patients is usually quite small. This remains a somewhat controversial category [5].
- 2 Regarding AN, there is more variability. The single criterion which is most commonly altered is amenorrhea, which is often omitted. Whether more liberal weight criteria should be used is unclear.
- 3 Regarding BED, the criteria suggested in the appendix of DSM-IV appear reasonable.

However, all of these suggestions leave a sizeable subgroup of patients with EDNOS unassigned. This, of course, raises interesting questions about how eating disorder diagnoses will be dealt with in the DSM-V. We can hope that some changes in the next edition of the DSM may well provide better guidance in terms of diagnostic issues in clinical trials.

Another issue relative to inclusion versus exclusion concerns comorbid psychopathology. In general, subjects who have active or recent alcohol or other substance abuse or dependence or are suicidal are excluded. Generally, other forms of psychopathology commonly encountered, such as mood and anxiety disorders and not uncommonly personality disorders, are not exclusion criteria, although blocking on comorbidity may be considered. Increasingly, research has shifted toward a focus on as few exclusion criteria as possible. In this field as in many psychiatric fields, there is increasing pressure to demonstrate the generalizability of findings to clinical samples.

Assessment/dissemination methodologies

Assessment is an extremely important area in psychopharmacology trials with eating disorder patients. The saying ‘garbage in, garbage out’ applies not only to the data participants provide about important variables of interest (e.g. depression or anxiety levels, health-related quality of life, eating disorder symptoms), but also designation of group membership, often determined by a clinician administered interview. Choosing assessments that consistently demonstrate excellent psychometric properties is important.

A number of self-report assessments are currently available to assess eating disorder patients in psychopharmacology trials. According to Pike and colleagues [6], the following self-report questionnaires are used most often to assess eating disorder patients:

- 1 The Questionnaire on Eating and Weight Patterns – Revised [7]: a 28-item self-report measure that has most often been used to identify and diagnose BED. This is the best available self-report instrument for BED.
- 2 The Eating Disorder Inventory – 2 [8]: a 91-item questionnaire that purports to measure behaviors, attitudes and traits thought to be clinically relevant to eating disorders. Widely used to measure eating disorder psychopathology.
- 3 The Three Factor Eating Questionnaire [9]: a 51-item assessment of three dimensions (cognitive restraint, disinhibition and hunger) of eating dysregulation associated with eating disorders.
- 4 The Mizes Anorectic Cognitions Questionnaire [10]: available as a 24-, 33- or 45-item questionnaire. It purports to assess the cognitive distortions associated with AN and BN.
- 5 The Bulimia Test – Revised [11]: a 36-item assessment of compensatory behaviors, binge eating and weight/shape concerns associated with BN. Also widely used.
- 6 The Eating Disorder Examination Questionnaire [12]: a 38-item self-report measure that is modeled after an interview assessment (described below). The EDE-Q purports to assess key pathology associated with eating disorders. Self-report of binge eating is problematic however, and interview assessment is preferred when feasible.

Besides these commonly used measures, several other self-report measures are relatively popular, for example, the Eating Attitudes Test [13]. Also, other types of measures, such as health-related quality of life assessments, are gaining popularity and being used more frequently. Recently developed health-related quality of life measures specifically developed for and validated with eating disorder patients have recently become available [14].

In addition to self-report measures, interviewer-administered assessments are also available. Two semi-structured interviews are most frequently used with eating disorder patients:

- 1 The Structured Clinical Interview for DSM-IV (SCID) [15]: for diagnosis of Axis I disorders. State-of-the-art for Axis I assessment.
- 2 The Eating Disorder Examination (EDE) [16]: for the assessment of eating disorder diagnosis and psychopathology. The EDE interview provides diagnostic criteria information based on DSM-IV, and also provides four subscale scores of key pathology that are associated with eating disorders: restraint, eating concern; weight concern and shape concern. Best available interview for diagnostic assessment and assessment of eating-related psychopathology.

Finally, clinical interviews are also used to assess eating disorder patients. Both observer-based rating scales and unstructured interviews have been used under the general rubric of clinical interviewing to assess the central features of eating disorders.

12.3 Methodological/statistical issues

A detailed account of methodological considerations in randomized controlled trials is provided by Meinert [17]. Readers interested in statistical issues are referred to the statistical guidelines developed by the International Committee of Harmonisation [18] and the International Journal of Eating Disorders [19]. A brief description of some of the methodological and statistical issues encountered in eating disorder research is provided below.

Randomization, stratification and blocking

The goal of randomization is to assign patients to treatments on the basis of chance occurrence, thereby minimizing differences between treatment groups that may influence outcome. Any differences between randomized treatment groups are due solely to chance and are unrelated to the treatment to which they are assigned. Most eating disorders studies involve *fixed randomization* where assignment probabilities remain constant over the course of the trial. In contrast, *adaptive randomization* uses assignment probabilities that change as a function of the distribution of previous assignments, observed baseline characteristics or observed outcomes. Fixed randomization schemes will be described below. Adaptive randomization schemes are described in detail by Kalish and Begg [20] and Rosenberger and Lachin [21].

All fixed randomization procedures can be characterized in terms of three properties: assignment probabilities, the number of strata and the block size. The *assignment probabilities* indicate the chance of assignment to each treatment. Most eating disorder studies employ equal probabilities of assignment for all treatments (i.e. 0.50/0.50 for a two-group study; 0.33/0.33/0.33 for a three-group study etc.). However, there may be some circumstances (e.g. costs, safety, prior data and anticipated variability in response) in which non-uniform probabilities are used. For example, in some drug studies higher drop-out rate may be posited for certain groups and an inadequate

investigator may be compounded to bias the randomization if this occurs. *Stratification* refers to the number of predefined categories into which patients are placed prior to randomization. A common variable used to stratify patients in eating disorder trials is baseline severity (e.g. high vs. moderate severity). Another commonly used stratification is higher or lower BMI in studies of AN. A third example would be the presence or absence of comorbid depression in BN trials. The goal of stratification is to reduce variation in the outcome due to the stratification variables. Stratification has the greatest impact on small trials involving 20 or fewer patients per treatment group, and has minimal impact on designs involving 50 or more patients per group [22].

The *block size* describes the number of patients that are randomized in a given sequence. For example, a block size of eight in a two-group trial would result in eight patients being randomized in a given sequence, four to each treatment (assuming equal assignment probabilities). Blocking achieves a relative balance of patients assigned to treatments over time, thereby removing a potential source of bias. Blocking should be used for studies conducted over an extended period of time (months or years) or when the patient population is expected to change over the course of the study.

Adherence assessment

One of the crucial elements of eating disorders treatment research is the assessment of the degree of adherence to the treatments being delivered. This can include a variety of factors such as the number of completed sessions, the amount of treatment actually received at each session (e.g. dose of medication) and the specific content of treatment being delivered. Frequently in studies using both pharmacotherapy and psychotherapy, psychotherapy sessions are taped and rated by experts in terms of the degree to which the content actually being delivered corresponds to prescribed treatment components. For example, Agras and colleagues [23] developed an instrument to rate the specific components of cognitive behavioral therapy being delivered to patients with BN in a multi-center trial. Another measure relevant to this topic is the Hill Process Rating System [24] which provides an empirically validated measure of treatment integrity and process. Medication management visits can also be taped and monitored for content. Such assessments are crucial in the conduct of such trials. This type of monitoring not only allows the investigator to supervise and direct therapist behavior, but also serves as a powerful reminder to therapists for the need for treatment manual adherence.

Statistical power and sample size

Statistical power is the probability of finding a significant difference between treatments in a study given that a difference actually exists. Statistical power is determined by the significance level (α), the magnitude of difference between treatments and the sample size [25]. Greater statistical power is achieved by using a higher significance level, comparing treatments with greater differences and increasing the sample size. Lack of statistical power has been a major problem in AN treatment research.

In a field such as eating disorders, where the efficacy of treatments is often quite modest, it is important to ensure that treatment studies are designed with adequate statistical power. A variety of textbooks [17, 25, 26], stand-alone software programs (e.g. G-Power, PASS) and integrated statistical applications (e.g. SAS, SPSS) are currently available for calculating statistical power and determining the sample size necessary to achieve adequate power.

Statistical analysis plan

A statistical analysis plan should be prepared prior to the initiation of the eating disorders research trial. This plan serves to ensure that the primary questions of interest can be adequately addressed. This analysis plan should include items such as a power analysis and sample size estimation, the primary and secondary hypotheses to be evaluated, a specification of the primary and secondary outcome measures and specific analyses to be conducted.

Trial monitoring

One of the primary tasks of the statistical personnel during the course of the study is the ongoing monitoring of the trial. This should include monitoring of recruitment rates in relation to the recruitment goals, verifying that all enrolled patients have provided written informed consent and meet inclusion/exclusion criteria, ensuring that the protocol is being followed (e.g. the correct assessments are being completed at each study visit), monitoring patient characteristics, checking the integrity and completeness of the collected data (i.e. are all items being completed), verifying the data entry procedure, evaluating retention and follow-up rates and monitoring adverse events. In the event of multi-site trials, monitoring should be performed separately at each site to ensure that all sites are compliant.

Missing data

Most, if not all, eating disorder treatment studies will have some missing data. Schafer and Graham [27] have described a variety of approaches for handling missing data. Most of these methods assume that observations are missing randomly, an assumption which is almost always false. Methods that involve deleting cases (e.g. complete case analysis) and replacing missing values based upon some rule (e.g. mean substitution, last observation carried forward) are generally discouraged in favor of methods that use all available data (e.g. hierarchical linear models [28]) or replace missing values using maximum likelihood or multiple imputation methods [29]. The ability of the study to provide useful information about the efficacy of eating disorder treatments is severely compromised when too many data are missing.

Statistical analyses

A variety of excellent textbooks are available which provide a detailed description of statistical analysis considerations in randomized controlled trials (RCTs) [17].

Particularly relevant to eating disorders, Kraemer and Thiemann [30] have argued that RCTs can provide important information about who is most likely to improve (i.e. predictors of outcome), for whom a particular treatment may work (i.e. moderators of treatment) and the mechanisms through which a treatment may achieve its aims (i.e. mediators of treatment). Eating disorders research has recently begun to utilize this methodology for identifying predictors, moderators and mediators in various eating disorder treatments.

12.4 Pharmacotherapy trials

Pharmacotherapy trials in the area of eating disorders have resulted in mixed data regarding efficacy, effectiveness and long-term outcome. Many pharmacotherapy trials have tended to use extensive exclusion criteria, and few have looked at long-term outcome. Among the eating disorders, BN has been most comprehensively studied and several medications have been found to be efficacious. More recently, pharmacotherapy trials have also accumulated for the treatment of BED, currently designated as an EDNOS. Medication has typically demonstrated favorable results in BED treatment, although findings must be evaluated in the context of the high placebo response rate observed in this population. AN has been the subject of comparatively few pharmacotherapy trials, particularly controlled trials. In the investigations of AN that have been published, little efficacy has been realized with pharmacological treatment.

Eating disorder pharmacotherapy trials are at times conducted in unique settings where the inclusion of other active treatments is often the rule rather than the exception. This is particularly exemplified in inpatient studies of AN, where patients are typically undergoing nutritional and/or medical rehabilitation programs, frequently with concomitant psychotherapy. As these treatments often lead to weight gain independently, there may be little opportunity for a medication to demonstrate additional efficacy. Thus, the full effect of the drug alone may not be apparent. Several issues should be considered when reviewing the eating disorder pharmacotherapy literature and are discussed as follows.

Design/duration

A variety of study designs are used in pharmacotherapy research in eating disorders. Reviews of the literature reveal an abundance of case report, case series and other open label trials which are uncontrolled and not randomized. Fewer RCTs have been published.

There are significant limitations of uncontrolled trials. First, the subjects of these reports are often patients who are not responsive to traditional treatments. Therefore, it may be difficult to establish the unique contribution, if any, of the medication being considered. Second, the reports are often biased, in that usually only positive reports are published providing a potential overestimation of efficacy. These types of reports can influence prescribers greatly and may lead to inappropriate prescribing of medications that may, indeed, lack efficacy or even have harmful consequences. For

example, positive case reports of amitriptyline for the treatment of AN were published early on [31]. Subsequently, RCTs were performed which demonstrated a lack of efficacy of amitriptyline for AN treatment [32, 33] coupled with significant adverse effects [33]. Therefore, translating case reports, case series and other uncontrolled data into clinical practice in the absence of an RCT is in many cases premature.

Although extrapolating findings from these uncontrolled trials directly to clinical practice is not recommended, these data are valuable for the identification of potential agents to examine in the more rigorous RCT paradigm. Examples from the eating disorder literature involving this sequence of uncontrolled to controlled trials are readily available. For instance, Kaye *et al.* [34] found beneficial effects with fluoxetine in an open-label trial in AN. Subsequently, two RCTs were conducted to examine this issue further, as will be discussed subsequently when we discuss relapse prevention [35, 36]. Another example is the research regarding the uses of second generation antipsychotics (SGAs) for treatment of AN. Case reports initially appeared in the late 1990s. Controlled trials were first published in 2008 [37, 38] with small numbers of subjects and unclear results, demonstrating the need for further trials with a larger *n*. In BN, ondansetron appeared efficacious in an uncontrolled trial [39] and this was subsequently supported in an RCT [40]. The BED literature reveals a series of investigations with the compound topiramate, first consisting of case series [41], then an open-label trial [42] and finally RCTs which suggested efficacy for the drug [43, 44]. BED in particular requires controlled trials prior to advocating a treatment due to the high placebo effect.

Another issue in considering pharmacotherapy trials concerns the involvement of the pharmaceutical industry. Generally, only industry has access to new molecules. Also, the cost of RCTs can be extreme. The relative lack of interest in funding eating disorder research by industry makes RCTs more infrequent. Eating disorders are associated with relatively low prevalence rates compared to other psychiatric conditions such as anxiety disorders and depression, as well as evidencing a more prominent application of non-drug treatments. Therefore, it is logical to surmise that funding RCTs in the interest of obtaining an eating disorder treatment indication in the package labeling has not been a priority of the pharmaceutical industry.

The duration of the controlled and uncontrolled trials is a point of concern. Many of the uncontrolled reports vary in duration and often long-term follow-up is absent. Even the controlled trials seldom cover more than a few weeks. A rarity is a trial with a duration of six-months or one year. This may limit generalizability, as the majority of eating disorder patients will require long-term treatment. Ideally, shorter term controlled trials are used to establish efficacy and are followed by longer term treatment trials to evaluate the sustainability of the effects. In BN treatment, the Fluoxetine Bulimia Nervosa Collaborative Study Group [45] studied the effects of fluoxetine over eight weeks in a large RCT and established the efficacy of this medication for BN treatment. Subsequently, a 52-week trial was performed by Romano *et al.* [46] to examine the longer term relapse prevention effects of this medication on BN. The drug was found to prevent relapse, but the results are difficult to interpret because of a very high drop-out rate that left very few patients still enrolled at the end of one year.

It is also beneficial to have more than one RCT concerning a particular treatment. This is imperative to demonstrate whether findings are replicable across studies. For example, in 2001 Kaye *et al.* [35] showed positive results with fluoxetine in a randomized, placebo-controlled one-year maintenance trial of AN. In 2006, a larger one-year placebo-controlled RCT was performed to examine this issue and found negative results [36]. This example will be subsequently discussed further, but serves to highlight the utility of evaluating multiple data sources.

Another issue to consider when evaluating RCTs is sample size, which can be particularly problematic in conditions with low prevalence rates such as the eating disorders. A trial with inadequate sample size may be underpowered to detect statistically significant differences and may leave the reader with an inappropriate conclusion about medication efficacy. Lack of power has been a major problem in AN treatment research. To facilitate determination of whether sample size is adequate in a particular report, measures of effect size and estimated power should be sought. The problem of sample size in AN studies has led to the development of multi-center trials; by necessity, these will be the standard in the future.

Other issues worthy of mention which can affect the quality of an RCT include whether it is a single-site or a multi-center trial. Multi-center trials generally offer the advantage of larger sample sizes, but may be a disadvantage if trial procedures are performed differently across sites. Therefore, results from multi-center trials should be examined for consistency between centers. Discrepant results by site may necessitate the completion of additional research prior to drawing conclusions. Also, baseline differences between groups (such as in body weight, frequency of comorbid conditions, concomitant treatments) can significantly influence results and should be statistically controlled for when present. A technique used to avoid this is stratified randomization, where participants are matched between groups at baseline on key variables of interest. Differences can also be addressed in the analysis using analysis of covariance.

Finally, it is important to consider whether the RCTs take into account treatment effects on comorbid conditions. Eating disorder participants have high rates of comorbidity, particularly with psychiatric disorders such as anxiety and depression. As an example, it has been established that antidepressants reduce binge eating and purging frequency in BN, independent of effects on depression [47]. Therefore, while RCTs are the gold standard for examining pharmacotherapy efficacy, readers must remain critical of their evaluation of trial methodology, results and conclusions.

Acute/relapse prevention

Investigations of the efficacy of pharmacotherapy interventions are often concerned with acute treatment efficacy. Thus, the trials occur in subjects who are exhibiting the maximum level of symptoms in an acute setting. In the area of eating disorders, lack of previous evidence of potential efficacy of drug treatments may necessitate the continuation of the standard treatments for the condition during the trial. This is true particularly for AN studies which are conducted in patients that are considerably underweight and may be medically unstable. With the ongoing concurrent non-drug therapies, which are effective for weight gain, the effects of the drug may be obscured.

Relapse prevention studies are useful in identifying efficacy of agents in preventing reoccurrence of symptoms in patients who have initially responded to treatment. An example is the randomized double-blind study reported by Walsh [36] concerning prevention of relapse in weight-recovered AN subjects with fluoxetine treatment over one year. This study was well controlled and had objective criteria for relapse. Fluoxetine was found to have no effect compared to placebo in preventing relapse. Some researchers have speculated that the divergent findings of these maintenance trials may be partly due to the observation that, in the earlier trial, some patients were enrolled prior to achieving full weight restoration [35]. Also, psychotherapy was not uniform among all participants in the first trial. This study also illustrates the need to know when a treatment does not work and the costs and risks of the treatment are not justified.

Inpatient/outpatient/community

Clinical trials may occur in any location that can supply the patient population that the investigator wishes to study. Inpatient trials are the usual settings for acute efficacy studies in AN, and are associated with unique risks as well as benefits. Additional risks that come into play in an inpatient trial include severity of the condition, concurrent treatments, informed consent and cooperation of the subjects. In the acute treatment setting, the patient may not agree with being in the hospital and their interest in volunteering for an experimental drug treatment may be low. However, the inpatient setting can provide close monitoring of subjects for adverse effects and compliance with study procedures.

Outpatient studies are usually conducted in patients with AN who are less ill than the inpatient trials, and in BN and BED patients in general. By virtue of having somewhat less severe symptomatology, subjects may be more willing to volunteer and comply with study procedures. However, confounding issues in the person's life may not be appreciated by the investigator. The subject may not be compliant with the medication. Other stresses that they are experiencing may interfere with drug effect and cloud the results. Drug compliance is often an issue. The investigator should consider the applicability of various methods to determine compliance such as pill counts and blood level assessments; inactive markers in the formulation of the investigational agent which can be detected in a urine sample, such as riboflavin [48], should be included. Other methods to enhance subject retention in the trial need to be explored. These techniques include subject payment for each visit or inexpensive gifts upon reaching a milestone point in the study. These retention techniques must be carefully balanced to compensate participants appropriately for time and/or effort without using incentives that may be coercive.

Controls

Controls in psychiatric studies can present ethical issues. Generally, placebo controls are only appropriate in studies involving conditions that are not progressive such that a delay in treatment would result in a worsening of the subject's condition. Numerous

placebo-controlled RCTs have been successfully performed in AN, BN and BED. Another design would be the use of an active control. Thus, all the subjects are receiving some level of treatment although the effects of the experimental treatment would not be fully known. In any of these designs, there is a risk for the blind to be compromised by the therapeutic or side effects of the investigational drug. Depending on the drug effects, an active placebo may be used. This would be a placebo that is an active drug that shares a side effect profile with the investigational agent but not a therapeutic potential. Another possible solution in a study that is using more than one drug is to present the side effects of both drugs together on one form. A subject will know if he/she develops an upset stomach; it may be a side effect. He/she should report it to the investigator, but it could be associated with either of the drugs.

Another possible control group would be a 'wait list' control which would consist of subjects randomized to a wait list and not receiving treatment. This technique has been used frequently in eating disorder research, but has become less popular as reference treatments have been established. Problems with this technique include the need for the illness to be non-progressive and the retention of subjects in the control group. Usually this method is used for studies in which the independent variable is difficult to blind such as a therapy technique or a surgical procedure. Such studies are now rare in BN and BED, given established therapies.

AN vs. BN vs. EDNOS-BED

In considering the three broad diagnoses in the eating disorder field, AN, BN and EDNOS-BED, each presents unique requirements that guild the design of research studies. However, there are several common principles that apply to each. First, target symptom assessments that are as objective as possible on which to base the study must be identified or developed. Obviously criteria such as weight are objective measures. Binge eating, purging and psychopathology symptoms are all subject to interpretation by the participant as well as the assessor. Therefore, it is imperative that psychometrically valid instruments are used and inter-rater reliability is monitored throughout trials. While rating scale scores are useful, the translation of a change in score to effect an outcome may be problematic. Secondly, adequate controls are necessary. It is almost impossible to find an intervention for BED that will not work at least to some extent in a portion of subjects. Results of a 2008 meta-analysis of controlled BED pharmacotherapy trials show that pharmacological treatments are associated with short-term remission from binge eating in 48.7% of patients, compared to 28.5% of patients who achieve remission on placebo [3]. Thus, an open label study may not provide much information.

Considering the individual conditions, several reviews summarize the current state of the pharmacological treatment literature to date [49, 50]. AN has proven particularly resistant to treatment with pharmacological agents. Antidepressants have received the most extensive research, but have not proven helpful for increasing body weight or improving depression. The majority of recently completed and ongoing research trials in AN are focused on the SGA agents. To bring more potentially useful compounds to investigation, it will be important to make further advances in

determining the pathophysiology of the illness. A greater understanding of the neurobiological etiologies and consequences of AN would help to design new molecules to explore.

Currently it may be more helpful to focus on the measurement of the core AN symptoms rather than weight gain. A review of pharmacological treatment of AN by Powers and Santana [49] describes potential medication targets, including weight gain and maintenance, obsessive-compulsive symptoms, cognitive deficits, anxiety and phobic symptoms in particular, depressive symptoms, delusions, body disturbances and dissatisfaction with quality of life. Without improvement in the compulsive symptoms, anxiety regarding weight gain and distorted self image, no pharmacological treatment will be able to offer long-term effectiveness.

Pharmacotherapy trials in BN have assessed the efficacy of various compounds, particularly antidepressants. Reviews of this literature suggest that all antidepressants are at least somewhat helpful. The notable exception to this is bupropion, the trial of which had to be prematurely terminated due to the emergence of seizures in four participants [38]. Indeed, fluoxetine carries an FDA indication for the treatment of BN. To date, this is the only medication that carries this designation in the treatment of an eating disorder.

As mentioned above, one problem with BED is that (at least, acutely) just about every drug works for a period of time. An issue to be resolved is the benefit of reduced binge eating in the face of no effect on weight. Ideally, improvements in both of these parameters would be desirable and would presumably increase treatment acceptance by patients.

Investigator initiated trials vs. contracted clinical trials

In light of the relative lack of interest in eating disorder research on the part of the pharmaceutical companies, investigators may have to initiate the contact to obtain grant funds. There are basically two types of research trials that can be explored. First, the contracted clinical trial usually represents a multi-site study which has been designed by the pharmaceutical sponsor. The primary and secondary outcome criteria will have been chosen by the sponsor and the protocol design is usually fixed. Thus, there is very little input that the principal investigator at a study site has into the development of the question of interest or the method of answering the question. Possible advantages of this type of relationship are the opportunity to gain experience with new compounds that are under development and the possibility that the subjects may experience more benefit than the current therapies provide. These types of trials are usually closely monitored by the sponsor particularly if the trial is designated as a 'pivotal trial', a designation that indicates that the study will be submitted to the FDA to support the request for an indication to treat the condition under study. Whether the study will be published often depends on its results. However, mandatory trial registration on the National Institute of Health's clinical trials web site assures that the data will be available.

The second type of interaction with the pharmaceutical sponsor is an investigator initiated trial (IIT). All aspects of this type of study are designed by the investigator.

Usually most companies will have a program such as this to fund research investigators, but different sponsors will have different types of programs and requirements. However, this is a situation where the principal investigator's interest in a question must be shared by the company in order to obtain funds. This can often be the case. Budgets for these trials are smaller than the large contracted studies. An important issue in these negotiations is the right to publish the data regardless of the outcome of the study. Investigators should seriously consider whether the grant is worthwhile if they do not have publication rights. The investigator needs to be responsible for what is contained in the manuscript. To explore the potential for IIT availability in specific areas, it is usually best to contact the medical science liaison associated with the sponsor of the drug of interest.

12.5 Pharmacotherapy/psychotherapy combined trials

The lack of evidence for pharmacotherapy treatments as the primary intervention for any of the eating disorders is striking, and suggests that investigators need to think more creatively in developing new pharmacological strategies with these patients. This has also led to a broad focus on combined psychotherapy and psychopharmacology trials.

Most such trials have focused on BN and BED. The use of antidepressants versus placebo and the use of cognitive behavioral therapy (CBT) versus no treatment in the outpatient treatment of BN have been studied several times. A series of trials in this area have been completed and although the results are open to interpretation, in general the findings suggest that CBT is superior to medication management, although there may be some additional benefit for some patients in using the combination [51]. There have also been some drug and psychotherapy trials in BED, although the literature is far from well developed. Again, CBT appears quite useful, and a number of medication strategies have also been useful in targeting binge eating, although only a few resulted in significant weight loss. Innovative approaches need to be developed in examining various treatments in combinations or sequentially to target both binge eating and body weight outcome in those with BED. For example, one might first target binge eating and then, if weight loss does not result, institute a separate assessment targeting body weight.

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12.6 Summary

Pharmacotherapy trials of eating disorder patients have shown a significant role for drug therapy for those with BN and BED. AN is relatively unique among psychiatric disorders in that no drug therapy has been shown to be effective. Trials in eating disorder patients have generally been modest in size and relatively brief, both at least

partly attributable to the lack of interest on the part of the pharmaceutical industry in this group of patients. That many patients are diagnosed as EDNOS leads us to consider that criteria need to be broadened beyond AN and BN, allowing relatively small subgroups of eating disorder patients to be identified.

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13

ADHD Clinical Trials

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Abstract

In this chapter selected clinical trials, published since 2001, evaluating the efficacy and safety of long-acting stimulants (amphetamine and methylphenidate) and non-stimulants (including atomoxetine and guanfacine) in the treatment of attention-deficit/hyperactivity disorder (ADHD), are reviewed. Data for drugs approved by the Food and Drug Administration for the treatment of ADHD are examined and data from other drugs are presented. Differences in onset of action, duration and side-effect profiles are discussed.

Key Words

ADHD; attention-deficit/hyperactivity disorder; stimulants; amphetamine; methylphenidate; atomoxetine; guanfacine; modafanil

13.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder with an estimated worldwide prevalence of 5.29% [1]. Symptoms begin in childhood and often continue through adolescence and into adulthood [2]. Patients with ADHD suffer from significant impairment in occupational, family and social functioning.

Immediate release stimulants have been used to successfully treat ADHD for decades but have the disadvantage of requiring multiple daily doses. With the need to take several doses per day, compliance can be a significant issue. Many long acting stimulant formulations have been shown to be effective in the treatment of ADHD. Since the Food and Drug Administration approved osmotically controlled-release oral delivery system (OROS) Methylphenidate (Concerta) in 2000, several long-acting stimulant formulations have been approved. Some have been d,l-methylphenidate

formulations including Metadate CD approved in 2001, Ritalin LA approved in 2002 and Daytrana approved in 2006. The intermediate acting isomer d-methylphenidate, Focalin was approved in 2001 and the long acting Focalin XR was approved in 2005. The most recently approved stimulant was the prodrug lisdexamfetamine (Vyvanse) in 2007. In addition, there is one non-stimulant atomoxetine (Strattera) which was approved in 2002. Clinical trials which led to the approval of these drugs are reviewed in this chapter. Also included are post-marketing trials that further clarify unique characteristics of a particular formulation or demonstrate efficacy in specific populations. Due to the large number of trials conducted, only selected trials published since 2001 are included in this review.

Clinical trials of long-lasting mixed amphetamine salts SPD465 (Shire Pharmaceutical Development) and a long-acting guanfacine which received letters of approval from the FDA in 2007 are also discussed. In addition, other compounds that have been studied for the treatment of ADHD are reviewed. These include drugs marketed for other indications including modafinil and bupropion. Modafinil was studied in several double-blind placebo-controlled trials and shown to be effective in the treatment of ADHD ($n = 933$). However, one subject developed a serious adverse reaction: a Stevens–Johnson rash. After review of trials, in 2006 the FDA Pharmacologic Drugs Advisory Committee recommended against approval of modafinil to treat ADHD until further safety data is available (FDA Center for Drug Evaluation and Research CDER hearing, 23 March 2006).

Because of their changing effects on ADHD symptoms at different times during the day, stimulants can be studied in a unique laboratory school setting [3, 4]. Imagine as many as 18 children with ADHD arriving around 6 a.m. and staying at the study site until 8 p.m. Depending on the protocol, as many as half of these children will receive placebo when they are all administered medication at the same time. This laboratory school method requires all assessments to be completed at specific times, and boasts a high staff to subject ratio. There are two teachers and two raters in the classroom of up to 18 children. This has often been described as every teacher's dream – but one teacher reminded me that it is not every teacher's dream to have all students diagnosed with ADHD, several of whom are unmedicated. Children complete a 10 minute math test (permanent product measure of performance or PERMP) and a 10 minute academic game during the usual 30-minute classroom sessions. They are observed by trained raters who complete the SKAMP (Swanson, Kotkin, Atkins, M/Flynn, Pelham) scale, a 13 item scale that includes subscales for attention and deportment, for each subject during each classroom session [5]. By the end of the day, some subjects grow weary of testing – 'how many more of these *testes* do I have to take?' asked one little girl. Between classroom sessions kids have fun working on crafts, watching movies or doing physical activities and eating. The data gathered from the lab schools is incredibly important in understanding the pharmacodynamic properties of the medications studied and most of the subjects have a great time.

The drugs are reviewed mainly in order of recency of approval, then the medications that have received an 'approvable' letter, and finally those that have not been approved for an ADHD indication are discussed.

13.2 Lisdexamfetamine (Vyvanse)

Lisdexamfetamine dimesylate (LDX), a therapeutically inactive compound in which the amino acid l-lysine is covalently bound to d-amphetamine, was developed to enhance safety, tolerability and decrease abuse liability of d-amphetamine. Once ingested, d-amphetamine and l-lysine are gradually released from the prodrug in an enzymatic reaction. LDX has been shown to have a reduced variability in C_{max}, T_{max} and area under the curve (AUC) as compared to mixed amphetamine salts extended release (MAS-XR) [7]. Also, in the Phase III study, caregivers continued to notice significant improvements in ADHD symptoms to early evening compared to placebo. LDX was approved by the FDA in 2007 to treat children ages 6–12 and in 2008 for the treatment of adults with ADHD. Also, LDX was shown to be more effective than placebo at 13 hours after dosing in a laboratory classroom study [6].

Several double-blind placebo-controlled studies have been completed with LDX. The first trial was a Phase II analog classroom crossover study using MAS-XR as an active comparator [7]. Fifty-two 6–12 year-olds with combined or hyperactive-impulsive ADHD subtypes were given MAS-XR, starting at 10 mg per day during an open-label dose optimization phase. The dose of MAS-XR was optimized to either 10, 20 or 30 mg daily based on response using the change in the ADHD-RS (ADHD rating scale) total score. Subjects then participated in the double-blind crossover phase. After a practice classroom day, subjects were divided into three cohorts based on their optimal dose of MAS-XR:

- group A received one week each of MAS-XR 10 mg/day, LDX 30 mg/day or placebo;
- group B received one week each of MAS-XR 20 mg/day, LDX 50 mg/day or placebo; and
- group C received one week each of MAS-XR 30 mg/day, LDX 70 mg/day or placebo

in random sequence. Fifty subjects completed the trial.

The primary efficacy variable was the Department Subscale of the SKAMP. Children in all groups had significantly greater improvement while receiving MAS-XR and LDX compared to placebo ($p < 0.001$). The most common adverse events reported during the double-blind phase were decreased appetite (6%), upper respiratory infection (2%), insomnia (8%) and anorexia (4%) for LDX.

Pharmacokinetic properties of LDX were also analyzed during the final classroom day. After administration of MAS-XR (30 mg) the median T_{max} for d-amphetamine was 6 hours (range 3.0–12 hours) and the median T_{max} for d-amphetamine after administration of LDX (70 mg) was 4.5 hours (range 4.5–6 hours). The coefficient of variance (CV) was also measured for multiple parameters. For LDX, the %CV for T_{max} was 15.3%, C_{max} 20.3% and AUC 21.6% from time zero to the last

quantifiable concentration. For MAS-XR, the %CVs were: 52.8% for T_{max}, 44.0% for C_{max} and 42.8% for AUC [8].

The second trial to assess efficacy and tolerability of LDX was a four-week phase III multi-center, double-blind, placebo-controlled, forced-dose parallel-group study comparing 30, 50 and 70 mg doses of LDX to placebo [9]. In this trial, 290 children aged 6–12 years old with ADHD were randomly assigned to one of the above four groups. The primary efficacy measure was the ADHD-RS-IV, with the Conners' Parent Rating Scale (CPRS) and Clinical Global Impression Improvement (CGI-I) scale used as secondary measures. There were 230 subjects who completed the study. At the endpoint, effect sizes based on ADHD-RS-IV ratings were 1.21 in the 30 mg group, 1.34 in the 50 mg group and 1.60 in the 70 mg group. Improvement in ADHD-RS scores was significant from baseline to endpoint in all LDX-treated groups ($p < 0.001$). The CPRS was completed by parents at approximately 10 a.m., 2 p.m. and 6 p.m. on one day each week. Parents rated their children as significantly improved on LDX compared to placebo on the CPRS at each time point starting at week 1 and continuing throughout the study ($p < 0.01$).

The most common adverse events (AEs) reported were decreased appetite, insomnia, upper abdominal pain, headache, irritability, vomiting, weight decrease and nausea. The only significant change in vital signs was a mean 4–5 beats per minute increase in heart rate in the 70 mg LDX treated group compared to placebo.

The next trial was a long-term, open-label, multi-center, single arm study of LDX [10]. Subjects were 6–12 years of age with ADHD and qualified for one of the above trials. There were 274 subjects enrolled. Participants were seen weekly for the first four weeks for dose titration, then monthly during the following 11 months. LDX was started at 30 mg and titrated to an optimal dose based on ADHD-RS-IV ratings and side effects. Dose could be changed at any visit, but could not be lower than 30 mg or exceed 70 mg per day.

Significant improvement in ADHD-RS-IV scores was observed as early as week 1 and continued at each subsequent visit ($p < 0.0001$). At endpoint, for the intent to treat (ITT) population, the mean ADHD-RS-IV change in total score was -27.2 ± 13 points. This change was a 60% improvement from baseline ($p < 0.0001$). CGI-I scale ratings of 'much' or 'very much' improved were given for 95% of subjects who finished the 12-month study. There were 125 subjects who discontinued before completing the trial. AEs were typical for stimulant treatment and discontinuation rates secondary to AEs were similar to those reported in previously published long-term studies with atomoxetine and long-acting stimulants. Those events occurring in more than 5% of patients included decreased appetite, headache, weight decrease, insomnia, upper abdominal pain, upper respiratory infection, irritability, nasopharyngitis, vomiting, cough and influenza. Most adverse events (97.5%) were rated as mild to moderate by the investigators. No clinically significant physical exam, laboratory, vital signs or electrocardiogram (ECG) changes were reported.

LDX has also been studied in adults aged 18–55 years old in a double-blind placebo-controlled, randomized, parallel-group, four-week fixed-dose titration study. The study enrolled 420 adults with moderate to severe ADHD [11]. Subjects were randomized to LDX 30, 50, 70 mg or placebo in a ratio of 2 : 2 : 2 : 1. Of these

subjects, 349 completed the four-week study. The primary efficacy variable was the change from baseline to endpoint of the ADHD-RS-IV total score. The mean ADHD-RS total score at baseline was approximately 40. At endpoint, improvement in ADHD-RS scores was significant in the LDX groups compared to the placebo group (placebo = -8.2, LDX 30 mg = -16.2, LDX 50 mg = -17.4, LDX 70 mg = -18.6; $p < 0.0001$ for all active groups). The Pittsburgh Sleep Quality Index (PSQI) was also administered at baseline and endpoint. There were no significant changes in sleep quality across treatment groups.

Adverse events caused 21 (6%) subjects in the LDX group to discontinue compared to one subject in the placebo group. The most common treatment emergent adverse events were anorexia, anxiety, decreased appetite, diarrhea, dry mouth, feeling jittery, insomnia and nausea. No serious adverse events were thought to be related to the study drug. For pulse, a 3.0–5.6 beat per minute increase was reported at endpoint compared to no change for placebo. There were no clinically significant changes reported in systolic blood pressure, diastolic blood pressure, QRS interval or QTc-F interval on ECGs.

13.3 Methylphenidate transdermal system (Daytrana)

The methylphenidate transdermal system (MTS) delivers methylphenidate continuously through the skin. In the patch, a multipolymeric adhesive layer containing methylphenidate is attached to a transparent backing. This system has several advantages compared to orally administered methylphenidate. First pass metabolism is avoided, resulting in the need for lower total doses of medication. Additionally, it is useful for children who cannot swallow capsules, gives wear time flexibility and allows for easy monitoring of compliance.

The MTS was studied in a randomized, double-blind, placebo-controlled, crossover laboratory classroom with a wear time of 9 hours [12]. Subjects were 6–12 year-olds diagnosed with ADHD. After screening, subjects began an open label, dose optimization period lasting five weeks. Subjects began on the 12.5 cm² dose and dose was maintained or increased based on change in ADHD-RS-IV of at least 25% with tolerable side effects. Dose escalation occurred with increases to 18.75 cm², then 25 cm² and 37.5 cm² respectively. At the end of the optimization phase, subjects entered the laboratory classroom phase. Subjects were randomized to receive one week of placebo and one week of MTS at their optimized dose. The primary efficacy variable was the SKAMP Department subscale measured at pre-dose and 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours after dosing during the two double-blind classroom days. MTS application sites were also evaluated by the investigator at each visit to determine patch adhesion, irritation and subject discomfort.

For this trial, 93 subjects enrolled and 80 completed the open label phase. A total of 79 subjects completed the randomization phase. For the MTS treatment group, SKAMP-D scores were significantly improved compared to placebo at all time points ($p < 0.0001$, effect size 0.93). The most common adverse events reported during

dose optimization included decreased appetite, anorexia, headache, insomnia and upper abdominal pain. MTS had no clinically significant effects on mean vital signs. Slight transient erythema at the patch site was common. Most subjects reported no discomfort or only mild discomfort and most had no irritation or only mild skin irritation. MTS adherence was very good. For more than 86% of observations, patch adherence was greater than 90% at the end of the classroom day.

The laboratory classroom study documented 12 hours of effect with a 9-hour wear time for the MTS. A second study focused on duration of stimulant effect in subjects who wore the MTS for shorter time periods. This trial was a randomized, double-blind, multi-center, placebo-controlled, three-way crossover laboratory classroom study of 4- and 6-hour wear times of the MTS in 6–12 year old subjects [13]. After a 5 week dose optimization phase, subjects completed a practice classroom day and then three blinded classroom days wearing two patches (one placebo and one MTS at optimized dose or two placebo patches). During each blinded classroom day, one patch was removed after wearing it for 4 hours and the second was removed after 6 hours of wear. For this trial, 128 were enrolled, and 11 discontinued prior to randomization. During the dose optimization phase, subjects started with the 10 mg (12.5 cm²) MTS and the dose was titrated weekly to 15 mg (18.75 cm²), 20 mg (25 cm²) or 30 mg (37.5 cm²) based on response on the ADHD-RS-IV. Subjects who did not achieve an acceptable reduction in ADHD-RS-IV ratings or who were unable to tolerate the MTS were discontinued.

On blinded laboratory classroom days, subjects completed 30-minute classroom sessions. The sessions were completed immediately before patches were applied and at 2, 4, 6, 8 and 10 hours after placement. The SKAMP Department scale was the primary efficacy variable. For both wear times, efficacy was noted at the first time point measured after application and peak effects were noted in SKAMP ratings at 4 hours for the 4-hour wear time and 6 hours for the 6-hour wear time. Medication effect decreased by 2 hours after MTS removal and SKAMP scores were similar to pre-dose measurements 6 hours after removal.

Approximately 99% of adverse events were reported as mild to moderate. Insomnia in two subjects and irritability and affect lability in one subject each were reported as severe. The most common AEs were decreased appetite, headache, insomnia and abdominal pain. The MTS was generally well tolerated with 20.1% (10 mg), 19.6% (15 mg), 22.5% (20 mg) and 17.3% (30 mg) of subjects in each group noted as having more than minimal erythema. More than mild discomfort was reported by 3% of subjects wearing the 10 mg patch and 2.2% with the 15 mg patch, 4.8% for the 15 mg patch and 6.0% for the 30 mg patch. Only one subject discontinued due to itching at the patch application site.

13.4 Dexmethylphenidate (Focalin)

The commercial formulation of methylphenidate (d,l-MPH) contains equal amounts of the d and l-threo isomers. Dexmethylphenidate hydrochloride (d-MPH) is the chirally pure active d-isomer of d,l methylphenidate. This active d-isomer

was developed to be administered at half the dose of d,l methylphenidate. Pharmacodynamics and plasma concentrations of d-threo-methylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride were compared in a double-blind, placebo-controlled crossover laboratory school study in children with ADHD. The efficacy of methylphenidate was shown to reside in the d-isomer in this study [14].

Wigal *et al.* [15] compared d-MPH to d,l MPH and placebo to determine efficacy, safety and duration of the drug in a randomized double-blind study. In this trial, 132 subjects aged 6–17 diagnosed with ADHD received medication or placebo; d-MPH ($n = 44$), d,l-MPH ($n = 46$), placebo ($n = 42$) twice a day for four weeks. The primary efficacy measurement was the change from baseline to last study visit on the Swanson, Nolan and Pelham Rating Scale (Teacher SNAP) as rated by each subject's teacher. The SNAP-ADHD contains 18 items that correspond to DSM-IV diagnostic criteria. Secondary measures included the parent SNAP rated at 3 p.m. and 6 p.m. for the previous 2 hours on weekend days and the investigator-rated CGI-I. Following screening there was a 1-week, single-blind placebo, lead-in prior to 4 weeks of double-blind treatment. For those randomized to study drug, d-MPH was initiated at 2.5 mg twice a day and d,l-MPH was initiated at 5 mg twice a day. The first dose was given between 7 and 8 a.m. and the second dose was given between 11:30 a.m. and 12:30 p.m. During the flexible dose titration period, medication was increased depending on therapeutic response. The dose could be increased to a maximum of 10 mg twice a day for d-MPH and 20 mg twice a day for d,l-MPH.

Only 2% of subjects were placebo responders and ineligible to randomize. One hundred and nineteen (90%) of subjects completed the study. The primary efficacy measure showed significantly greater improvement with both treatment groups compared to placebo (d-MPH $p = 0.0004$, d,l-MPH $p = 0.00042$). The effect size was 1.0 for both active treatment groups. Mean changes on the parent-rated SNAP were also significant for both active groups at 3 p.m., but only for the d-MPH group at 6 p.m. The average final daily dose for the d-MPH group was 18.25 mg (85% of subjects received 20 mg/day) and 32.14 mg for the d,l-MPH group (69% of subjects received 40 mg/day). CGI-I ratings of 'much improved' or 'very much improved' were reported for 22% of subjects receiving placebo, 67% of subjects receiving d-MPH and 49% of subjects receiving d,l-MPH.

The most commonly reported AEs were headache, abdominal pain, rhinitis, nausea and anorexia. Significant weight loss from 5 to 18% of baseline body weight occurred in 12 subjects: two subjects in the placebo group, four subjects in the d-MPH group and six subjects in the d,l-MPH group.

13.5 Dexmethylphenidate extended release (Focalin XR)

Dexmethylphenidate hydrochloride extended release (d-MPH-ER) was developed using the Spheroidal Oral Drug Absorption System (SODAS) technology. With d-MPH-ER, 50% of the drug is released immediately and 50% released 4 hours later. This drug is FDA approved for treatment of ADHD in children, adolescents

and adults. In laboratory classroom studies, d-MPH-ER has been shown to have a significant effect beginning at 30 minutes and continuing to 12 hours after dosing.

The efficacy and safety of d-MPH-ER was evaluated compared to placebo in a randomized, double-blind, placebo-controlled, parallel-group study in 103 subjects aged 6–17 years with ADHD [16]. There was a 2-week screening phase followed by 7 weeks of treatment. Subjects began at 5 mg/day of d-MPH-ER or placebo. Those started on d-MPH-ER could increase the dose up to 30 mg of d-MPH-ER by week 5. The primary efficacy variable was the change from baseline to final study visit on the Conner's ADHD/DSM-IV Scale-Teacher (CADS-T) version. The CADS-T was completed at baseline and weekly during the trial. The intent-to-treat population included 97 (52 d-MPH-ER treated and 45 placebo treated) subjects. The mean final dose of d-MPH-ER was 24.0 ± 7.1 mg/day for those on active treatment. For the CADS-T total score, the adjusted mean change from baseline to the final visit was 16.3 for the d-MPH-ER group and 5.7 for the placebo group ($p < 0.001$) and the effect size was 0.79.

The most common adverse events reported in either group were decreased appetite, headache and upper abdominal pain. Six subjects in the d-MPH-ER group lost $\geq 7\%$ of baseline body weight. The mean decrease in weight was 0.5 kg in the d-MPH-ER group while subjects in the placebo-treated group gained an average of 0.4 kg.

Several laboratory classroom studies have been completed using d-MPH-ER to determine time of onset, duration of action, efficacy and tolerability. In an analog classroom setting (d-MPH-ER), 20 mg/day was compared to placebo in children aged 6 to 12 years old with ADHD who had been treated with and responded to methylphenidate 40 mg or the nearest equivalent (OROS methylphenidate 36 mg) [17]. Subjects were randomized to receive one week of (d-MPH-ER) and one week of placebo. At the end of each week subjects participated in a full day laboratory classroom. Sixty-eight subjects were randomized and 67 completed the study. The primary efficacy measure was the adjusted mean change from pre-dose in the SKAMP combined score at 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours post-dose. SKAMP combined score changes from pre-dose were significantly greater with d-MPH-ER than with placebo at all time points measured (0.5–12 hours post-dose: $p < 0.001$). Effect size at 12 hours was 1.49.

The most common AEs were upper respiratory tract infection, gastroenteritis and allergic rhinitis. There was one serious adverse event, not related to d-MPH-ER treatment. Mean vital sign changes were minor. There were no significant laboratory or ECG findings.

Brams *et al.* [18] completed a randomized, placebo-controlled, crossover laboratory classroom study in which change from pre-dose to 0.5 hours for d-MPH-ER was compared to placebo on the SKAMP combined score was the primary efficacy variable. A total of 86 subjects were randomized to receive d-MPH-ER and placebo. Significant improvements in the SKAMP combined score were observed at 30 minutes after dosing compared to placebo and were, maintained throughout the 8 hours measured.

d-MPH-ER was given to 221 adults (ages 18–60) in a multi-center, randomized, fixed-dose, placebo-controlled study to evaluate its efficacy [19]. Subjects were

randomized to receive d-MPH-ER 20, 30, 40 mg/day or placebo for 5 weeks. Subjects were started at d-MPH-ER 10 mg/day and dosage was titrated weekly in 10 mg/day increments. The primary efficacy variable was the mean change from baseline to final visit in the ADHD-RS total score. ADHD-RS total scores were significantly improved for all d-MPH-ER groups compared to placebo (−7.9), d-MPH-ER 20 mg/day (−13.7, $p < 0.01$), d-MPH-ER 30 mg (−13.4, $p < 0.05$) and d-MPH-ER 40 mg/day (−16.9, $p < 0.001$). Subjects who completed the double-blind study were eligible to enter a six-month open-label extension study. d-MPH-ER was started at 10 mg and titrated to a maintenance dose of between 20 and 40 mg/day. Change in ADHD-RS from the final double-blind visit to the final open-label visit was the primary outcome measure. Both groups showed significant improvement at endpoint. A further change of mean ADHD-RS scores of 8.4 during open-label treatment was seen for subjects previously treated with d-MPH-ER, while subjects who initially received placebo demonstrated a further decrease of 10.2 during the open-label study. There were no clinically notable changes in vital signs.

13.6 Atomoxetine (Strattera)

Atomoxetine is a presynaptic norepinephrine transporter inhibitor. The plasma half-life for most individuals is approximately 4 hours. Approximately 5–10% of individuals have a cytochrome P450 2D6 isoenzyme polymorphism which leads to a longer plasma half-life for atomoxetine. Since atomoxetine is not a controlled substance, it is more convenient for patients to obtain but has the disadvantage that capsules must be swallowed whole. The efficacy and safety of atomoxetine administered once-daily in a six-week, randomized, double-blind, placebo-controlled trial was studied in children and adolescents aged 6–16 years old diagnosed with ADHD [20]. The primary efficacy measure was the ADHD-RS-IV total score. For this study, 171 subjects were assigned to a treatment group, 85 received placebo and 85 received atomoxetine. Atomoxetine was initiated at 0.5 mg/kg/day for the first three days, then increased to 0.75 mg/kg/day for the remainder of the first week. Dose was then increased to 1.0 mg/kg/day for the next three weeks. At week 4, the dose could be further increased to 1.5 mg/kg/day if subjects had a CGI severity of >2 .

Decreases in mean ADHD-RS-IV total score were significant starting at 1 week after randomization and at all later visits. Mean change in ADHD-RS-IV total score from baseline to endpoint was −12.8 for the atomoxetine group and −5.0 for the placebo group. The mean dose of atomoxetine at endpoint was 1.3 mg/kg. Adverse events occurring in at least 5% of subjects and significantly more frequently on atomoxetine than placebo ($p < 0.05$) included decreased appetite, nausea, vomiting, asthenia and dyspepsia. The authors noted that most episodes of nausea and/or vomiting lasted 1–2 days and that 16 of the 19 subjects who experienced these side effects continued in an open label extension study of atomoxetine. Atomoxetine has also been evaluated in longer term studies.

In a multi-site randomized, placebo-controlled, international trial, atomoxetine was given to children and adolescents aged 6–15 years old for nine months after an initial 12-week open-label treatment period [21]. A total of 416 subjects completed the

12-week study and were randomized to receive atomoxetine ($n = 292$) or placebo ($n = 124$). Mean ADHD-RS total score at entry into the 12-week study was 41.3 and at endpoint was 18.0. Relapse was defined as a change in ADHD-RS total score to 90% of baseline severity and increase in CGI-S of at least 2 points. Mean days to relapse was longer in the atomoxetine treated group: 217.7 days compared to 146.1 days for the placebo group and 22.3% of atomoxetine-treated subjects relapsed compared to 37.9% of placebo-treated subjects ($p = 0.002$). Mean dose of atomoxetine was 1.57 mg/kg/day at randomization and 1.56 mg/kg/day at endpoint. Few subjects discontinued due to adverse events, 3.1% ended participation in the atomoxetine-treated group and 0.8% of subjects in the placebo group ($p = 0.293$). Mean weight gain was significantly less in the atomoxetine-treated group (1.2 kg) than in the placebo group (3.3 kg) ($p < 0.001$). There were no clinically significant differences in chemistry, liver function tests, hematology or QT intervals between the drug and placebo groups.

Atomoxetine was also shown to be effective in two short-term, multi-center, double-blind, randomized, placebo-controlled studies in adults ($n = 448$) with moderate ADHD symptoms [22]. Subjects were randomized to receive atomoxetine or placebo for 10 weeks. The primary efficacy assessment was the total of the Inattention and Hyperactivity/Impulsivity subscales of the Conner's Adult ADHD rating scale (CAARS). After an initial medication washout, all subjects received 2 weeks of placebo prior to randomization. Placebo responders were not randomized. After randomization, atomoxetine was dosed twice a day with a starting dose of 60 mg/day. Dose could be increased to 90 mg/day after 2 weeks and to 120 mg/day after 4 weeks. In study I, of 448 subjects screened and 280 subjects randomized, 141 received atomoxetine and 139 received placebo. In study II, 388 subjects were screened and 256 were randomized. Of these, 129 received atomoxetine and 127 received placebo. Subjects who were not randomized due to response to the placebo lead-in included 19 (6.0%) in study I and 12 (4.2%) in study II.

In both studies, subjects treated with atomoxetine had significant reductions in the CAARS Total ADHD Symptom Score. In study I, the mean Total ADHD Symptom Score decreased by 9.5 compared to a 6.0 point decrease for the placebo group ($p = 0.005$). In Study II, the CAARS Total ADHD Symptom Score decreased by 10.5 in the atomoxetine-treated group and by 6.7 in the placebo group ($p = 0.002$). Mild increases in mean systolic blood pressure and heart rate were noted. There were no clinically significant changes in laboratory results. Adverse events were reported by more than 5% of atomoxetine-treated subjects and significantly more frequently than placebo included dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, dizziness, difficulty attaining or maintaining erection and sweating.

Adult ADHD symptoms have also been shown to be significantly improved with long-term treatment of atomoxetine [22]. In an interim analysis of a long-term, open-label study with the safety and efficacy of atomoxetine in adults with ADHD treated with a maximum of 160 mg atomoxetine daily, results from 384 subjects who participated in the trial for up to 97 weeks were reported. The primary efficacy measure was the 18-item CAARS-nv:SV (screening version). At the time of analysis,

259 (67.4%) of subjects had discontinued. Of these, 25% discontinued due to lack of efficacy and 10.9% due to an adverse event. Mean treatment duration was 40 weeks. The mean CAARS-Inv:SV total ADHD symptom scores decreased by 33.2% from 29.2 at baseline to 19.5 at endpoint ($p < 0.001$). The most common adverse events reported by at least 10% of subjects were dry mouth, headache, insomnia, erectile dysfunction, nausea and constipation.

13.7 Extended release methylphenidate (Ritalin LA)

This extended release methylphenidate formulation was developed using the proprietary SODAS. For this compound, 50% is released immediately and 50% released 4 hours later. The efficacy and safety of this compound was evaluated in a randomized, double-blind, placebo-controlled, multi-site study in 161 children aged 6–14 years who were diagnosed with ADHD [24]. After a 1 week placebo washout, subjects were randomized to receive extended release methylphenidate 10–40 mg or placebo. The primary efficacy measure was the change from baseline to the end of the 2-week double-blind treatment in the CADS-T total subscale score. There were 134 subjects included in the ITT analysis. Mean change from baseline in the CADS-T Total subscale was -10.7 for extended release methylphenidate compared to $+2.8$ for placebo ($p < 0.0001$), effect size was 0.90. Adverse events were mild to moderate.

13.8 Modified release methylphenidate (Metadate CD)

Modified release methylphenidate (MPH MR) contains immediate release and extended release forms of methylphenidate in a 30 : 70 ratio. The drug was designed to have two peak serum levels of methylphenidate: one 1.5 hours after dosing and a second peak at 4.5 hours [25]. The efficacy and safety of MPH MR was evaluated in a randomized, double-blind, placebo-controlled, multi-site study in children with ADHD aged 6–16 years old [26]. After a 1-week, single-blind placebo washout, subjects were randomized to receive MPH MR or placebo for three weeks. Subjects started on 20 mg MPH MR or placebo and could be titrated to 40 mg or 60 mg depending on response. The primary efficacy measure was the Conners' Teacher Global Index completed with teachers via telephone around 10 a.m. and 2 p.m. during three days of each treatment week. There were 321 children randomized (158 to MPH MR and 163 to placebo). The Conners' Teacher Global Index in the MPH MR group decreased from a baseline score of 12.7 ± 7.2 to 4.9 ± 4.7 in the last week of treatment while the placebo group score decreased from 11.5 ± 7.3 at baseline to 10.3 ± 6.9 ($p < 0.001$). Effect size was 0.78 during the last week of treatment. The most common adverse events were headache, anorexia, abdominal pain and insomnia. The only AE that occurred significantly more often in the MPH MR group was anorexia ($p = 0.007$).

13.9 Mixed amphetamine salts extended release (Adderall XR)

Mixed amphetamine salts (Adderall) is a racemic mixture of the dextro- and levo- isomers of amphetamine in a 3 : 1 mixture containing d-amphetamine sulfate, d-amphetamine saccharate, d,l-amphetamine aspartate monohydrate and d,l-amphetamine sulfate. It has been shown to last 5–7 hours after administration [27]. MAS XR was designed to release active medication in two pulses 4 hours apart. MAS XR 20 mg is bioequivalent to 2 doses of 10 mg MAS administered 4 hours apart. Pharmacokinetic studies have shown that MAS XR has similar absorption to MAS but a prolonged T_{max} [28]. Several pivotal trials are reviewed including studies in children, adolescents and adults. The laboratory classroom study in children showed that the higher doses of MAS XR took effect earlier and improved behavior longer. In the adult studies, a significant dose-response relationship was not shown.

A randomized, double-blind, crossover analog classroom study of MAS XR was conducted to assess the efficacy and safety of three doses of MAS XR 10, 20 and 30 mg compared to placebo and an active control (MAS 10 mg) in 51 children aged 6–12 years who were diagnosed with ADHD [29]. Subjects underwent a 1-week washout period and were then given 20 mg MAS XR and pharmacokinetic (PK) sampling was completed. Subjects who tolerated the 20 mg MAS XR dose were randomized to receive each of the five treatments administered at 7:30 a.m. during study classroom days and during the week after the Saturday classroom. Classroom assessments were completed at pre-dose and at 1.5, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours after dosing. The primary efficacy measures were the SKAMP Attention and Deportment subscales. Results indicated that higher doses of MAS XR were associated with more improvement in attention and behavior during the classroom days. Significant improvement in SKAMP Attention and Deportment was shown at MAS XR 30 mg at all post-dose time points ($p < 0.01$). For MAS XR 20 mg, deportment was significantly improved ($p < 0.01$) at all times except at 12 hours. For the MAS XR 10 mg dose, deportment was significantly improved from 4.5 to 9.0 hours after dosing. For MAS 10 mg, SKAMP deportment was significantly improved from 1.5 to 10.5 hours post-dose. Adverse events included anorexia, nervousness, insomnia, abdominal pain, emotional lability, anxiety, depression, movement disorder, headache and asthenia. No serious adverse events were reported.

The efficacy and safety of MAS XR in 287 adolescents aged 13–17 years diagnosed with ADHD was evaluated in a 4-week, randomized, double-blind placebo-controlled, parallel-group study [30]. The study consisted of a washout phase from 1–4 weeks, a double-blind phase during which subjects were randomized 1 : 1 : 1 : 1 to receive MAS XR 10, 20, 30 or 40 mg/day or placebo. All subjects on active drug started on a dose of 10 mg MAS XR. Those randomized to the 10 mg/day group continued on this dose during the 4 weeks of the study. Subjects in the other active drug groups had dose increased by 10 mg/day weekly until reaching their target dose.

The ADHD-RS-IV was the primary efficacy measure. Subjects in all active dose groups had significant improvement in the ADHD-RS-IV scale beginning

at the end of week 1 ($p < 0.001$) with mean decrease in ADHD-RS-IV scores of 17.8. The largest improvement was seen with total score change in the MAS XR 20 mg/day group with a decrease in mean ADHD-RS-IV scores of more than 20 points.

Adverse events included anorexia/decreased appetite, headache, insomnia, abdominal pain, weight loss, dizziness, nervousness, emotional lability, somnolence and dry mouth.

Subjects who participated in the 4-week study were eligible to participate in a 6-month open-label efficacy and tolerability study of MAS XR dosed at 10–60 mg per day [28]. The ADHD-RS-IV and CGI-I were used to determine efficacy. For the first 4 weeks subjects were seen weekly, then monthly for the duration of the study. MAS XR was started at 10 mg daily and increased by 10–20 mg weekly up to a maximum dose of 60 mg daily based on response. During monthly visits the dose could be adjusted by 10 mg.

Most of the 138 subjects entering the study (78.3%) completed it. More than 80% of subjects were dosed with 20–40 mg daily of MAS XR during the entire study. The mean ADHD-RS-IV total scores for the intent-to-treat population decreased significantly at endpoint (-7.9 , $p < 0.0001$). The mean decrease in ADHD-RS for subjects who did not receive MAS XR in the double-blind study was (-16.1) and for subjects who received MAS XR in the previous study was (-5.5).

Many subjects (25%) experienced weight loss during the study. Mean body weight decreased by 5.2 lbs from baseline to endpoint for the entire population. However, the heaviest subjects lost the most weight. The most common treatment-emergent adverse events were anorexia, weight loss, headache, nervousness, insomnia and abdominal pain.

MAS XR has also been studied in the treatment of adult ADHD [31]. In a multi-site, randomized, double-blind, controlled, parallel-group trial of MAS XR, 255 adults aged 18–76 received placebo, MAS XR 20, 40 or 60 mg daily. This was a forced-dose escalation study. The main efficacy ratings were the ADHD-RS and the Conners' Adult ADHD Rating Scale Short Version Self-Report (CAARS-S-S) at 4 hours post-dose and 12 hours post-dose.

The mean baseline ADHD-RS total scores ranged from 31 to 33 and the mean CAARS-S-S ADHD index scores ranged from 20 to 23. Mean ADHD-RS total scores at endpoint were 18.5 for the 20 mg/day MAS XR group, 18.4 for the 40 mg/day group and 18.5 for the 60 mg/day group ($p < 0.001$ for all groups). No dose-response effect was detected. For subjects who completed the study, 61% who received placebo had at least a 30% reduction in ADHD-RS total scores. For all active dose groups compared to placebo, the CAARS-S-S ADHD index was significantly improved at 4 and 12 hours post-dose.

Adverse events reported most commonly were dry mouth, anorexia/decreased appetite, insomnia and headache. Adverse events led to discontinuation for 24 subjects. The most common adverse events causing discontinuation were insomnia, agitation, anxiety and nervousness. There were three subjects withdrawn because of cardiovascular AEs (tachycardia and hypertension). One subject had increased liver enzymes and one chest pain (etiology unknown). Mean vital sign changes were not

considered clinically significant. There were no clinically significant cardiovascular changes on ECG.

MAS XR was also studied in a long-term safety and efficacy study in adults [32]. This trial was a 6-month open-label extension study for the above double-blind study. Subjects were seen weekly for the first four weeks then monthly. The primary efficacy measure was the ADHD-RS. There were 255 subjects eligible to enroll in this study. Of those, 223 enrolled in the study and 147 (66%) discontinued prior to completing the 24-month study.

Subjects were started on MAS XR 20 mg/day and the dose was increased as clinically indicated. At endpoint, there were significant decreases in ADHD-RS-IV scores compared to baseline ($p < 0.001$) for subjects who received placebo in the previous study (-11.6) and subjects who continued MAS XR (-5.7). At the month 24 visit, 16% of subjects were receiving 20 mg/day MAS XR, 28% of subjects were receiving 40 mg/day and 56% were receiving 60 mg/day. The most common treatment-related adverse events were agitation, anorexia, dry mouth, headache, insomnia, nervousness and weight loss. Incidence of treatment-emergent adverse events declined over time.

13.10 OROS methylphenidate (Concerta)

Osmotic controlled-release formulation of methylphenidate (OROS MPH) was developed to produce an ascending plasma profile with peak MPH concentrations occurring from 6 to 8 hours after dosing. In clinical trials, efficacy has been shown at 2 hours after dosing in a laboratory classroom [33] and continuing to 12 hours after dosing. OROS MPH is currently approved to treat ADHD in children, adolescents and adults. The adult indication was received in June 2008. It has the disadvantage of the capsule having to be swallowed whole. In addition to the short term studies, a 2-year trial was also completed with OROS MPH. These results indicate that the compound continues to be effective long term and its effect on growth is mild.

In a 28-day randomized double-blind, placebo-controlled trial, 282 6–12 year-old subjects diagnosed with ADHD were assigned to receive placebo, immediate release methylphenidate dosed three times per day or OROS MPH [34]. Subjects who had been treated with MPH in the previous 4 weeks ($n = 210$) were enrolled directly in the study and those who had not previously received MPH were enrolled in an open-label dose-titration study ($n = 111$) lasting 1–4 weeks. All previously untreated subjects were started on 18 mg OROS MPH and dose was increased to 36 and 54 mg as appropriate. Subjects who had previously taken MPH were assigned to an OROS MPH dose equivalent to approximately three times their previous immediate release (IR) MPH dose. To maintain blinding, all subjects received three OROS capsules (active or placebo) and one IR capsule at 7:30 a.m. and additional active or placebo IR capsules at 11:30 a.m. and 3:30 p.m.

Of the 282 subjects who were distributed evenly among groups, 5 discontinued prior to treatment and 71 discontinued early. Discontinuations due to lack of efficacy

included 38 subjects on placebo, 11 on OROS MPH and 10 on IR MPH. Average total daily dose was 29.5 mg for IRMPH and 34.3 mg per day OROS MPH. Doses were not changed once subjects entered the double-blind study. The primary efficacy measure, the Teacher IOWA Conner's, showed significant improvement by the end of week 1 compared to placebo ($p < 0.001$) for both OROS MPH and IR MPH and continued to endpoint. Effect sizes were 1.02 for IR MPH and 1.05 for OROS MPH. Most adverse events were rated as mild. The most common adverse events were headache, upper respiratory infection, abdominal pain, cough, pharyngitis, vomiting and otitis media.

Subjects aged 6–13 years who had participated in previous controlled studies with MPH and were MPH responders were recruited for a 24-month study to determine long-term OROS MPH safety and efficacy [35, 36]. Subjects were assigned to one of three dose groups (18, 36 and 54 mg daily) based on dose given in the prior study. Doses were adjusted during monthly visits at investigator discretion. Subjects were also allowed to have doses reduced or to stop medication on non-school days and to take medication holidays. Efficacy was determined using the IOWA Conner's rating scale (completed by parents and teachers) and the Global Assessment scale.

Of the 407 subjects included in the study, 289 (71.0%) completed 12 months of treatment. At the end of the 12 months, 61 (15%) were taking the 18 mg dose, 163 (40%) were taking the 36 mg dose and 183 (45%) were taking the 54 mg dose. During the first 12 months, 39.8% of subjects did not have a dose change, 19.7% had dose increases and 38.4% of subjects had both dose increases and decreases.

During the second year, a further 49 subjects discontinued. Mean daily dose of OROS MPH increased from 35.2 mg at baseline to 44.2 mg at the end of the study. Parents/caregivers rated effectiveness as 'good' or 'excellent' for 87% of subjects at month 3 and 95% at the end of the study. Investigator efficacy assessments during the second year of treatment ranged from 91 to 95% 'good' or 'excellent'. Most adverse events were mild and the most common AEs were headache, insomnia, decreased appetite, abdominal pain and tics.

Effects of OROS MPH on growth were minimal. The z score for height at baseline was -0.022 and change in height at 21 months was -0.063 . Height for study completers was calculated to be 0.23 cm less than expected for age. Weight calculations were similar. The z score for weight at baseline was 0.163 and 0.093 after 21 months of treatment and calculated to be 1.23 kg less than expected for age.

In a multi-site, double-blind placebo-controlled study, the efficacy and safety of OROS MPH was evaluated in 220 adolescents aged 13–18 years with ADHD. There was a 1-week washout, an open-label dose-optimization phase of up to 4 weeks, a 2-week double-blind phase comparing the individual optimized dose to placebo and an 8-week open-label phase with the individually optimized dose of OROS MPH [37]. During the open-label dose-optimization phase, OROS MPH was started at 18 mg and could be increased weekly based on response. If response criteria was not met at 72 mg subjects were discontinued. During the double-blind phase, ADHD symptoms were assessed using the ADHD-RS. Subjects were allowed to enter the 8-week open-label phase after completing the double-blind phase, or if they discontinued from the double-blind phase due to lack of efficacy.

There were 177 subjects who completed the dose titration phase and were randomized to the double-blind phase. Subjects were titrated to the following optimal doses: 18 mg/day ($n = 13$, 7.4%), 36 mg/day ($n = 49$, 28%), 54 mg/day ($n = 50$, 28%) and 72 mg/day ($n = 65$, 37%). The mean ADHD-RS score at baseline was 31.26 and was 10.64 at the end of dose titration. During the double-blind phase, 14 subjects withdrew from the OROS MPH group due to lack of efficacy and 23 withdrew from the placebo group due to lack of efficacy. ADHD-RS scores on OROS MPH compared to placebo was highly significant ($p = 0.001$).

Treatment-related adverse events occurring during the open-label titration included headaches, decreased appetite, insomnia and abdominal pain. There was one serious adverse event of suicidal ideation in a subject with a history of depression which resolved after medication discontinuation. The authors noted that there was a higher placebo response rate (31%) for the adolescent study compared to 17% for a previous study in 6–12 year olds. Several factors were thought to contribute to the higher placebo response including the time of year, dose optimization and the age group, since hyperactivity and impulsivity are less common in the older children.

13.11 Guanfacine extended release

Guanfacine is an alpha-2 adrenergic receptor agonist that is thought to have a positive effect on symptoms of ADHD through stimulation of postsynaptic, alpha-2A-adrenoceptors in the prefrontal cortex [38].

The efficacy and safety of guanfacine extended release (GXR) was evaluated in a double-blind, multi-center, placebo-controlled, fixed-dose escalation study in 345 subjects aged 6–17 years (mean age 10.5 years) diagnosed with ADHD [39]. Subjects were assigned to one of four treatment groups: placebo, GXR 2 mg/day, GXR 3 mg/day or GXR 4 mg/day in a 1 : 1 : 1 : 1 ratio dosed each morning. The ADHD-RS-IV was the primary efficacy measure. All subjects who were randomized to one of the GXR groups started with 1 mg/day and dose was increased weekly in 1 mg/day increments with the highest dose of GXR given during weeks 4 and 5. At the beginning of week 6, GXR dose was decreased weekly in 1 mg/day increments.

Subject completion rate was 62%. Change in ADHD-RS-IV total scores from baseline to endpoint was significant in all GXR groups compared to placebo. The mean decrease in ADHD-RS-IV scores across all GXR groups was -16.7 compared to -8.9 for placebo. Least squares mean endpoint changes from baseline adjusted for placebo were -7.70 (95% CI -12.25 to -3.15 ; $p = 0.0002$) in the 2 mg/day group, -7.95 (95% CI: -12.5 to -3.40 ; $p = 0.0001$) in the 3 mg/day group and -10.39 (95% CI: -14.97 to -5.82 ; $p < 0.0001$) for the 4 mg/day group. Effect size was 0.64 for the 2 mg/day group, 0.66 for the 3 mg/day group and 0.86 for the 4 mg/day group. Changes were also evaluated based on weight and were significant in the 0.05–0.08 mg/kg group, the 0.09–0.12 mg/kg group and the 0.13 to 0.17 group but not in the 0.01 to 0.04 mg/kg group.

The most common adverse events reported were somnolence, fatigue, upper abdominal pain and sedation. Cardiac parameters were not significantly changed

with treatment compared to baseline. There were no significant changes in height and weight.

13.12 SPD465

SPD465 is a compound composed of mixed amphetamine salts in a triple-bead formulation, designed to provide ADHD symptom control for up to 16 hours. Two studies in an adult workplace environment evaluated the duration of effect of SPD465 compared to placebo. In these studies, adults aged 18–55 diagnosed with ADHD were evaluated while completing multiple tasks including math problems (PERMP) during a 16-hour period in a simulated work environment. In one study [40], SPD465 25 mg was statistically significantly superior to placebo from 4 hours post dose ($p < 0.01$) to 16 hours post dose ($p < 0.0001$). In the second study [41], SPD465 50 and 75 mg were compared to placebo and PERMP total scores were statistically better than placebo at all post dose time points measured from 2 hours through 16 hours ($p < 0.0001$).

The efficacy and safety of SPD465 was evaluated in a 7-week, randomized, double-blind, multi-center, parallel-group, dose optimization study of 272 adults (aged 18–55) diagnosed with ADHD [42]. The primary efficacy measure was the ADHD-RS-IV and eligible subjects were required to have an ADHD-RS-IV score of at least 24 at baseline. Subjects were randomized 1 : 1 to SPD465 or placebo. Dosing started at 12.5 mg/day and could be increased weekly to 25, 50 or 75 mg/day to achieve an optimum dose defined as a decrease in ADHD-RS-IV total score of at least 30%. The ITT population consisted of 136 subjects in the SPD465 group and 132 in the placebo group. The mean change in ADHD-RS-IV score from baseline to endpoint was –14.3 in the SPD465 group and –6.3 in the placebo group. The difference in least squares mean changes from baseline to endpoint was significantly better in the SPD465 group compared to placebo ($p < 0.0001$). For the SPD465 group, 68.6% completed the study and 55.5% completed in the placebo group. Of these, 7.3% of the SPD465 group discontinued due to lack of efficacy compared to 22.2% in the placebo group. The most common treatment-emergent adverse events in the SPD465 group were insomnia, dry mouth, decreased appetite, headache and decreased weight. Most were described as mild to moderate, but 11 subjects on active treatment reported severe adverse events, most commonly insomnia.

There was one serious adverse event, a possible transient ischemic attack. There were 23 subjects who discontinued secondary to an adverse event, 17 from the SPD465 (most common reasons included elevated blood pressure, palpitations, insomnia and irritability) and 6 from the placebo group (most commonly due to elevated blood pressure). Changes in mean vital signs, ECG and laboratory measures were minor.

13.13 Modafinil

Modafinil is a wake-promoting agent that has been shown to selectively activate neurons in animals that have projections through the cerebral cortex. Its exact

mechanism of action is unknown [43]. Modafinil has been studied in several randomized, placebo-controlled trials in children and adults with ADHD.

In a 9-week, flexible-dose, multi-site, randomized, double-blind, placebo-controlled study of modafinil film-coated tablets (170–425 mg), 200 children and adolescents aged 7–17 diagnosed with ADHD were assigned to once-daily medication or placebo. The primary efficacy measurement was the change from baseline to last observed post-baseline visit for the teacher rated ADHD-RS-IV. Subjects were randomized 2 : 1 to receive modafinil starting at 85 mg which was titrated to an optimal dose of 170–425 mg or matching placebo. Of randomized subjects, 131 received active medication and 67 received placebo.

Most (60%) subjects on active medication were titrated to 425 mg/day of modafinil. The mean dose was 361.4 mg/day. Of the 34 subjects who discontinued due to lack of efficacy, 15 were on modafinil and 19 were on placebo. Mean change in the ADHD-IV School Version from baseline to the final visit was –17.5 for subjects on modafinil compared to –9.7 ($p < 0.0001$) for subjects on placebo. Effects size for the ADHD-RS-IV School Version was 0.63 and for the ADHD-RS-IV Home Version was 0.78. Significant differences with modafinil compared to placebo were noted at week 1 and all later visits. The most common adverse events ($p < 0.05$ compared to placebo) in the modafinil treated group were insomnia, headache, decreased appetite and weight loss. No clinically significant changes in heart rate, systolic blood pressure, diastolic blood pressure or ECG were found. Weight changes between the placebo and modafinil treated groups were significant ($p < 0.0001$). Mean weight decrease in the modafinil group was 0.6 kg compared to a 1.3 kg weight gain in the placebo group [44].

13.14 Bupropion XL

Bupropion XL is an antidepressant that was studied in a randomized, placebo-controlled, multi-site 8-week trial of ADHD in 162 adults. Subjects were randomized to drug or placebo in a 1 : 1 ratio. The primary efficacy scale was the ADHD-RS and response was defined as a 30% decrease in ADHD-RS score at endpoint compared to baseline. Subjects started on 150 mg/day of bupropion XL for 1 week, then the dose was increased to 300 mg/day weeks for weeks 2–4. The dose of bupropion XL could be further increased to 450 mg if ADHD-RS improvement was $<30\%$, CGI was >2 and side effects were tolerable. There was a 1-week follow-up after the end of the study. At endpoint, 53% of subjects on bupropion compared to 31% of subjects on placebo were responders ($p = 0.004$). Significant difference in number of responders on drug compared to placebo was noted as early as week 2 ($p = 0.01$). Adverse events occurring in more than 5% of subjects treated with bupropion XL included headache, dry mouth, insomnia, nausea, nasopharyngitis, dizziness, constipation, irritability, fatigue, tinnitus, somnolence and upper respiratory tract infection [35].

13.15 Discussion

With all of the medications available to treat ADHD, how does one decide which medication to use? All of the drugs reviewed have been shown to be effective and have tolerable side effects. Only those approved by the FDA to treat ADHD will be discussed further. There are a few head-to-head studies comparing effectiveness. Atomoxetine was shown to be less effective than MAS XR in a 5-week double-blind laboratory classroom study of 203 6–12 year olds with ADHD [45]. Changes in the mean SKAMP deportment scores from baseline were significantly larger for MAS XR (−0.56) than for atomoxetine (−0.13). The SKAMP deportment effect size for MAS XR in this study was 1.12 compared to the effect size for atomoxetine of 0.2. However, atomoxetine has the advantage of not being a controlled substance, offering convenience when compared to stimulants.

With all of the long-acting stimulants available, how does one choose between them? Onset and duration of action tailored to the patient's particular needs should be major considerations. For example, only one stimulant (d-MPH-ER) has been shown in multiple studies to separate from placebo at 30 minutes after dosing. This drug may be the best choice for a patient who has the most difficulties early in the morning. A direct comparison of d-MPH-ER to OROS methylphenidate (OROS MPH) showed significant improvements in SKAMP combined scores at 2 hours for d-MPH-ER compared to OROS MPH. However, OROS MPH had a greater effect at the end of the 12-hour day [46, 47]. A comparison of modified release methylphenidate (MPH MR) and OROS MPH showed that MPH MR had superior effects on ADHD symptoms in the morning, while OROS MPH was superior in the early evening [48]. A patient who has the most difficulties with ADHD symptoms later in the day may benefit more from OROS MPH than other formulations. However, LDX has been shown to last longer than any of the other FDA approved stimulants, with efficacy lasting 13 hours. LDX may also be preferable to MAS XR because of its lower PK variability.

What's on the horizon? GXR and SPD465 have both received approvable letters. A clinicaltrials.gov search shows that ABT-089, a neuronal nicotinic acetylcholine receptor agonist, is being studied. Additionally, a long-acting clonidine hydrochloride formulation and memantine hydrochloride are being evaluated in clinical trials. The need for effective and convenient medications with improved adverse event profiles to treat ADHD will continue to drive research and development.

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14

Autism and Asperger's Spectrum Disorders

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Abstract

Although Asperger's and Autism are considered pervasive developmental disorders, there remains controversy as to whether they are similar disorders on opposite ends of the spectrum, or completely independent entities. Genetic studies can assist in answering these diagnostic questions, but there are limitations inherent in these methods. The author presents new psychopharmacological approaches to treating Autism and Asperger's syndrome focusing primarily on novel uses of existing medications for treatment of specific symptoms (e.g. attention, mood) rather than targeting diagnostic categories.

Key Words

Autism; Asperger's spectrum; Psychopharmacology; serotonin

14.1 Introduction

Classification of childhood-originated neuropsychiatric disorders has shifted dramatically over the course of the twentieth century and beyond. Noticing unusual behaviors in childhood, and related neurological symptoms, is probably as old as mankind. However, with the advent of effective antibiotics, it has become possible to treat disorders which are chronic, not obviously infective and persistent from childhood throughout the rest of life.

The central notion of autism, credited in large measure to the writings of Kanner, is that certain children appear early in development to live lives unto themselves, with a large degree of apparent disregard for parents and other people [1]. Their physical health is usually robust. They have varying degrees of language development. Their motor development often appears largely, if not entirely, normal. However, beyond

these spectra, they appear to respond largely to internal stimuli. It may be difficult to engage their attention, even for very short periods of times (seconds). Their usual self-care milestones may be restricted, or reached only with exceptional degrees of behavioral reinforcement.

Asperger's syndrome was originally viewed as an entirely different, discrete entity, unrelated to autism. The defining characteristic, or symptomatology, was thought to be a quite skewed misreading of social cues. This is a child who is into herself/himself and, yet, does appear to relate to the world. Unlike the autistic child, the one with Asperger's syndrome supposedly relates, but in ways that appear to be peculiar or fanciful to both peers and adults. Such children might well mature and find places in the adult world. However, they would likely be isolated, in professions or jobs which required minimal interaction with others. As with autism, conventional measures of intelligence could display a broad range from dull to normal to bright.

A confounding variable is the diagnosis of childhood schizophrenia. The assumption behind this epithet is that, on the schizophrenic spectrum, some present with the classical symptoms at an early age. Traditionally these were said to be delusions, hallucinations and other varieties of thought disorder. (It was also the case that these had to occur in the absence of diagnosable mental retardation.) Only later did the nomenclature begin to sweep more broadly to include mood disorders and behaviors, with or without the thought disorder, as alternative presentations of schizophrenia.

14.2 Individual entities versus a spectrum disorder

A non-trivial question, relevant to the application of therapeutic treatments, is whether we are dealing here with individual, independent entities or whether Asperger's syndrome and autism belong to the same spectrum. There are advocates and arguments on both sides and the jury is out on the subject. For a variety of reasons, which we elaborate upon below, we come down on the side of complexity with varying degrees of expression – 'penetrance' in the older genetic language – and unique combinations of symptoms.

One of the earliest formulations of childhood disorders may provide a still relevant framework for thinking about developmental delays in children. This is perhaps Anna Freud's major contribution to the theory of psychiatry. Anna Freud described what she called 'continua' of development [2]. Basically, what this means is that, for a given realm of development, we can define a series of milestones ('benchmarks') that generally have to be reached in a monotonic sequence in order for further abilities and skills to be available to the child. These continua include (but presumably are not limited to) thought, speech and language; motor strength and facility; and interactions with adults (and siblings and peers). The rates, degrees and intricacy of a child's achievements of such milestones are individualized. However, especially in the first few years of life, observation has led to expectable norms of time in which these maturational steps are thought usually to be achieved.

Several caveats are necessary in discussing continua of development. First, the rate of development in a given sphere may differ significantly from others, at least early-on. Everyone has observed that some children may take their first steps by

nine months of age. Yet, there is no necessary correlation with the expression of their first words. In some instances the continua are interactive, so that the rate limitations in one sphere may eventually limit the other. However, in general, wide differences in meeting an array of benchmarks are compatible with eventual 'normal' range development.

Second, environment plays a major role in influencing the expression of a number of normal behaviors. At the extreme, deprivation of parental interaction, affection and encouragement can lead to major delays in a number of continua. It was, in fact, this observation in children separated from their parents that led early theoreticians to articulate the importance of nurturance upon early childhood development. More recently, researchers have shown that even such extremes of deprivation can be overcome to a significant extent by major interventions perhaps as late as age two or even beyond [3].

Third, and most immediately relevant to the purpose of understanding the impact of medications and other therapeutic interventions, there are differences among both individuals and groups which may be explained (at least partly) by genetics. Until recently, when the elaboration of the genome dramatically changed the direction of much of human genetic research, it was easier to achieve agreement among clinicians to the effect that observations depended upon both cultural and in-born genetic factors. A common example, extended from the motor sphere, is that black children in America regularly walk several months earlier than white. Is this because of cultural emphases, genetics or both? Again, there are arguments for all sides of the question.

A curiosity of human nature-versus-nurture controversies is that, the more basic the genetic research, the more consensus there is among investigators upon such questions. For instance, it is quite unlikely that any bacterial geneticist would have responded to such controversy, any time within at least the last quarter century or longer, except to exclaim, 'Of course, one cannot speak about one without defining the other'. A fundamental method for finding bacterial genetic mutants is to change their environments radically, thus favoring the surviving altered individuals.

In psychiatry Kety *et al.* showed that this type of thinking could help begin to define the component of schizophrenia contributed by genetics [4]. This innovative strategy of selecting twins adopted out at birth became a fundamental strategy for examining the possible genetic contribution of various human behavioral diseases, such as alcoholism [5]. In a brilliant turnaround of this idea, David Reiss and colleagues undertook one of the largest studies of human behavior in research history [6]. In an elegant, exceptionally complex design, they defined the 'non-shared environment' as that part of the lives of children and adults which could not be explained by an adopted-out genetic component.

Regrettably, this kind of sophisticated research design is yet to be applied to Asperger's syndrome or autism. The time is ripe, for many of the obstacles to such large-scale observational studies have now been overcome. What work has been done has been to apply the basics of the research on the human genome to autism, on the assumption that it is an independent disorder. There is now a growing accumulation of small studies pointing to the possibility of various 'candidate genes' which may explain at least part of the variance due to genetic differences from the herd.

The limitations of the over-emphasis upon the genome should by now be becoming painfully obvious:

- 1 The genes identified in various studies are multiple. Although there are now some instances of replication of a gene from one study to another or one population to another, the numbers of these are modest. Indeed, the numbers of subjects (ss) in any of these individual studies, or even those which have been replicated is, at best, fewer than 100 [7].
- 2 Largely as an effort to overcome these limitations, a larger multi-site collaborative was organized. This larger study, probably the most comprehensive to date, also reported multiple genes as being apparently relevant to autism. The largest contribution which any of them appeared to make to the overall variance was about 5% – modest, at the most optimistic estimate [8].
- 3 On both theoretical, as well as empirical grounds, there is good reason to think that simply expanding the size of the database will not improve our ability to drill down deeper into the genome.
 - (a) If, in fact, autism is on a continuous spectrum with Asperger's syndrome (or, quite possibly, even if not), there is every reason to believe that its origin is polygenic. Indeed, there may be multiple autisms with varying genetic contributions.
 - (b) A judicious reading of many studies over many years suggests considerable overlap and continuity among a variety of presentations of autism and Asperger's syndrome [9–11]. At the very least, if individual variability is so great, it will make the effort to parse out study groups for genetics much more difficult. Also, where this may be achievable, the cost of creating a relatively 'pure' sample may be the loss of generalizability to other sub-groups of the disorders.
 - (c) There are design issues for larger study and intervention trials which are quite substantial, and may be difficult to overcome. Perhaps the most relevant one is the notion that 'larger is better', for example that enlarging the sample size through collaboratives will increase the likelihood of greater specificity. In fact, in another recent major study of psychiatric illness, the opposite was the case [12]. In a review of these studies, an astute statistician pointed out that larger collaboratives of human behavioral studies risk diluting diagnostic accuracy for example, as well as contributing to other sources of increased variance. (For more detail about such issues, see Chapter 18)

Later, after reviewing some of the developments in clinical trials for autism and Asperger's spectrum disorders, this chapter will conclude with some ideas about fresh approaches to these disorders. In particular, it will examine and suggest how 'thinking out of the box' about different notions of psychopharmacology and other forms of treatment may open up new avenues to augment present approaches.

14.3 Recent psychopharmacological approaches to autism and Asperger's spectrum disorders

As has been suggested above, a reasonable approach to reviewing and understanding psychopharmacological interventions in these disorders is to think of these as attempting to attack one or another of the various spectra which constitute the underlying diseases. For some purposes, the following sections have subsumed varieties of presentation under the umbrella of Asperger's spectrum disorders.

In particular, medication trials, mostly small and some larger, have been directed towards:

- 1 social isolation, since anxiety disorders often accompany the isolation; alternatively, the entire presentation may be labeled as (or predominated by) variations on 'anxiety';
- 2 mood disorders;
- 3 attention and focus problems: at the extreme, worthy of being diagnosed as attention deficit disorder (ADD) (see Chapter 13, this chapter is restricted to the particulars which appear to be applicable to Asperger's spectrum disorders); and
- 4 cognition and memory.

Social isolation and anxiety disorders

The hypothesis that a relatively severe deficit of serotonin might explain the social isolation of Asperger's spectrum disorders is a relatively old one. Among the first generation of antidepressant medications were certain tricyclics which are thought to be more serotonergic than others. Until well into the 1960s, and even beyond, there were two major competing hypotheses about the underlying biochemical explanation of depression: one school claimed this was a central nervous system (CNS) deficit of serotonin and the other of norepinephrine. When the more serotonergic compounds became available, a natural next experimental step was to try them for autism (at the time this was clearly considered a discrete entity).

The results, in short, showed little or no improvement for the target behaviors [13–16]. This frustration remained the norm until a new generation of compounds emerged, the serotonin-specific reuptake inhibitors (SSRIs). Beginning with fluoxetine, half a dozen variations on SSRIs have been developed.

The SSRIs have proved to be largely benign, at least much less prone to unwanted effects (so-called side effects) than the first generation compounds. Not surprisingly, they have now been tried in a number of studies in children with Asperger's spectrum disorders, as well as (more commonly by far) in children with depression or anxiety disorders. We therefore know an increasing amount about their efficacy, and more about their safety. (It should be noted, however, that no one has yet mounted the kind of large, systematic, replicable trials which would be needed to gain FDA

approval for any of these compounds to be licensed for the treatment of children or adolescents.)

A recent review addresses the presumptive state of the art in pharmacological treatments for autism spectrum disorders [17]. Large-scale trials are few and far between. Some medications have been shown to be useful, which have been found to be useful in related behavioral issues. For instance, the alpha-2 adrenergic agonists clonidine and guanfacine have shown some promise, where ADD is a co-morbid concern. Preliminary, small trials have been conducted with beta-blockers and buspirone (a serotonergic compound with a non-SSRI mechanism), both of which might be expanded. The review also identified d-cycloserine – a n-methyl d-aspartate (NDMA) partial agonist – and tetrahydrobiopterin, a co-factor in the biosynthesis of catechoamines and serotonin, as possible other avenues for exploration.

What can we reasonably conclude from these trials?

- 1 There may be some modest, but significant gain for selected children with Asperger's spectrum disorders to undergo trials of an SSRI (or, more than one in sequence, depending upon tolerability). Some studies certainly show promising positive results on social isolation.
- 2 Where anxiety or depression are co-morbid conditions, there are additional good reasons to consider treating with SSRIs. In fact, the case is undoubtedly stronger for their use for treatment of these conditions whether alone, together or with Asperger's spectrum disorders, than for SSRI use in Asperger's without such co-morbidities.
- 3 A reasonable hypothesis worth pursuing in subsequent trials is that previous trials have continued to suffer from the difficulty of achieving high enough serotonin levels in the CNS. This could possibly be achieved by dosing more aggressively. To date, clinicians usually have hesitated to do this – and possibly for good reason. High-dose SSRI treatment has certainly been reported in adults [18], but it is good judgment to worry about such dosing with children and adolescents. The long-term outcome of treatment with SSRIs in children and adolescents is little known, especially for sustained treatment. (What we do know suggests that unanticipated long-term consequences may well be unusual or rare; the FDA definitions of 'unusual' and 'rare' are effects which may occur in less than 5/1000 and 1/1000, respectively.) With proper oversight, monitoring and well-informed consent, these might be avenues worth pursuing.
- 4 The effects of multiple medications taken over the same periods are even less well studied. For example, methods of 'augmentation' or serotonergic compounds have been in use for several decades or more, and are considered standard practice. The basic strategy is to attempt to achieve more serotonergic effect by adding a compound presumably operating from a different biochemical mechanism. The SSRIs all work at the post-synaptic receptor part of the inter-neuron chains; lithium as augmentation, buspiron, certain third-generation antipsychotics and other compounds have all been reported useful in this role.

In fact, a reasonable guess is that, for clinical practice, it is probably becoming more and more common to engage in such (more rational) polypharmacy. Practice has outrun systematic clinical trials science. The latter needs to catch up in order to better inform practicing clinicians.

Mood disorders

When discussing mood disorders, especially as they occur in Asperger's spectrum disorders, the reference is usually to depression. However, the understanding of mood disorders has been shifting to a significant degree. The next edition of the American Psychological Association (APA) nomenclature will almost certainly look different and will probably be considerably more complex.

For present purposes, when we use the term 'major depressive disorder' we mean a condition of depressed mood which occurs most days, most of the days, for at least two weeks. (In practice, most depressions which are reported to clinicians have been going on for considerably longer, probably months.) The old 'neurotic depression' is now largely subsumed under 'dysthymic disorder', which basically means a milder, chronic depression which continues for months or longer and often returns, even after brief remissions (which may be 'spontaneous'). (For more details of these and related conditions, see Chapter 12.)

The area in which thinking about mood disorders may well be changing the most is in defining bipolar disorder(s) and the related diagnoses and symptomatology. Moods may vary greatly from one person to another, and among groups. For example, mania has been widely recognized for more than a century as a hallmark for the diagnosis of manic depressive illness. However, we have also learned the following.

- 1 Many conditions originally diagnosed as unipolar depressions may (sometimes after many years or recurrence) erupt at some point into a bout of mania. This makes it essentially impossible to make a definitive diagnosis of unipolar depression, except with the caveat 'to date'.
- 2 By far more common presentations of activation in the course of mood disorders are periods of irritability, anger and anxiety, alone or together in various combinations. (They may also be co-temporaneous with depressive episodes.) Sometimes these are definitive enough to merit the designation 'hypomania' but at other times not, either by virtue of milder symptomatology, shorter duration or simply limited self-reports or corroborating descriptions.
- 3 Given point (2) above, the question for treatment often arises: when does mood stabilization make more sense than treating with antidepressants, certainly as monotherapy? It is well known that non-psychiatrists under-diagnose mood-destabilized disorders, and commonly over-treat with SSRIs. Although this often works satisfactorily, at other times (with all good intentions) it can worsen the mood disorders.

Pragmatically, the present application of our new knowledge about mood disorders is to suggest that perhaps different avenues of drug treatment for mood disorders

in Asperger's spectrum disorder are worthy of investigation. In particular, many children – and adult Asperger's patients – may become easily irritated. They may also have low thresholds for anger or agitation. These are exactly the qualities which usually direct clinicians to think differentially about employing mood stabilizers.

The idea of trying out mood stabilizers may also be theoretically intriguing. The class of 'mood stabilizers' has now been shown to hold a possibly small double-digit number of compounds which are helpful in some patients. One of the things which is interesting about this class is that, to date, there is no unifying single biochemical explanation of how they work.

The original (and still widely useful) was lithium carbonate. There are a variety of lines of basic research suggestive of its mechanisms in the CNS. They range from membrane stabilization [19] to more recent work, suggesting that lithium may actually have some serotonergic-boosting properties in the CNS.

We were not able to discover details of any clinical trials of lithium as a treatment for Asperger's syndrome, either as a primary or as a secondary agent [20, 21].

The largest group of mood stabilizers presently employed consists of compounds originally licensed to treat seizure disorders. Exploration in this area dates back to independent observations by two groups, in Japan and the US, suggesting the possible mood-stabilizing properties of carbamazepine (still used in this way). Valproic acid is now perhaps the most widely prescribed mood stabilizer. More recent additions include lamotrigine.

Despite the commonality of anti-epileptic properties of these compounds, there is no well-established connection between their antiseizure potency and their mood-stabilizing utility. Moreover, other compounds with mood-stabilizing properties may not only have no antiseizure but, in some cases (antipsychotics), may actually contribute to a lowering of the seizure threshold. There is also no evidence that mood disorders are somehow seizure driven.

Reports of the use of anticonvulsants as treatments for mood disorders in Asperger's spectrum disorder are limited [22–24].

To date, the compounds which might serve as mood stabilizers in Asperger's spectrum disorder generally described in the scientific literature are antipsychotics, in particular the so-called 'atypicals'. Of these, one of the most intensive development campaigns went into examination of the data for risperidone (Risperdal) as a treatment for autism. The pharmaceutical manufacturer (Janssen) invested considerable resources in building a case, much of it from secondary data derived from previous clinical trials rather than prospective comparison studies. Target symptoms were probably largely about behavioral control: for example, helping calming and managing agitation. Apparently the firm felt there were sufficient *ss* and data from the original trials work to argue that there were statistically significant impacts upon such behaviors, even although the original data were from treatment trials of schizophrenia (risperidone's original licensure).

The American FDA did not, however, accept these arguments (nor wholly reject them either), but asked for additional clarification. This certainly required more data analysis and, ideally, would have been best addressed by the instigation of prospective trials in autism. To date, Janssen has not publicly shown any interest in pursuing

this avenue. (In fact, as their patent on Risperdal was waning, they poured their support into an alternative compound, Paliperidone, a separately patented metabolite of Risperdal, now independently licensed.) [27–29]

Other atypicals have also been reported as showing similar effects, at least in smaller (generally open-label) studies and case reports. These include olanzapine (Zyprexa) [30–33], quetiapine (Seroquel) [34–36] and clozapine (Clozaril) [37–39].

Even if these atypicals were to be established more robustly as useful agents for the treatment of autism, there remains the disquieting concern about their possible, as yet largely unknown, long-term effects in human beings. The most worrying of these is the possibility of Tardive Dyskinesia (TD). It is now well known that some of the atypicals may precipitate or contribute to TD over a number of years [40]. The reports to date are largely from adult schizophrenics. Studies in children and adolescents report relatively low levels of TD [41–43]. There may be reason to think that schizophrenia is a condition in which patients are pre-disposed to extra-pyramidal syndromes, including TD [44]. However, this area of study is non-consensual. The trials (e.g. of risperdal) and possible licensure would lead to the treatment of large numbers of children and adolescents, open-ended and conceivably over many years. Earlier work on TD with the phenothiazines strongly suggests that the rates of occurrence of TD, severity and likelihood of reversibility of TD upon cessation of the drugs are related to both dosages and length of times of exposure. More troublesome is the fact that in some patients, even when the offending agents are discontinued, TD may continue (although probably not worsen). There are no established methods of predicting which patients may be particularly vulnerable to TD.

Having said all this, admittedly somewhat nihilistically, what can be the good news? It is mainly that, since these various groups of compounds and members of each group have different biochemical properties, pursuing these clues may lead to different avenues of drug treatment.

Moreover, there are yet other receptors discovered in the CNS which may conceivably have some role in regulating mood disorders. A leading candidate is the NMDA receptor complex. Compounds licensed for other purposes have been rediscovered to attack this receptor. An example is baclofen, which has recently been tested as a CNS medication. Whether this receptor is primary, or further down the chain in regulating CNS functions, at the very least it suggests a whole range of possible medications not previously considered.

Another example of such work is the combination of pre-clinical and early clinical testing which centers around cycle adenosine monophosphate (AMP), another possible precursor to enzymes thought to be crucial to mood regulation and receptors in the CNS [45].

Cognition, memory and attention

A series of compounds have been developed and licensed to treat Alzheimer's disease, the official name for senile dementia.

The first of these was Cognex®. Its mechanism, and that of most of the compounds to follow it until recently, is to bolster muscarinic transmission in the CNS. The preclinical basis for investigating these compounds is based largely on the fairly

robust finding of decline in muscarinic receptors in the hippocampus, correlated with cognitive diminution. Cognex was unique when first licensed, in that it was the first compound reported to improve Alzheimer's significantly. However, (i) as is still true of other compounds since licensed, it does not alter the eventual downhill course of the underlying illness and (ii) in the case of Cognex, the side effect profile is quite significant and daunting. In fact, 30–40% of Alzheimer's patients, or more, may not tolerate the side effects of Cognex. The FDA may well have licensed it at the time only because there were no other choices available. Cognex is probably used infrequently not that more benign muscarinic re-enforcers have been developed.

The next in this series of compounds to be licensed was donepezil (Aricept®). Donepezil is both effective and considerably more tolerable (statistically) than Cognex, and is one of the leading antimuscarinic agents. The relevance to the present discussion is that, not long after being licensed, reports began to appear of its use in other illnesses notable for their symptomatic deficits in cognition, memory and attention. Moreover, the clinical impression (not well studied) has been growing that donepezil may have mood-lifting properties, at least in Alzheimer's patients (whether primary or secondary to cognitive enhancement).

- 1 In vivo, with the best histories and laboratory examinations, it is difficult to impossible to differentiate pure Alzheimer's disease from a mixture with vascular dementia. An obvious next set of clinical trials was therefore to measure the impact of donepezil upon vascular dementia by selecting patients whose dementia (as best could be determined) was likely to be largely due to vascular disease in the brain. In short, donepezil appears to be of value [46, 47]. Another similar dementia is so-called Loewy body dementia (named for specific pathognomonic microscopic finding). Here, too, donepezil is reported to have significant cognitive-enhancing properties [48]. It therefore seems likely that the pro-cognitive effects of donepezil might be more widely applicable than simply to Alzheimer's patients.
- 2 A small series of reports has appeared, employing donepezil to treat autism [49, 50]. As in its use for dementia, some of the target population seems to respond with improved cognition, greater ability to follow instructions, more appropriate social responses and even possible improvements in language and communication skills.
- 3 Last, but not least, donepezil has now been reported to be a possible (third line choice?) agent for the treatment of ADD in addition to dementias or autism. The ideal situation for using donepezil may be for patients who have failed to respond well to, or tolerated poorly, stimulants and atomoxetine. Also, when a child or adult appears to understand and remember immediate information or instructions, but then cannot reproduce these in intermediate or longer term frameworks, it is conceivable that donepezil may have a particular niche [51–53].

Although stimulants are undoubtedly employed widely for attention problems in children and adults with Asperger's syndrome, the risk of increasing irritability and

destabilizing mood is a significant one. Asperger's spectrum patients, at least theoretically, may be more prone to this than other people.

Given the reported promise of donepezil, not surprisingly other compounds licensed to treat Alzheimer's have successively been reported to have value in autism. These include the other antimuscarinic compounds, reminyl (Razadyne®) [54–56] and rivastigmine (Exelon) [57]. More interesting is the first appearance of such work using memantine (Namenda). Memantine has a different mechanism of action, notably activation of the NMDA receptors in the CNS (see above) [58–61]. In theory, memantine could also have mood-stabilizing properties [62–64]. It is also the case that a more complex treatment regimen, combining Alzheimer's drugs with mood stabilizers, could be more effective than either alone. This also remains an intriguing but untested hypothesis.

14.4 Recapitulation

The nature of autism and Asperger's spectrum disorders remains, alas, elusive. Still, the volume of progressive work on these disorders is impressive and rapidly growing. More optimistically, the armamentarium of treatment possibilities has also significantly expanded, if still on a largely experimental basis. Not only are there a series of good and rational options to try to help Asperger's spectrum patients with particular problems on various developmental continua, but the possibilities of combined treatments are now numerous.

We have not reviewed behavioral modification as a treatment for autism, or for Asperger's spectrum disorders. It is worth mentioning that there have been a series of case reports over the years of successful, in the long term, intensive behavioral modification regimens for even some severely autistic children [65, 66]. Possibly without exception, these treatments were extraordinarily labor-intensive and expensive. Essentially, they required intense behavioral modification re-enforcement during the entire waking hours of the patient, for many months, and generally for years. This is why such treatments have never gained wide acceptance as standard methods. On the other hand, they lend credence to the sentiment for cautious optimism that treatment can have significant positive outcomes. The challenge is to find versions of treatments that are economic and practical.

We have spoken of the limitations of genetic investigations of autism and (to a lesser degree) Asperger's syndrome(s). The other side of this coin is the genuine possibility that, as candidate genes are tested in vitro in order to understand their mechanisms, more, more specific and more potent treatment options may well emerge.

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15

Pharmacological Treatments of Impulse Control Disorders

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Abstract

Impulse control disorders (ICDs) are commonly defined as the failure to resist an impulse, drive or temptation to perform harmful acts. In the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) the following disorders are included in the section ‘Impulse control disorders not elsewhere classified’: intermittent explosive disorder, pyromania, kleptomania, trichotillomania and pathological gambling. Common to all these disorders are repeated failures to resist impulses to perform harmful acts. This chapter gives a brief outline of clinical characteristic and pharmacological treatments of each of these disorders. Pharmacological trials with selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, opioid antagonists, mood stabilizers and anti-epileptics have demonstrated potential effectiveness of pharmacological treatments for ICDs. However, several studies have limitations such as poor designs, relying on single cases, small sample sizes and lack of adequate control groups. More controlled studies in this area are needed to establish the effectiveness of pharmacological treatments for different ICDs.

Key Words

pharmacological treatment; impulse control disorders; intermittent explosive disorder; pyromania; kleptomania; trichotillomania; pathological gambling

15.1 Impulse control disorders

In the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), five separate disorders are outlined in the section ‘Impulse control disorders not

elsewhere classified': intermittent explosive disorder (IED), pyromania, kleptomania, pathological gambling (PG) and trichotillomania (TTM). In the section 'Impulse control disorders not otherwise specified', skin picking, compulsive shopping and compulsive sexual behavior are included.

The essential feature of ICDs is the failure to resist an impulse, drive or temptation to perform an act that is harmful to the person him/herself or to others. Common in ICDs is that the individual feels an increasing tension or arousal before engaging in the behavior, and experiences pleasure, gratification or relief when committing the act. After the act is carried out, there may or may not be regret, self-reproach or guilt [1].

Many of the underlying behaviors in ICDs, such as gambling and shoplifting, are common in the general populations. However, only a small portion of the individuals performing these behaviors do it as a response to irresistible impulses or urges and can be classified as an ICD. In addition to the similarity of symptoms for these disorders, they also have similar ages at onset and courses [2]. However, the sex ratio seems to differ among the different disorders [1, 2]. With the exception of PG, all of these disorders are considered to be rare [2], and little research exists concerning epidemiology and treatment efficacy. Studies of phenomenology have shown that ICDs may be related to mood disorders, anxiety disorders and substance use disorders [2]. Although ICDs can often be significant disabling, these disorders often go undiagnosed and untreated [3].

Neurobiology of impulse control disorders

Apart from the possible phenomenological relationship with other disorders, the nature of the core symptoms of ICDs allows us to make assumptions about the underlying neurobiology. Serotonin, which is a central neurotransmitter in behavior initiation/cessation, has been suggested to be involved in the failure to resist impulses which is the core criteria of ICDs as serotonergic dysfunction is often related to impulsivity [4]. Norepinephrine is involved in arousal and excitement, and might be central in the increasing arousal experienced before committing the impulsive behaviors [4]. Dopamine is a neurotransmitter central in the reward and reinforcement systems in the Ventral Tegmental Area and the Nucleus Accumbens, and it has been hypothesized that this reinforcement system is likely to be involved in the rewarding feeling of pleasure when committing the act [4]. In addition, opioids are usually involved in feelings of pleasure and urges, and it has also been suggested that this substance is involved in the rewarding, pleasurable experience when committing the act. Due to the reinforcing properties, opioids have also been assumed to contribute to the urges experienced before committing the certain behavior. Since all the neurotransmitters and neurotransmitter systems mentioned here have been assumed to play a central role in ICDs, they have in clinical practice and in clinical studies been targets for pharmacological interventions of ICDs.

Most studies of the neurobiology of ICDs have focused on the hypothalamic-pituitary-adrenal axis, on serotonin, norepinephrine, glucose metabolism and on EEG data. The most consistent findings have suggested abnormalities, particularly in the serotonergic and, to a lesser extent, in the noradrenergic systems [2].

Although Kim [5] suggests that symptoms of ICDs are generally refractory to psychotherapeutic or pharmacologic treatments, several pharmacological treatments have recently proven effective in the treatment of such disorders. Still, few controlled trials have been conducted and no empirically validated pharmacological treatments exist for these disorders. As little research investigating the efficacy of treatments for ICDs have been conducted, our understanding of efficacious and well-tolerated pharmacotherapies for ICDs lags behind those for other major neuropsychiatric disorders [3]. PG is the most common ICDs, and has received the most clinical and research attention. This chapter will give a brief outline of the clinical characteristics of ICDs, and present empirical research on pharmacological treatments for each of these.

15.2 Pathological gambling

Gambling can be defined as an activity that involves an attempt to win money by staking money on uncertain events [6]. For most people, gambling is a leisure activity without negative consequences. However, others develop excessive gambling behavior which has severe negative consequences for the gambler and his or her relationships with family members, friends or colleagues. According to DSM-IV-TR, the essential feature of PG is '*persistent and recurrent maladaptive gambling behavior that disrupts personal, family or vocational pursuits*' which is not better accounted for by a manic episode [1]. The lifetime prevalence of PG is between 1 and 3% in the adult population of North America. The prevalence is even higher for adolescents [7–9]. The prevalence of gambling is assumed to be on the rise due to expanding gambling opportunities and the general social approval of the gambling industry [10, 11]. Consequently, the need for effective treatment seems to be self-evident. Most of the treatments of PG have been conducted within the behavioral, cognitive and cognitive-behavioral spectrum [12]. Recently, however, several studies have been conducted investigating different pharmacological approaches to the treatment of PG.

Pharmacological treatments of pathological gambling

Evidence suggests the involvement of both serotonergic, noradrenergic, dopaminergic and opioidergic systems in the etiology of PG [13], and pharmacological treatments targeting these neurotransmitter systems have shown promising results in the early stages of understanding and treating PG [14]. These systems are related to the mechanisms that underlie behavioral disinhibition (serotonergic system), reward mechanisms (dopaminergic and opioidergic system) and arousal (noradrenergic system) associated with impulse control and addictive disorders [15]. Although PG is classified as an impulse control disorder, it has also been described as an obsessive-compulsive spectrum disorder within the impulsive cluster [16]. Potenza *et al.* conducted a functional magnetic resonance imaging (fMRI) study of gambling urges in pathological gamblers [17] and found that PG has neural features more similar to other ICDs and distinct from those of obsessive-compulsive disorders.

Hollander *et al.* [14] outline several psychopathological domains within PG which could conceivably be targeted for treatment: impulsive symptoms (arousal), compulsive symptoms (anxiety reduction) and addictive symptoms (symptoms of withdrawal). Pharmacological treatments of PG have usually involved the administration of either opioid antagonists, antidepressants or mood stabilizers [14]. Opioid antagonists block the effects of endogenous endorphins on central opiate receptors and inhibit dopamine release in the nucleus accumbens, involving reward, pleasure and urge mechanisms [14]. Several studies have also specifically indicated that pathological gamblers may be characterized by serotonergic dysfunction [18]. Most of the antidepressants drugs used in the treatment of PG are selective serotonin reuptake inhibitors (SSRIs) which appear to have anti-compulsive and anti-impulsive effects [14]. Mood stabilizers have proven effective in treating mania, and recent studies have also demonstrated effectiveness in treating other impulsive disorders such as borderline personality disorder, disruptive behavior and TTM [14]. It has been suggested that impulse control disorders and bipolar spectrum disorders may be related, and the impulsivity in PG seems to resemble that of bipolar disorder. The co-morbidity between bipolar disorder and PG has been estimated to be as high as 30% [19]. Mood stabilizers are assumed to have anti-impulsive effects [20], and hence are assumed to potentially be effective in the treatment of PG.

A recent meta-analysis of clinical trials using pharmacological interventions to treat PG identified 130 potential studies, but only 16 studies met the criteria for inclusion in the meta-analysis: (i) the target problem was PG, (ii) the treatment was pharmacological, (iii) the study was written in English and (iv) the study reported outcomes particularly pertaining to gambling [21]. A total of 597 subjects were included in the outcome analyses of these studies. Table 15.1 gives an overview of the included studies [19, 20, 22–35]. The analyses showed that at post-treatment the pharmacological interventions were more effective than no treatment/placebo, yielding an overall effect size (ES) of 0.78 (95% CI = 0.64, 0.92). A multiple regression analysis showed that the magnitude of ESs at post-treatment was lower in studies using a placebo-controlled condition compared to studies using pre-post design (without any control condition). No differences between the three main classes of pharmacological interventions (antidepressants, opiate antagonists and mood stabilizers) were detected.

15.3 Trichotillomania

TTM is defined as hair loss due to a patient's irresistible urge to pull out his/her hair [1]. The sites of hair pulling may include any part of the body on which hair grows, but the most common sites are the scalp, eyebrows and eyelashes. Hair pulling usually occurs in states of relaxation and distraction (e.g. when reading a book), but may also occur under stressful circumstances. Usually increased tension is present immediately before hair pulling, and the act is followed by gratification, pleasure or a sense of relief. According to the DSM-IV, the disturbance must cause significant distress or impairment in either social, occupational or other important

Table 15.1 Studies examining the effectiveness of pharmacological treatments for pathological gambling [21].

Study	Trial	Design	Mean dose at endpoint (mg/d)	Duration (wk)	N ^a	Mean age	Attrition ^b (%)	Proportion males (%)	Formal diagnosis	Treatment response
Black [22]	Bupropion vs. placebo	Open-label	400	8	10	44.6	0.0	40.0	Yes	70% partial/complete remission
Blanco <i>et al.</i> [23]	Fluvoxamine vs. placebo	Double-blind	200	24	32	42.1	59.4	65.6	Yes	73% complete remission
Dannon <i>et al.</i> [24]	Topiramate vs. fluvoxamine	Single-blind	200 and 200, respectively	12	20	34.9	35.5	100.0	Yes	Topiramate and fluvoxamine: 75% complete remission 25% partial remission
Dannon <i>et al.</i> [25]	Bupropion vs. naltrexone	Single-blind	424 and 116, respectively	12	25	29.1	30.6	100.0	Yes	Bupropion: 75% complete remission 25% partial remission Naltrexone: 23% partial remission
Grant <i>et al.</i> [26]	Paroxetine vs placebo	Double-blind	20–60	16	71	45.4	44.7	60.5	Yes	59% partial/complete remission

(continued overleaf)

Table 15.1 (continued)

Study	Trial	Design	Mean dose at endpoint (mg/d)	Duration (wk)	N ^a	Mean age	Attrition ^b (%)	Proportion males (%)	Formal diagnosis	Treatment response
Grant <i>et al.</i> [27]	Nalmefene (25, 50 and 100 mg) vs. placebo	Double-blind	25, 50 and 100, respectively	16	146	46.0	64.7	56.5	Yes	59% partial/complete remission
Grant and Potenza [28]	Escitalopram vs. placebo	Open-label pre-treatment	25.4	11	13	55.8	30.8	53.8	Yes ^c	62% partial/complete remission
Hollander <i>et al.</i> [19]	Fluvoxamine vs. placebo	Double-blind	195	8 + 8 (crossover)	15	38.9	23.1	100.0	Yes	70% partial/complete remission
Hollander <i>et al.</i> [29]	Lithium-carbonate vs. placebo	Double-blind	1150	10	29	44.5	27.5	58.6	Yes ^d	83% partial/complete remission
Kim and Grant [30]	Naltrexone vs. pre-treatment	Open-label	157	6	17	44.6	17.6	41.2	Yes	Most patients improved
Kim <i>et al.</i> [31]	Naltrexone vs. placebo	Double-blind	187.5	11	45	48.6	19.6	33.3	Yes	75% partial/complete remission
Kim <i>et al.</i> [32]	Paroxetine vs. placebo	Double-blind	51.7	8	45	49.3	8.9	33.3	Yes	48% complete remission 13% partial remission

Pallanti <i>et al.</i> [33]	Nefazodone vs. pre-treatment	Open-label	345.8	8	12	48.5	14.3	71.4	Yes	25% complete remission 50% partial remission Lithium carbonate: 61% partial/ complete remission Valproate: 68% partial/ complete remission
Pallanti <i>et al.</i> [20]	Lithium carbonate and Valproate vs. pre-treatment	Single blind	1200 and 1500, respectively	14	42	31.6	26.2	76.%	Yes	74% partial/ complete remission 33% complete remission 54% partial remission
Sáiz-Ruiz <i>et al.</i> [34]	Sertraline vs. placebo	Double-blind	95.0	24	60	38.9	38.3e	90.0	Yes	
Zimmerman <i>et al.</i> [35]	Citalopram vs. pre-treatment	Open-label	34.7	12	15	44.1	40.0	60.0	Yes	

^aThe number for which the data analyses are based.

^bDiscontinued medication or withdrew from the study after randomization.

^cIn addition to the DSM-criteria for pathological gambling the patients also fulfilled the criteria for at least one anxiety disorder.

^dIn addition to the DSM-criteria for pathological gambling the patients also fulfilled the criteria for a bipolar spectrum disorder.

areas of functioning [36]. Although TTM has been sparsely studied and may be under-diagnosed, the lifetime prevalence is estimated to be 0.6–3.6% [37].

Pharmacological treatments of trichotillomania

The most common treatments for TTM are habit-reversal therapy (HRT), pharmacotherapy with fluoxetine or sertraline (SSRI) and pharmacotherapy with clomipramine (tricyclic antidepressant). A recent systematic review [38] compared the efficacy of behavioral treatment (HRT) and pharmacotherapy with either SSRI or clomipramine. Seven studies [39–45] met the criteria for inclusion in the study: (i) randomized clinical trial with control group or comparison group with active treatment, (ii) blinded assessment of the clinical outcomes, (iii) primary diagnosis of TTM and (iv) comparison of HRT, SSRI and clomipramine to each other or to a control condition. A total of 157 patients were included in the overall analysis in the systematic review (see Table 15.2). Six different outcomes were examined: (i) SSRI vs. control condition, (ii) clomipramine vs. control condition, (iii) HRT vs. control condition, (iv) HRT vs. SSRI, (v) HRT vs. clomipramine and (vi) clomipramine vs. SSRI.

A total of 72 completers from four different studies investigating the effect of SSRI vs. a control condition contributed to the first outcome. None of the four studies reported significant differences between SSRI and control conditions, and in the overall meta-analysis no significant differences between SSRI and the control conditions were found either ($z = 0.09$, $p = 0.93$). The overall estimated ES was 0.02 (95% CI = -0.32 , 0.35).

Two studies investigated the effects of clomipramine. They comprised 24 completers, demonstrating a significant treatment effect favoring clomipramine when compared to control conditions (ES = -0.68 , 95% CI = -1.28 , -0.07). HRT was compared to control conditions in three trials, involving a total of 59 completers contributing to the analysis. The overall meta-analysis demonstrated beneficial effects of HRT compared to the control conditions (ES = -1.14 , 95% CI = -1.89 , -0.38) [38]. Two of these studies demonstrated a significant effect of HRT compared to the wait-list/placebo control condition [41, 44]. Only one study, Minnen *et al.* [45] compared HRT ($n = 14$) with SSRI ($n = 11$). There was no statistical significant difference between these two. However, there was a tendency toward a better effect of HRT compared to SSRI (ES = -0.73 , 95% CI = -1.60 , 0.14). One study [41] comparing the effects of HRT ($n = 5$) and clomipramine ($n = 6$) found a significant difference in favor of HRT (ES = -1.74 , 95% CI = -3.23 , -0.25). No blinded studies directly comparing the effects of clomipramine with SSRI were included in the meta-analytic review [38].

The results from the systematic review showed that HRT was the most effective treatment for TTM when practiced in this particular setting (by experienced clinicians in academic research settings). HRT demonstrated the largest ESs of these interventions. Compared to the most prevalent pharmacological treatments for TTM, clomipramine and SSRI, HRT demonstrated superiority. Clomipramine also demonstrated efficacy for TTM when compared to placebo or active control condition, while SSRI did not prove effective when compared to control conditions. This

Table 15.2 Studies examining the effectiveness of pharmacological treatments for trichotillomania.

Study	Trial	Design	Dose per day at endpoint	Duration (wk)	N ^a	Mean age	Attrition (%)	Proportion females (%)	Treatment response
Swedo <i>et al.</i> [43]	Clomipramine vs. placebo	Crossover trial, double-blind	Mean 180.8 mg Max 250 mg	10	13	31.6	0	100.0	23% complete remission 69% partial remission
Christenson <i>et al.</i> [39]	Fluoxetine vs. placebo	Crossover trial, double-blind	Mean 77.5 mg Max 80 mg	18	16	31.6	23.8	93.8	No response
Strichenwein and Thornby [40]	Fluoxetine vs. placebo	Crossover trial, double-blind	Mean 78.8 mg Max 80 mg	12	16	39.0	23.8	87.5	No response
Ninan <i>et al.</i> [41]	Clomipramine vs. placebo HRT vs. waitlist control HRT vs. clomipramine	Randomized, parallel group trial, blinded assessment of outcome	Mean 116.7 mg Max 250 mg	9	16	33.4	30.4	81.3	HRT: 80% complete remission 20% partial remission Clomipramine: 67% partial remission
Van Minnen <i>et al.</i> [45]	HRT vs. waitlist controlHRT vs. fluoxetine	Randomized, parallel group trial, blinded assessment of outcome	Mean 60 mg Max 60 mg	12	40	31.3	7.0	95.0	HRT: 64% remission Fluoxetine: No response

(continued overleaf)

Table 15.2 (continued)

Study	Trial	Design	Dose per day at endpoint	Duration (wk)	N ^a	Mean age	Attrition (%)	Proportion females (%)	Treatment response
Dougherty <i>et al.</i> [42]	Sertraline vs. HRT Sertraline and HRT	Randomized, parallel group, Double-blind	Max 200 mg	22	24	28.7	16.2	95.8	Single modality: 15.4% remission Dual modality: 54.5% remission
Woods <i>et al.</i> [44]	HRT vs. waitlist control	Randomized parallel group trial, blinded assessment of outcome	–	12	25	33.4	10.7	92.0	66% remission

^aThe number on which the data analyses are based.

finding is not in line with earlier reviews where SSRIs are recommended as the preferred pharmacological treatment for TTM [46].

However, methodological limitations of the trials included in this systematic review may have influenced these conclusions [38]. Firstly, no single clinical rating scale was used consistently in the included studies to assess severity and improvement of TTM symptoms, and it is possible that the different rating scales used have different sensitivity to detect changes in TTM severity. Secondly, most of the studies did not report the number of subjects with co-morbid Obsessive Compulsive Disorder (OCD), which quite frequently co-occur with TTM. Subjects with co-morbid OCD would probably respond to SSRI and clomipramine since these are both first-line treatment for OCD. Thirdly, all of the parallel-group trials included trial completers only in the analyses, which may have affected the results. Future studies should investigate whether HRT can demonstrate efficacy against more rigorous control conditions accounting for the non-specific effects of therapy, and determine if HRT is effective in treating TTM beyond the few sites where it is currently practiced [38].

15.4 Kleptomania

Kleptomania is characterized by recurrent failure to resist impulses to steal items even though the items are not needed for personal use or for their monetary value [1]. Increased sense of tension is usually experienced before the theft, and pleasure, gratification or relief when committing the theft. Many report guilt, remorse and depression afterwards. The stolen objects are often affordable and of little value to the individual and are often given away, discarded or secretly returned afterwards [1].

The disorder is disabling and often goes undiagnosed in clinical practice [47]. So far, no prevalence studies in general populations have been conducted. Hence the prevalence in these populations is unknown [48]. However, several studies of clinical samples suggest that the disorder is not uncommon. A recent study of psychiatric inpatients ($n = 204$) with multiple disorders found prevalence rates of 7.8 and 9.3% for current and lifetime diagnosis of kleptomania, respectively [49]. The fact that the current and lifetime prevalence rates are almost identical suggests that the condition is chronic if not treated [47]. One study of 107 patients diagnosed with depression found a prevalence rate of kleptomania of 3.7% [50] and, in a study of patients with substance abuse ($n = 79$), a prevalence of 3.8% was found [51]. Two studies of patients diagnosed with PG found that 2.1 and 5%, respectively, also met the criteria for kleptomania [52, 53]. The condition appears, however, to occur in less than 5% of shoplifters. Evidence suggests that approximately two-thirds of the individuals with kleptomania in clinical samples are female [1]. The onset of kleptomania usually occurs during adolescence, although early childhood onset and late adulthood onset have been reported [1].

Kleptomania was originally classified within the OCDs spectrum. However, recent evidence – such as clinical characteristics, familial transmission and treatment response – suggests that it has important similarities with addictive disorders and mood disorders. Kleptomania has also been shown to frequently co-occur with substance abuse [47].

Pharmacological treatments of kleptomania

The etiology of kleptomania is unclear, and little evidence concerning possible neurobiological correlates of the disorder exists [47]. It has been hypothesized that dysfunctions in the serotonergic system in ventromedial prefrontal cortex contribute to poor decision-making characteristics of individuals with kleptomania [54]. Evidence also suggests a non-specific serotonergic dysfunction as lower levels of platelet 5-hydroxytryptamine (5-HT) transporters (evaluated by means of binding of 3H-paroxetine) have been found in kleptomaniacs ($n = 20$) as opposed to healthy controls [55]. There have also been reports of kleptomania occurring after damage to the orbitofrontal–subcortical circuits of the brain [56]. Neuroimaging techniques have shown significantly decreased white matter integrity in inferior frontal regions of kleptomaniacs compared to controls [57]. This supports the hypothesis that kleptomaniacs may not be able to control and resist impulses to steal [48].

Antidepressants, mainly SSRIs, have been considered the treatment of choice for kleptomania as for other ICDs [58]. However, evidence from case reports of responses to serotonergic medication in kleptomania have shown inconsistent results [47]. In one study using open-label escitalopram in the treatment of kleptomaniacs ($n = 20$), 79% reported improvement in stealing behavior. The responders were randomized to continue medication or receiving placebo. After the double-blind phase, 43% of those receiving medication and 50% in the placebo group no longer remained abstinent. There was no statistical difference in the treatment effect between the escitalopram and the placebo condition [59]. Still, it has been argued that there may exist patients suffering from a subtype of kleptomania sharing common features with OCD who may respond well to SSRIs [47]. Grant [47] suggests that kleptomaniac behaviors may be far more heterogeneous than initially thought, and that antidepressants or mood stabilizers may be beneficial for those kleptomania subjects with significant mood symptoms who may shoplift due to subsyndromal mania or depression. However, more well-controlled studies in this area are needed.

According to Grant [47], emerging evidence suggests that SSRIs may lack effectiveness in treating kleptomania but that lithium, anti-epileptic and opioid antagonist seem to show promising results. No controlled studies of mood stabilizers or anti-epileptic medications in the treatment of kleptomania have been published, but case reports of lithium, valproate and topiramate have shown that these medications may be effective [47]. A case series of three patients treated for kleptomania showed that treatment with topiramate was effective [58]. The biological mechanism of this effect is unknown, but is hypothesized to be related to the disinhibition of GABA input in the nucleus accumbens area, targeting the arachidonic acid cascade [58]. Studies with controlled designs are needed to confirm these preliminary findings. Lithium alone, or in combination with fluoxetine, has been associated with improvement in kleptomania in several reports [2, 58, 60]. However, some case studies of lithium as monotherapy or lithium augmentation have shown no effects in the treatment of kleptomania [47].

The efficacy of opioid antagonist in kleptomania has recently been examined because of the possible relationship and similarities to addictive disorders. The urge or craving state that people with kleptomania experience before engaging in the

problematic behavior, and the hedonic experiences during the behavior, much resemble that of addictive behaviors. Opioid antagonists are assumed to work indirectly on dopamine reducing the subjective experience of reward and urges seen in kleptomania [61]. In one open-label study with naltrexone ($n = 10$) for 12 weeks (mean effective dose was 145 mg/day), 80% reported significant reduction in urges to steal and 20% reported complete remission of the symptoms [61]. A longitudinal study of naltrexone as monotreatment for kleptomania ($n = 17$) found that 76.5% had reduction in the urges to steal and 41.1% ceased to steal [62] at the most recent follow-up, where the mean duration of follow-up was 481.9 ± 280.9 days after baseline. Table 15.3 summarizes controlled studies of pharmacological treatments of kleptomania [59, 61, 62].

15.5 Pyromania

The essential feature of pyromania is repeated episodes of deliberate and purposeful fire setting, where the patient experiences tension or affective arousal before committing the act. There is also a fascination with, interest in, curiosity about or attraction to fire and its situational contexts. The patient usually experiences pleasure, gratification or release of tension when setting the fire and witnessing its effects and participating in its aftermath [1]. Research on pyromania has mainly focused on the criminal population. Although pyromania is considered to be a rare disorder [1], a recent study of psychiatric inpatients ($n = 204$) revealed that 3.4% met the DSM-IV criteria for current pyromania, whereas the lifetime prevalence was 5.9% [49]. Fire setting during adolescence does not necessarily reflect symptoms of pyromania, but may be a symptom of various psychiatric disorders [63]. A recent study of adolescent psychiatric inpatients ($n = 102$) found that, after excluding patients who set fire due to other disorders such as conduct disorder, bipolar disorder, psychotic disorders, substance use disorders and developmental disorders, seven patients met the criteria for current pyromania [64].

Pharmacological treatments of pyromania

To our knowledge, only one relatively large study of pharmacological treatment of pyromania has yet been published. The study recruited 14 adults and 7 adolescents with lifetime DSM-IV pyromania from inpatient and outpatient studies of impulse control disorders. Of the 21 subjects, 14 had previously received treatment for psychiatric disorders, and only two had received treatment specific for pyromania. All 14 had received psychotropic medication, but only two had received medication specifically prescribed for pyromania symptoms. Partial or complete remission of pyromania urges and behavior were reported in 6 of the 14 cases (see Table 15.4). The medications used included topiramate, escitalopram, sertraline, fluoxetine and lithium. In three of the cases, pyromania symptoms recurred when the medication was discontinued. In the cases not responding to psychopharmacology, different medication had been tried: fluoxetine, valproic acid, lithium, sertraline, olanzapine, escitalopram,

Table 15.3 Studies examining the effectiveness of pharmacological treatments for kleptomania.

Study	Trial	Design	Mean dose at endpoint (mg/d)	Duration	N ^a	Mean age	Attrition (%)	Proportion women (%)	Treatment response
Abujaiude <i>et al.</i> [59]	Escitalopram vs. placebo	Open label	20	4–7 wk	11	46.0	15.4	81.8	79% improved 43% partial remission 57% complete remission
Grant and Kim [61]	Naltrexone	Open label	148	12 wk	10	37.0	33.3	70.0	20% partial remission 70% complete remission
Grant [62]	Naltrexone	Retrospective longitudinal study	135.3	3 yr	17	39.6	0	70.6	36% partial remission 41% complete remission

^aThe number of subjects included in the analyses

Table 15.4 Pharmacological treatments of pyromania: an overview [63].

Pharmacologic treatment for pyromania (N = 14)									
SSRI				Mood stabilizer		Antipsychotic		Anti-epileptic	
Citalopram n = 1	Escitalopram n = 3	Sertraline n = 2	Fluoxetine n = 2	Lithium n = 2	Olanzapine n = 1	Valproic acid n = 1	Clonazepam n = 1	Topiramate n = 1	
No response	2 partial/ complete remission 1 no response	1 partial/ complete remission 1 no response	1 partial/ complete remission 1 no response	1 partial/ complete remission 1 no response	No response	No response	No response	Partial/ complete remission	

citalopram and clonazepam [63]. Treatment with escitalopram, sertraline, fluoxetine and lithium has demonstrated inconsistent results and, beyond the above-mentioned study, the rest of the pharmacological treatment literature on pyromania comprises single case studies. More research in this area is therefore needed in order to draw conclusions about the effectiveness of pharmacological treatment for pyromania.

15.6 Intermittent explosive disorder

IED is characterized by repeated episodes of serious assaultive acts or destruction of property that are out of proportion to any provocation or precipitating psychosocial stressor, and are not due to the direct physiological effects of a substance or better accounted for by another mental disorder [1]. Thus, IED must be distinguished from episodes of aggressive behavior that are due to antisocial personality disorder, borderline personality disorder, psychotic disorder, manic episode, conduct disorder or attention-deficit/hyperactivity disorder. IED usually starts during adolescence [65], and is more prevalent among males [1]. A recent prevalence study showed that the lifetime and last year prevalence rates of IED in the United States were 7.3 and 3.9% respectively [65]. High levels of co-morbidity with mood, anxiety and substance use disorders are reported [65, 66].

Pharmacological treatments of intermittent explosive disorder

Results from an epidemiologic study in the US showed that the majority (60.3%) of those diagnosed with lifetime IED had received treatment for emotional problems, but only 28.8% had received treatment specifically for IED [65]. It has been hypothesized that dysregulation of the serotonergic system and mild brain injuries may be central in the etiology of IED. The medications offered in treatment of patients with IED are mainly SSRIs, mood stabilizers and beta-blockers. However, the efficacy of these medications has mainly been determined through case reports, and controlled trials are needed to confirm the utility of these medications [66]. To the best of our knowledge, no randomized controlled trial of pharmacotherapy for IED has been conducted.

15.7 Conclusions

Common features of ICDs include urges, pleasure-seeking and inability to resist impulses. Several studies have demonstrated dysfunctions in neurotransmitter systems involved in these mechanisms, which may be targeted through pharmacological treatment. Pharmacological trials of different ICDs have shown promising results and demonstrated potential effectiveness of pharmacological treatments for these disorders. Still, several studies have limitations such as poor designs, relying on single cases, small sample sizes and lack of adequate control groups. More controlled studies in this area are needed to establish the effectiveness of pharmacological treatments for different impulse control disorders.

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SECTION IV

Special Issues in Psychopharmacology

16

Potential Benefits of Herbal Medicine for Schizophrenia: from Empirical Observations to Clinical Trials

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Abstract

This chapter provides an overview of the potential benefits of herbal medicine used in the treatment of schizophrenia. Naturally occurring compounds may possess anti-schizophrenic potential. A variety of herbal preparations can serve as additional treatment to enhance antipsychotic effects and reduce antipsychotic-induced adverse effects. The chapter also discusses search strategies for antischizophrenic herbal agents. It addresses specific issues that may arise in the conduct of clinical studies of herbal medicine in schizophrenic patients, including: individualized treatment strategies; placebo treatment issue in schizophrenic patients; quality controls and toxicological profiles of herbal preparations and herb-drug interaction.

Key Words

herbal medicine; schizophrenia; antipsychotic drugs; L-stepholidine; tardive dyskinesia; hyperprolactinemia; quality control; herb-drug interaction; clinical trial

16.1 Introduction

Since the 1950s, with the development of various classes of synthetic antipsychotic drugs, typical and ‘atypical’ agents, the prognosis and tolerability in the treatment of schizophrenia have been considerably improved [1]. Despite this, both clinical and functional outcomes are still unsatisfactory. There are a large portion of schizophrenic population who cannot obtain satisfactory responses to the currently available antipsychotic treatments [1], particularly for the negative symptoms and cognitive disturbance [2, 3]. Furthermore, over 90% of the patients experience relapses within two years, largely due to the discontinuation caused by intolerability to antipsychotic-induced adverse effects [4, 5]. In order to overcome these shortcomings, strenuous attempts have been made to search for alternative strategies that could improve the outcomes of the current pharmacotherapy.

As a widely recognized alternative therapy, herbal medicine has attracted growing interest from the psychiatrist community worldwide. This is evidenced by the fact that numerous studies have been reported on the therapeutic effects of various herbal preparations in psychiatric disorders [6–9]. As a result, the use of herbal medicine for the treatment of psychotic disorders has also acquired increasing attention over the past decade [10, 11]. This chapter will provide an overview of potential benefits of herbal medicine in the treatment of schizophrenia, discuss search strategies for herbal medicines having antischizophrenic potentials and address specific issues that are frequently encountered in the conduct of clinical studies of herbal medicine in schizophrenic patients.

16.2 Potential benefits of herbal medicine used in the treatment of schizophrenia

Traditionally, herbal medicines could be defined as the preparations and products mainly in powder, tablet, capsule, soft-gel or liquid form prepared from single or several herbal materials or extractives based on traditional medicine doctrine, individual empirical observations or evidence-based studies [12, 13]. More broadly, naturally occurring compounds should also be included in herbal medicine [14, 15]. In fact, nearly 25% of today’s conventional drugs directly or indirectly originated from medicinal plants. Many psychoactive drugs were discovered through the investigations of herbal remedies [16–18]. Based on this broader definition, the potential benefits of herbal medicine for schizophrenia are mainly reflected in two aspects: numerous compounds isolated from herbal medicines are potential candidates that may be developed into new antischizophrenic drug. *L*-stepholidine (*l*-SPD) is such a representative compound. Various herbal preparations and products can also serve as additional therapy to improve the outcomes of antipsychotic treatments.

L-stepholidine: a natural antipsychotic compound

An apparent challenge in the treatment of schizophrenia is persistent negative symptoms and cognitive impairments [2, 3]. Numerous studies have shown that the

currently available antipsychotic agents, typical and atypical, are ineffective or less effective in treating both clusters of symptoms [19–21]. To make matters worse, long-term use of some conventional antipsychotics may themselves reduce and even damage cognitive function [22]. On the other hand, despite there being as yet no naturally occurring drugs approved for psychotic disorders, several novel compounds isolated from medicinal plants have been shown to possess antipsychotic effects in animal models and preliminary clinical studies [9, 23]. Among them, *l*-SPD is well investigated, and the most promising agent to be developed for clinical use.

L-SPD is a leading compound of tetrahydroprotoberberines (THPBs) initially isolated from the Chinese herb *Stephania sinica* Diels in 1980s [24]. Since local people often used various preparations of *Stephania* to alleviate pain and mood problems as well as inflammatory conditions, it was speculated that some compounds contained in the herb might possess central nervous effects [24]. Early studies have confirmed this speculation, revealing that several THPBs identified from the herb indeed have broad central effects, from subtypes of dopamine receptors to serotonin and adrenaline receptors [24, 25]. Among them, *l*-SPD displays the highest affinity to D₁-receptors and D₂-like receptors of all known THPBs but only low affinities to 5-hydroxytryptamine (5-HT₂) receptors and α_2 -adrenoceptors as well as rare affinity to several other transmitter receptors [24, 26]. More intriguingly, *l*-SPD serves as an agonist on D₁ receptors in the medial prefrontal cortex (mPFC), but as an antagonist on D₂ receptors in the subcortex, such as the ventral tegmental area-nucleus accumbens (VTA-NAc) pathway. A series of behavioral, electrophysiological and biochemical studies further confirm this dual action of *l*-SPD [24, 26–30].

Agents possessing such distinct pharmacological properties are believed to have specific therapeutic effects in treating the negative symptoms and the impairment of cognitive function observed in schizophrenic individuals. A large body of evidence has shown an association of the two symptom clusters with decreased D₁ receptor activity in the mPFC, while excessive dopamine activity, particularly subcortical D₂ receptor hyperactivity, is associated with the positive symptoms [24]. Indeed, recent studies of animal models have demonstrated that *l*-SPD not only reversed the apomorphine (APO)-induced disruption in the prepulse inhibition (PPI) and phencyclidine (PCP)-induced hyperlocomotion, but also significantly improved the social withdrawal and the novel objection recognition [26, 31]. Moreover, several controlled trials conducted in China have consistently demonstrated the robust effectiveness of *l*-SPD in treating both positive and negative symptoms. There were greater improvements on several symptom measures: a shorter latency to the clinical response and fewer adverse effects compared to the conventional agents such as clozapine, sulpiride and perphenazine [32–34]. The discovery of *l*-SPD has provided a good example for the development of novel antipsychotic drugs from herbal medicines.

Huperzine A: natural cognition-improving agents in schizophrenia

In addition to the negative symptoms, another cluster of lingering symptoms frequently observed in chronic schizophrenia includes cognitive impairments, mainly

manifesting as deficits in attention, motivation, problem solving, learning and memory [2, 35]. Cognitive impairment has posed a major obstacle to the patients' reintegration into society due to poor functional outcomes [35]. It is known that cognitive impairment is largely attributed to decreased central cholinergic function [36]. Enhancement of central cholinergic function by inhibiting acetylcholinesterase (AChE) is therefore believed to be an effective strategy for alleviating cognitive disturbance [37, 38]. However, most clinical trials testing AChE inhibitors, including donepezil, rivastigmine and galantamine, have failed to demonstrate a clear effect in improving cognitive function in schizophrenic subjects [37, 38]. This may reflect the limited efficacy of the currently available AChE agents.

Huperzine A (HupA) is an alkaloid initially derived from the Chinese herbal medicine *Huperia serrata* in 1980s and its chemical structure and pharmacological properties have been well identified [39, 40]. HupA is a potent reversible AChE inhibitor ($K_i = 20\text{--}40$ nM). The potency of inhibiting AChE is nearly 20–50-fold greater than for donepezil [39, 40]. HupA has been shown to have remarkable cognitive-enhancing effects in animal models. Its efficacy is comparable and even superior to donepezil and other AChE inhibitors in reducing cognitive symptoms in patients with memory disorders and Alzheimer's disease [9, 39, 40].

Based on these observations, we conducted an open-labeled trial evaluating the effectiveness of HupA as add-on therapy in schizophrenic patients who did not obtain satisfactory response to antipsychotic treatments and had apparent cognitive deterioration [41]. Nineteen hospitalized patients with treatment-resistant schizophrenia received 0.3 mg/day HupA additional treatment with the existing neuroleptic regimen for 12 weeks. The clinical outcomes were measured using the Scale for Assessment of Negative Symptoms (SANS) and the Mini-Mental State Examination (MMSE). Seventeen patients completed the study. We found that the addition of HupA resulted in a baseline-to-endpoint 32% reduction in mean SANS score and 14% increase in mean MMSE score. Furthermore, 47% of subjects (8/17) had at least 30% improvement on SANS score and 76% (13/17) displayed at least a 3-point increase in MMSE scores. These data suggest that HupA may be an effective AChE inhibitor in reducing cognitive impairments in schizophrenic patients. A large-scale controlled trial is needed to further confirm the beneficial effects of HupA in schizophrenic population.

The effectiveness of herbal preparations in treating psychotic symptoms

Over the past two decades, a considerable number of case and controlled studies evaluating the efficacy and safety of various herbal preparations in patients with psychotic disorders have been reported [10, 11]. Most of these studies, which were published in Chinese journals, were aimed at determining whether herbal preparations as adjuvant added to antipsychotic drugs could augment the therapeutic efficacy and reduce adverse side effects associated with antipsychotic treatment (discussed below). Although the majority of the studies may lack sufficient rigorously in design, many relatively high-quality controlled trials have demonstrated the

antischizophrenic potentials of some herbal medicine formulae as additional therapy (Table 16.1) [42–54].

The most salient conclusion is that, compared to antipsychotic treatment alone, the concomitant use of herbal preparations and conventional agents yields significantly greater improvements on the global, residual and specific cluster symptoms, including the negative symptoms, cognitive impairments, aggression and mood symptoms. Moreover, subjects in the combination treatments had shorter latencies to clinical response, much lower antipsychotic doses used and a lower incidence of discontinuation. These beneficial effects are further confirmed in a recent Cochrane systematic review with meta-analysis [10, 11].

It could therefore be concluded that the combination treatment with herbal medicines is an effective strategy for enhancing the therapeutic response to antipsychotic treatment. In addition, it may be pointed out that most herbal preparations used were polyherbal mixtures. In general, those are formulated based upon traditional medicine doctrine or individuals' empiricism, and often modified upon individual patient's clinical manifestations and at different stages of the illness. The individualized treatment strategy is an apparent advantage seen in many forms of traditional medicine therapy [55].

Compared to polyherbal preparations, there are only a few single herbal preparations such as Ginkgo biloba, which have been tested in schizophrenic subjects. While it is well documented that the standardized Ginkgo biloba extract EGb 761 is an effective herbal product in improving cognitive impairments and preventing cognitive decline in subjects with Alzheimer's disease and other cognitive problems [56], several controlled trials have also shown that EGb 761 as adjuvant added to the on-going antipsychotics (haloperidol, clozapine and olanzapine) significantly enhanced the therapeutic response on overall psychopathology, positive or negative symptoms in subjects with treatment-resistant schizophrenia (Table 16.1) [42, 45, 51, 54]. Patients treated with EGb 761 in combination with antipsychotics also displayed a lower incidence of adverse events, including extrapyramidal syndromes. The beneficial effects of EGb 761 observed were found to be associated with its antioxidant actions by inhibiting superoxide dismutase (SOD) activity [42, 57]. Based on these observations, one may consider Ginkgo biloba as an alternative agent to be employed for enhancing antipsychotic effects.

The benefits of herbal preparations in treating antipsychotic-induced adverse effects

Another challenge in the pharmacotherapy of psychotic disorders is to deal with a variety of adverse side effects. They are a major cause of poor compliance and discontinuation, especially in long-term maintenance treatment [58]. In addition to the potentials for enhancing antipsychotic effects, many herbal preparations have also been found to have the potential of reducing adverse effects frequently observed in antipsychotic treatment (Table 16.2) [59–82]. The adverse effects for which herbal medicines have been reported to be beneficial include: body weight gain, constipation, diarrhea, digestive dysfunction, enuresis, hyperprolactinemia, hypersalivation, leukopenia and tardive dyskinesia (TD).

Table 16.1 Herbal preparations as additional treatment with antipsychotic drugs demonstrated to be effective in treating schizophrenic patients in randomized controlled trials^a.

Reference	Schizophrenic subjects	Herbal preparations	Antipsychotic drugs alone	Duration and measures ^c	Outcomes ^d
[42]	Chronic	EGb of ginkgo biloba (n = 15)	Olanzapine (n = 14)	8 wk PANSS	The positive symptoms, but not the negative symptoms, were found to be significantly improved at endpoint.
[43]	Chronic	Xing-Shen-He-Ji (n = 30)	Several antipsychotics (n = 30)	3 mo SANS	SANS and several subscales were improved significantly greater in herbal additional therapy than antipsychotic alone.
[44] ^b	Chronic	A empirical herbal formula (n = 30)	Clozapine (n = 30)	16 wk BPRS, SANS, TESS	Significant greater improvement on all measures was present at week 8 through endpoint; clinical response rate was higher than clozapine alone; fewer incidence of adverse events.
[45]	Treatment-resistant	EGb of ginkgo biloba (n = 20)	Clozapine (n = 22)	12 wk BPRS, SANS, SAPS	The negative symptoms were improved significantly.
[46]	Acute and chronic	Meng-Shi-Di-Tan-Tang (n = 50)	Several antipsychotics (n = 46)	6 wk BPRS, PANSS, TESS	Patients in herbal additional therapy had significant greater improvement on BPRS and PANSS from week 2 through endpoint; clinical response rate was significantly higher; fewer adverse effects.
[47]	Residual symptoms	Da-Huang-San-Leng capsule (n = 46)	Several antipsychotics (n = 44)	16 wk BPRS, SANS, TESS	Total BPRS and SANS and several subscales were improved significantly greater at week 6 through endpoint, but the incidences of adverse events were indifferent.
[48] ^b	Cognitive impairment	A tonic herbal formula (n = 30)	Chlorpromazine (n = 30)	PANSS, several cognitive scales 8 wk	Memory, attention, task performance and the negative symptoms were improved significantly greater in herbal additional treatment.

[49]	First-episode	A modifiable herbal formula (n = 60)	Risperidone (n = 64)	8 wk PANSS	Greater improvements on total PANSS score and the positive symptoms were observed in the initial phase, but not the late phase of treatment. Herbal additional treatment also resulted in fewer adverse effects and lower risperidone dose used.
[50]	Chronic	Modified Dao-Tan Decoction (n = 34)	Risperidone (n = 31)	8 wk PANSS, TESS	Significant greater improvement on general psychopathology and the negative symptoms. Milder adverse effects and lower risperidone dose used.
[51] ^b	Chronic	Shu-Xue-Ning (ginkgo biloba extract) (n = 83)	Clozapine, Sulpitride, and/or haloperidol (n = 66)	12 wk SANS, BPRS, TESS	Greater improvement on SANS and BPRS and lower incidences of adverse events were observed at endpoint.
[52]	Chronic	Lian-Zi-Qing-Xin-Tang (n = 35)	Clozapine (n = 35)	6 wk PANSS, CGI, TESS	No significant differences in total PANSS and subscales, but social functions were improved significantly. Lower incidences of adverse events.
[53]	First-episode	Ding-Kuang-Zhu-Yu-Tang (n = 40)	Clozapine (n = 40)	8 wk PANSS, TESS	The negative symptoms were improved significantly, but clinical response rates were indifferent. Fewer adverse effects.
[54] ^b	Treatment-resistant	Ginkgo biloba extract (n = 56)	Haloperidol (n = 53)	12 wk BPRS, SANS, SAPS, TESS	Patients in the add-on therapy had greater improvement on SANS and SAPS; higher clinical response and fewer toxic effects on neurobehavior.

^aAll trials listed were described as randomized controlled design and herbal preparations were used as additional therapy with antipsychotics compared to antipsychotics alone.

^bDouble-blinding component was included in the design.

^cBPRS, Brief Psychiatry Rating Scale; CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; TESS, Treatment Emergent Symptom Scale.

^dAll better outcomes described are indicated for the combination treatment.

Table 16.2 Herbal preparations demonstrated to have the benefits in treating antipsychotic-induced adverse effects in clinical studies.

Adverse effects	Name of herbal preparations
Amenorrhea	Modifiable herbal formulations [59] Shakuyaku-kanzo-to [60]
Body weight gain	Jia-Wei-Ling-Gui-Shu-Gan-Tang [61] Modifiable herbal formulations [62]
Constipation	Qing-Shen-Yin [63] Qing-Re-Tang [64]
Diarrhea	Huang-Yuan-San [65]
Digestive dysfunction	Wen-Dan-Tang [66] An-Shen-Jian-Pi Liquid [67, 68]
Enuresis	Jia-Wei-Suo-Quan-Wan [69] Liu-Wei-Di-Huang-Wan [70]
Hyperprolactinemia	Peony-Glycyrrhiza Decoction (PGD) [71] Shakuyaku-kanzo-to [72, 73]
Hypersalivation	Modifiable herbal formulations [74] Ping-Wei-San [75] Lian-Zi-Qing-Xin-Tang [76] Huang-Yuan-San [77] Qing-Re-Tang [64]
Leukopenia	Zuo-Gui-Yin [78] Jia-Wei-Dang-Gui-Bu-Xue-Tang [79]
Tardive dyskinesia	Kamishoyosan [80] Yin-Gan-San [81] Radix Puerariae (Ge-Gen) [82]

TD is a severe and often irreversible motor condition caused by antipsychotic medications. While the efficacy of conventional therapy is less effective, two recent studies have shown the effectiveness of the herbal preparations called Kami-Shoyo-San and Yi-Gan-San (YGS) in schizophrenic patients with TD conditions [80, 81]. In the Kami-Shoyo-San trial [80], following 16 weeks of the adjunctive treatment in 49 subjects, an 18% (1.07-point) baseline-to-endpoint reduction in the total mean score on the Abnormal Involuntary Movement Scale (AIMS) was observed. Moreover, the effects were particularly apparent in the jaw, the tongue and the upper extremity. In the YGS trial [81], schizophrenic patients (n = 22) who had neuroleptic-induced TD received 7.5 g/day of YGS for 12 weeks. A significant reduction of AIMS total scores was found at endpoint, with a 56% decrease from baseline.

Hyperprolactinemia is also a common condition occurring in antipsychotic therapy, sometimes causing disrupted menstrual cycles, galactorrhea and sexual impairments. Dopamine agonists, such as bromocriptine (BMT), may be recommended if high prolactin (PRL) could not be improved following the reduction of antipsychotic doses [83]. However, the addition of dopamine agonists often aggravates psychosis and abnormal involuntary movements, which may be a greater risk than hyperprolactinemia itself [84].

Empirical evidence suggests that some herbal medicines could suppress high PRL. We recently completed a randomized crossover comparison of the herbal

medicine called Peony-Glycyrrhiza Decoction (PGD) and BMT against schizophrenic patients having hyperprolactinemia induced by risperidone [71]. Twenty ($n = 20$) schizophrenic females who were under risperidone maintenance treatment, diagnosed with hyperprolactinemia (serum PRL levels $>50 \mu\text{g/l}$) and experiencing oligomenorrhea or amenorrhea, were randomized to additional treatment. This consisted of PGD (45 g/day) followed by BMT (5 mg/day) or BMT followed by PGD at the same doses for 4 weeks each, with a 4-week washout period between the two treatment sessions. The severity of psychotic symptoms, adverse events, serum PRL, estradiol, testosterone and progesterone levels were examined at baseline and endpoint. PGD treatment produced a significant baseline-endpoint decrease in serum PRL levels, without exacerbating psychosis or changing other hormones (estradiol, testosterone and progesterone). The decreases of PRL in amplitudes were similar to those of BMT (24% versus 21–28%). Moreover, there were a significantly greater proportion of patients during PGD treatment than BMT showing improvements on adverse effects associated with hyperprolactinemia (56% versus 17%). These data indicate that PGD possesses comparable effects in suppressing high PRL and reducing the incidence of adverse events associated with hyperprolactinemia.

16.3 Possible psychopharmacological mechanisms of herbal actions

Apart from a limited number of naturally occurring compounds and single herbal preparations for which psychopharmacological properties have been relatively well elucidated, the actions of most herbal agents having antischizophrenic potentials remain unknown. This is largely because most herbal preparations are complex mixtures of chemical components with diverse biological and pharmacological actions. Despite this, behavioral and pharmacological studies have found that many herbal agents may exert their psychotropic effects through some components of the mechanisms known to be responsible for conventional psychotherapeutic actions, such as modulating D_1 and D_2 receptors, accelerating metabolism of dopamine (DA), and antagonizing excitatory receptors [9]. On the other hand, a considerable number of herbal extracts and constituents possess antioxidant and neuroprotective actions against neuronal cell death induced by exposure to excessive free radicals and neurotoxins [9]. It is well known that antioxidant and neuroprotective agents have the therapeutic potential in various psychiatric disorders, including psychotic disorders [85]. This may, to some extent, explain the beneficial effects of herbal medicines observed in treating psychotic symptoms and adverse side effects.

Another possible mechanism involving in herbal therapeutic actions is synergism, particularly for Chinese herbal medicine formulae. The doctrine of traditional Chinese medicine (TCM) believes that the therapeutic effects of formulated herbal preparations are superior to individual herbal preparations, because herb-herb interactions could yield synergistic effects and reduce undesirable side effects [55]. However, this synergistic mechanism remains to be further clarified with other scientific approaches.

16.4 Search strategies for herbal agents having antischizophrenic potentials

A key issue in the development of herbal medicine therapy for schizophrenia is to find the potential herbal agents. In fact, the introduction of most herbal medicines into today's psychiatry practice was initially based on the records of ancient pharmacopoeias, indigenous remedies, family-kept 'secret' formulae and even anecdotes [86]. Ancient pharmacopoeias in different regions of the world, including TCM, Indian Ayurvedic medicine, Japanese Kampo medicine, Korean herbal medicine and European and African medicine, have recorded numerous individual herbs and formulae claimed to have psychotropic potentials. These offer a vast repertory of useful information for modern psychiatric pharmaceuticals, including the development of effective herbal therapy for schizophrenia.

To characterize psychotropic effects, a broad range of neurobehavioral approaches have been applied to explore the properties of herbal agents purporting to have the psychotropic potential over the past decade. A large number of naturally occurring compounds, herbal constituents, formulae and preparations have been demonstrated to have positive effects in reducing psychiatric symptoms, including psychotic-like behavior [9].

Rodent stereotypic responses induced by dopamine stimulators, such as amphetamine (APT) and APO, represents an animal model of positive schizophrenic symptoms [87]. Herbal preparations that suppress such stereotypic responses may be suggested to have antischizophrenic potential. The evaluation of central depressant effects is another behavioral paradigm commonly used in the screening of antischizophrenic herbal agents. These extend barbiturate-induced sleeping time (hypnotic action), inhibit hyperlocomotor activity, suppress exploratory behavior in the maze and head dip test (HDT) and reduce conditioned avoidance response (CAR), all as observed in conventional antipsychotic drugs [9]. In addition, as mentioned earlier, we characterized antipsychotic effects of *l*-SPD by using PPI [26]. Since PPI could effectively mimic sensorimotor gating impairments observed in schizophrenia, it has been widely used for the screening of antipsychotic drugs [88].

In addition to the aforementioned clinical studies of herbal medicines in schizophrenic subjects, a large body of clinical study data has also accumulated for herbal medicine treatment of patients with other neuropsychiatric disorders such as depression, anxiety [7], Alzheimer's disease [89, 90] and Parkinson's disease [91–93]. In addition, studies have been made of conditions such as adverse side effects observed in antipsychotic therapy, including obesity [94] and hyperprolactinemia [95]. These data may be an alternative resource for the search of antischizophrenic herbal agents, particularly for specific symptom clusters and antipsychotic-induced adverse effects.

With the extensive utilization of phytochemical and ethnopharmacological methodologies in the research of herbal medicines, an increasing number of naturally occurring compounds and constituents have been isolated and identified. As a result, several phytochemical database systems have been established: the Traditional Chinese Medicine Information Database (TCM-ID) (<http://tcm.cz3.nus.edu.sg/group/>

tcm-id/tcmid.asp) [96], Chinese Herbal Constituents Database (CHCD) and Bioactive Plant Compounds Database (BPCD) [97, 98]. TCM-ID currently contains information for 1588 prescriptions, 1313 herbs, 5669 herbal ingredients and the 3D structure of 3725 herbal ingredients. The CHCD database contains 8411 compounds from 240 Chinese herbs and BPCD holds 2597 compounds, with chemical structures and known target specificities. These databases provide useful search tools to seek potential antischizophrenic and other psychopharmacological agents.

Like synthetic compounds, the target herbal agents also could be screened using high-throughput drug screen systems. This work has been done for herbal compounds at several enzymes [99, 100], neuropeptide FF2 receptor [101] and anticancer [102], but not yet for psychopharmacological targets.

Taken together, multiple information resources are now available for the search for novel antischizophrenic herbal agents, from ancient pharmacopoeias to the phytochemical databases (Figure 16.1). It should be noted that, unlike synthetic compounds, most herbal preparations have been used by local people for well-being and therapeutic purposes for centuries. Their therapeutic properties, clinical indications and toxicological profiles could be found in ancient literatures. Thus, a comprehensive search in both sets of ancient and modern information might be helpful in further developing exploratory and confirmatory studies.

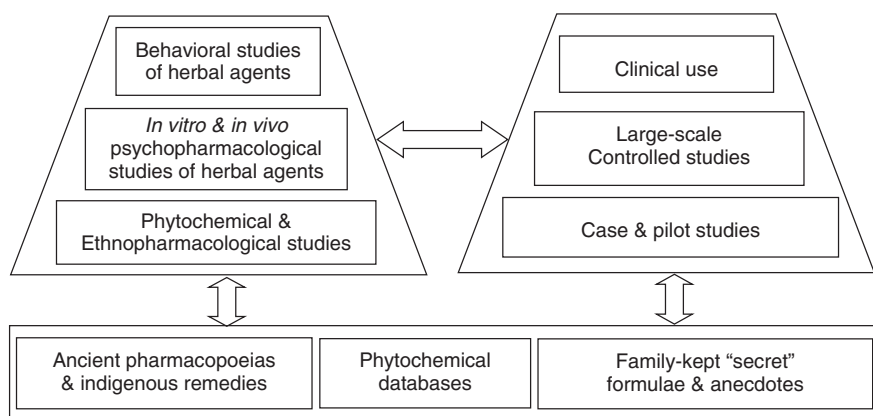


Figure 16.1 A schematic chart showing search strategies of antischizophrenic herbal agents.

16.5 Specific issues in the conduct of herbal medicine trials in schizophrenia

Individualized treatment strategy embodied in randomized controlled trial and other clinical study designs

As mentioned earlier, individualized treatment strategy is an apparent therapeutic advantage in many forms of herbal medicine therapy, such as traditional Chinese

and other Asian herbal medicines, and believed to produce better treatment outcomes than the non-individualized. Indeed, a randomized controlled study has shown that individualized herbal medicine formulation treatment was superior to a standard herbal medicine formulation in maintaining the achieved improvement in patients with irritable bowel syndrome (IBS) [103].

The design of herbal medicine trials, particularly for herbal medicine formulations, should therefore embody this advantage by tailoring herbal intervention regimes to meet the individual clinical manifestations and modifications at different stages of the illness. On the other hand, although randomized controlled trial (RCT) design is regarded as a 'gold standard' and has also become a prior option in clinical studies of herbal therapy [104, 105], it could be difficult for traditional RCTs to individualize treatment regimes to meet every subject's clinical presentations [106]. Moreover, most traditional RCTs require homogeneous samples of subjects, predetermined dose schedules and standard treatment procedures [107]. This may mean that traditional RCTs are capable of detecting overall group response to given drugs, but seem less sensitive in detecting individual subjects' responses.

To resolve this issue, the abovementioned IBS trial included an additional group of patients assigned to receive individualized herbal formulation treatment and was compared to placebo and a standard herbal formulation under double-blind conditions [103]. This design format has provided a good example for the inclusion of individualized herbal intervention in RCTs and deserves to be further investigated.

Considering the time and effort costs of traditional RCTs, an alternative design called a single case randomized controlled trial (SCRCT), also referred to as N-of-1 trial, RCT in an individual patient, or intrasubject-replication design, has been recommended for clinical studies of herbal therapy [108–110]. N-of-1 trials are within-patient randomized, double-blind and multiple crossover comparisons of two treatment regimens (one of which may be placebo), in which patients act as their own controls [111]. The N-of-1 trial can offer the highest level of evidence for the individual on the effectiveness of long-term symptomatic treatment of stable chronic conditions [111]. In fact, such designs have been extensively introduced into the research of psychiatric conditions with heterogeneous and variable characteristics, such as bipolar disorder [106]. Compared to traditional RCTs, SCRCTs could significantly increase the power for comparing and confirming treatment effects in individual subjects, and then reduce the duration and expenses of the study at large. Therefore, it may be particularly suitable for the investigation of long-term herbal medicine therapy in individual subjects with chronic conditions, such as chronic schizophrenia and exploratory trials of novel herbal preparations.

Nonetheless, it should be noticed that carryover effects may occur in crossover designs when an herbal preparation and a conventional drug are used alternately. Pharmacokinetically, the setup of a sufficient interval between crossover treatment sessions (washout period) roughly equivalent to five or more elimination half-lives could diminish carryover effects to maximum extent, although pharmacokinetic profiles of most herbal preparations currently used in clinical practice are unclear [112]. For example, in our recent crossover comparative study of PGD versus BMT on risperidone-induced hyperprolactinemia, the washout period was set up for as long

as 4 weeks [71]. On the other hand, based on the fact that many herbal agents have been found to have pharmacokinetic interactions with conventional agents, herb-drug interactions should be considered when herbal agents are used concomitantly with conventional drugs (see below).

Quality controls and toxicological profiles of herbal preparations

Like other herbal products, most herbal agents which have been tested in schizophrenic patients lack consistent quality controls [10, 11]. This is particularly reflected in polyherbal preparations, in which the quantity of herbs used, the proportion of individual herbs and the preparation procedures and forms may vary from one trial to another. For example, Free and Easy Wanderer Plus (FEWP, Jia-Wei-Xiao-Yao-San or Jai-Way-Shiau-Yau-San in Chinese or Kami-Shoyo-San in Japanese) has been widely used for the treatment of many psychiatric conditions, including antipsychotic-induced TD and tremor in schizophrenic subjects, depression, postmenstrual syndrome and panic disorders [80, 113–118].

However, as shown in Table 16.3, the proportions of each herb, preparation forms and doses used varied greatly among trials. This has made it difficult to compare the therapeutic efficacy and further identify effective individual herbs and constituents across the studies. In addition, the contents of pharmaceutically active constituents contained in herbal preparations may also vary with different herbal parts used, habitats, harvest seasons and extraction methods.

The determination of known bioactive constituents is believed to be an effective approach to establishing quality controls. A commonly used technique at present is chromatographic fingerprint analysis [119]. For instance, in our previous studies of FEWP for bipolar disorders and PGD for antipsychotic-induced hyperprolactinemia, several known ingredient compounds were measured using high-performance liquid chromatography (HPLC). The fingerprinting profiles were produced as references for future studies [71, 118]. In addition, there are many comprehensive electronic sources available for separation, extraction and measurement of components contained in natural products, such as the Cumulative CAMAG Bibliography Service (CCBS) and ACD/Chromatography Applications Database [119].

It should be pointed out that the quality controls must include toxicological profiles of herbal products, particularly the detection of toxic components such as heavy metals and adulterants. This is because there have been extensive reports about heavy metal contaminations of herbal products and adulterants with various conventional drugs, such as the psychoactive drugs diazepam and phenytoin, as well as poisoned cases related to the use of herbal preparations [120, 121].

Some herbal agents may have adverse effects and even neurobehavioral toxicities similar to those observed with conventional psychoactive drugs [120, 121]. For example, hypericum perforatum, an antidepressant herbal agent, can induce a manic episode [122]. Another herbal agent called valerian – often used as anti-anxiety agent – has been found to have broad adverse effects including tremor, headaches and abdominal pain [123]. Moreover, like many synthetic drugs undergoing metabolic activation to form reactive metabolites which are often associated with drug toxicity, some herbal components may also be converted to toxic or even

Table 16.3 Herbal components, proportion of each herb, form and dosage of the herbal preparation called Free and Easy Wanderer Plus (FEWP) in trials.

	[80]	[113]	[114, 115] ^a	[116]	[117, 118]
Herbal components (g, %) ^b					
Glycyrrhiza radix	0.67 (8.7)	1.5 (6.7)	1.5 (6.7)	2 (6.1)	1.5 (4.2)
Angelica radix	1 (13.0)	3 (13.3)	3 (13.3)	4 (12.1)	3.5 (9.7)
Gardenia fructus	0.67 (8.7)	2 (8.9)	2 (8.9)	2.5 (7.6)	3.5 (9.7)
Bupleurum radix	1 (13.0)	3 (13.3)	3 (13.3)	4 (12.1)	4.5 (12.5)
Zingiber officinale	0.33 (4.3)	1 (6.7)	1 (6.7)	4 (12.1)	4 (11.2)
Cortex moutan	0.67 (8.7)	2 (8.9)	2 (8.9)	2.5 (7.6)	3.5 (9.7)
Atractylodis rhizoma	1 (13.0)	3 (13.3)	3 (13.3)	4 (12.1)	3 (8.3)
Hoelen	1 (13.0)	3 (13.3)	3 (13.3)	4 (12.1)	2.5 (6.9)
Paeonia radix	1 (13.0)	3 (13.3)	3 (13.3)	4 (12.1)	3.5 (9.7)
Menthae herba	0.33 (4.3)	1 (6.7)	1 (6.7)	2 (6.1)	2 (5.6)
Scutellaria baicalensis	–	–	–	–	4.5 (12.5)
Total	7.67 (100)	22.5 (100)	22.5 (100)	33 (100)	36 (100)
Dosage ^c (g/d)	15	5	7.5	12	36
Form	NI ^d	Granulated	Powder	Powder	Capsules
Conditions treated	Antipsychotic-induced tardive dyskinesia	Climacteric depression	Antipsychotic-induced parkinsonism; premenstrual dysphoric disorder	Climacteric symptoms	Major depression and bipolar disorders
Country/regions	South Korea	Japan	Japan	Taiwan	China

^aFEWP preparations used are also registered as TJ-24 in Japan.
^bThe weight and proportion are indicated for herbal extractives in [80], but for crude herbal materials in [113–118].
^cDosage is indicated for crude weight in [117, 118] and extractives in [80, 113–116].
^dNI: No indication.

mutagenetic and carcinogenic metabolites [112]. Our recent preliminary study has found that a considerable number of schizophrenic patients were exposed concomitantly to both herbal medicines and antipsychotic drugs (see below). This may increase the risks of herbal toxicity, including herb-drug interactions. Additional cautions must be paid to toxicological profiles when clinical studies of herbal preparations are conducted in patients with schizophrenia.

Placebo issues in clinical trials of herbal therapy for severe psychiatric conditions

Additional caution may be required when placebo is introduced as a controlled treatment into blind, controlled studies of herbal intervention. Unlike synthetic drugs,

most herbal preparations possess special odors and colors so there may be difficulties in preparing placebos in physical appearance and smell completely indistinguishable from active herbal preparations in decoction, liquid and tablet forms. The most frequently used form at present is the encapsulation of placebo inert materials and herbal extractives into non-transparent capsules. Technically, the encapsulation may be an effective form to minimize the interference with odor and color at a great degree and maintain blinding conditions [124]. Nonetheless, such placebo preparations appear to be more valid in short-term trials of hospitalized patients than long-term trials of outpatients in maintaining blinding conditions, as drug dispensers could ensure hospitalized patients take medications without the chance of patients breaking drug codes.

However, in view of potential harmful consequences from untreated conditions, placebo-controlled treatments may be not allowed in certain ethical circumstances, particularly for monotherapy in patients with severe psychiatric conditions such as severe depression, bipolar disorders and schizophrenia, although many countries still require placebo-controlled trials for investigational new drugs (INDs) in these conditions. Ethical consideration has been reflected in most previous controlled studies of herbal intervention in schizophrenic patients, in which placebo or herbal preparations were generally used as additional and adjunctive therapy with antipsychotic drugs [11]. Thus, for the sake of patients' safety, active agents rather than placebo treatments may be included as comparators in comparative studies aimed to determine the therapeutic efficacy and safety of herbal medicine monotherapy in patients with schizophrenia.

The concomitant use of herbal preparations and antipsychotics and resultant interactions

Currently, we are conducting an epidemiological study determining the prevalence of the concomitant use of TCM and antipsychotic drugs in a population with schizophrenia (unpublished data). An interim analysis has shown that there were nearly 36% patients (106/297) who were concomitantly taking Chinese medicines for at least one month while under antipsychotic medication. In addition to various herbal products, from single to multiple herbal preparations, for example ginkgo and Chinese box twig (*Ramulus Buxi Sinicae*) to herbal formulations, many animal and mineral preparations were also used with psychiatry drugs.

The five most commonly used drugs with TCM were risperidone (50.0%), clozapine (23.6%), quetiapine (17.9%), haloperidol (15.1%) and olanzapine (13.2%). Although a major reason of TCM use in most patients was to reduce psychosis and drug-induced adverse effects, over 95% of patients did not realize the potential risks of concomitant use. While there were 61.3% patients (65/106) reporting that their psychotic symptoms and experience in adverse events were improved during the concomitant treatment, nearly 1/3 patients (35/106) claimed no differences compared to antipsychotic treatment alone and 5.7% patients (6/106) even reported the worsening of psychosis and adverse effects.

These findings are consistent with a previous study completed in the United States, showing that over 65% of patients with severe depression and anxiety sought alternative therapy, including herbal products, while receiving conventional treatments [125]. Likewise, as mentioned earlier, most herbal preparations included in schizophrenic studies were also concomitantly used as adjuvant added to antipsychotic drugs [11]. Thus, the combination use of herbal and conventional agents is a common phenomenon in populations with psychiatric illnesses. Such concomitant use could yield additive or confounding effects on the treatment outcomes in either positive or negative ways.

Regardless, as shown in Table 16.4 [126–133], there are currently only a few antipsychotic drugs which have been reported to interact with herbal preparations. Other classes of drugs were relatively well investigated, including: anticoagulants (warfarin, aspirin and phenprocoumon); sedatives and antidepressants (midazolam, alprazolam and amitriptyline); oral contraceptives; anti-HIV agents (indinavir, ritonavir and saquinavir); cardiovascular drugs (digoxin); immunosuppressants (cyclosporine and tacrolimus); and anticancer agents (imatinib and irinotecan) [134, 135]. Our study of FEWP in bipolar patients has found that, following 26 weeks of treatment, patients receiving a combination of the anticonvulsant mood stabilizer carbamazepine (CBZ) and FEWP displayed a significantly lower mean serum level of CBZ ($2.4 \pm 2.9 \mu\text{g/ml}$) compared to CBZ treatment alone ($5.6 \pm 5.8 \mu\text{g/ml}$), suggesting that the concomitant use of FEWP could lower blood CBZ concentrations [117]. Whether such pharmacokinetic interactions also occur with antipsychotic drugs is entirely unknown. It is known that a principal mechanism involving in herb-drug interactions is associated with cytochrome P450s

Table 16.4 Herb-antipsychotic interactions.

Antipsychotic drugs	Herbal preparations	Results of interactions	Subjects	Reference
Clozapine	Green tea	Reduce absorption of clozapine	Rats	[126]
Phenelzine	Ginseng	Headache, tremor, manic episode	Schizophrenic patients	[127, 128]
Fluphenazine	Betel nut	Tremor, stiffness, akathisia	Schizophrenic patients	[129]
Haloperidol	Valeriana officinalis	Increasing hepatic lipid peroxidation levels and dichlorofluorescein (DCFH); inhibiting hepatic delta-ALA-D activity; reducing locomotor activity	Rats	[130, 131]
Haloperidol	NR-ANX-C (a polyherbal formulation)	Reduce haloperidol-induced catalepsy	Mice	[132]
Haloperidol	Withania somnifera	Reduce haloperidol-induced catalepsy	Mice	[133]

(CYPs) [112, 135]. Since many antipsychotic drugs are substrates for CYPs [136], it might be speculated that pharmacokinetic interactions may also exist in the concomitant use of herbal and antipsychotic agents. On the other hand, whether pharmacodynamic interactions, for example synergistic or antagonistic interaction on the same drug target, are involved in herb-antipsychotic interactions also remains to be investigated further.

Through pharmacokinetical and pharmacodynamical mechanisms, herb-antipsychotic interactions may yield either beneficial or adverse and even toxic effects by altering drug metabolism, clearance, response, reducing or inducing toxicity, depending upon the drugs, herbs and patients [112, 135]. Therefore, in addition to evaluating the beneficial effects as done in most previous studies of herbal medicines in schizophrenia, the identification of potential herb-antipsychotic interactions (particularly adverse and toxic profiles) should be included in future studies.

16.6 Conclusions

A large number of herbal preparations have been demonstrated to have the potential to enhance antipsychotic efficacy and reduce antipsychotic-induced adverse effects. Herbal preparations may provide additional options in the treatment of schizophrenia. In addition, numerous naturally occurring compounds may be potential candidates for the development of new antipsychotic drugs. However, psychopharmacological mechanisms of most herbal agents remain to be elucidated. Many information resources are now available for the search of the antischizophrenic herbal agents, from ancient pharmacopoeias to phytochemical databases. Individualized treatment strategy represents an apparent therapeutic advantage in the use of herbal medicine formulations for chronic schizophrenia. SCRCT or N-of-1 trial is an alternative design to the randomized, controlled format.

We suggest that active agents rather than placebo treatment be included in comparative studies aimed to evaluate the efficacy and safety of herbal agent monotherapy in schizophrenic patients. Additional cautions may need to be paid to the quality controls and toxicological profiles of herbal preparations for schizophrenic patients.

The concomitant use of herbal and antipsychotic agents is a common phenomenon in schizophrenic patients, but little is known about the interactions in either pharmacokinetic or pharmacodynamic mechanism. The identification of potential herb-antipsychotic interactions deserves to be further investigated in future studies.

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17

Adverse Effects of Antipsychotics

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Abstract

Antipsychotics have now been used for over 50 years. They have benefited patients that would otherwise have been disabled by their symptoms and it has improved their quality of life. However, antipsychotics are no different from other drugs as they can cause minor but also serious adverse events leading to poor adherence, hospitalization and even death. Therefore, the medication's adverse effect profile is often an important deciding factor when choosing an antipsychotic. Sufficient data have been gathered over the past decade on the pharmacological profile and clinical adverse events to recognize that atypical antipsychotics (AAs) differ among themselves and they represent, as do conventional antipsychotics (CAs), a heterogeneous group of drugs. This chapter summarizes more recent data on antipsychotics adverse events. A number of recommendations are meant to reduce adverse events, decrease morbidity and mortality and increase medication adherence.

Key Words

atypical antipsychotics; conventional antipsychotics; adverse events; morbidity; mortality

17.1 Introduction

Most antipsychotics have similar efficacy for treating psychotic symptoms. The medication's adverse effect profile is therefore often an important deciding factor when

choosing an antipsychotic. For this reason, the field of adverse events has become a playground for pharmaceutical companies to compare in a favorable manner their product against other drugs. This stake may explain the perception that there are as many, if not more, publications on adverse events compared to therapeutic efficacy. Nevertheless, some adverse events are predictive for poor adherence to medication, especially if they perpetuate stigmatization (i.e. increase weight), create distress (i.e. akathisia) or cause medical problems (i.e. diabetes). Those complications may indirectly increase the risk of relapse, necessitating additional clinical interventions and hospitalizations. The rate of medication discontinuation due to adverse events has been estimated at 18% in chronic schizophrenic patients over 18 months [1] compared to 24% in first-episode psychosis over one year [2].

Major drug-related adverse events account for 2–12% of hospitalization. Among these patients, the prevalence of fatal adverse events is estimated at around 3–5% [3–5]. Antipsychotics are no different from other drugs as they can cause minor but also serious adverse events. This chapter summarizes more recent data on antipsychotics adverse events which, on one hand, contribute to medication poor adherence but also increase morbidity and mortality in an otherwise medically higher risk population.

17.2 Pharmacology of adverse events

All antipsychotics have binding affinity to dopamine D_2 receptors. However, atypical antipsychotics (AAs) differ from conventional antipsychotics (CAs) by their higher affinity to serotonin 5-hydroxytryptamine ($5-HT_2$) compared to dopamine D_2 receptors [6] and some AAs have faster dissociation rates from D_2 receptors [7]. CAs and AAs bind to multiple receptors and the adverse event profile will be dose dependent and vary in concordance with the medication affinity to these receptors [8, 9]. A summary of adverse events associated with antagonism of various receptors and binding affinity of antipsychotics for specific receptors are found in Tables 17.1 and 17.2, respectively. Careful examination of Table 17.2 reveals that both CAs and AAs form heterogeneous groups when comparing binding affinities to various receptors. Haloperidol and chlorpromazine are both CAs but chlorpromazine causes more sedation and weight gain because of its antihistaminic properties. At therapeutic doses, perphenazine and loxapine induce less extrapyramidal symptoms (EPSs) than haloperidol because they have some antiserotonin $5-HT_2$ activity, although less than AAs. The affinity of risperidone to D_2 receptors is greater than quetiapine and will induce more EPS and hyperprolactinemia. Therefore, one should be aware of meta-analyses which compare adverse events by pooling CAs and AAs, as this approach may minimize an adverse event associated with a specific antipsychotic; for example, a meta-analysis lumping data from various sources was utilized to compare the risk for diabetes with AAs against CAs [10]. Obviously, this approach minimizes the increased risk of diabetes associated with clozapine and olanzapine compared to other AAs and CAs.

Table 17.1 Adverse events associated with antagonism of various receptors.

Receptor	Associated adverse events
Dopamine D ₂	Extrapyramidal symptoms, hyperprolactinemia, sexual dysfunction
Serotonine 5-HT _{1C}	Weight gain
Serotonine 5-HT _{2A}	Hypotension
Serotonine 5-HT _{2c}	Weight gain, hyperglycemia
Noradrenergic α_1	Hypotension
Noradrenergic α_2	Priapism
Histamine H ₁	Sedation, concentration, weight gain, hypotension, hyperglycemia
Acetylcholine M ₁	Memory deficits, constipation, urinary retention, blurred vision, xerostomia

Table 17.2 Receptor binding affinity of antipsychotics to specific receptors.

	D2	5-HT _{2A}	5-HT _{2C}	α -1	H ₁	M ₁
Aripipazole	5+	4+	2+	2+	2+	–
Chlorpromazine	3+	4+	+	4+	3+	3+
Clozapine	+	4+	2+	4+	4+	4+
Haloperidol	5+	2+	–	3+	+	–
Loxapine	4+	3+	+	2+	3+	2+
Olanzapine	3+	4+	2+	3+	4+	4+
Perphenazine	4+	4+	–	3+	3+	+
Quetiapine	2+	2+	–	3+	3+	2+
Risperidone	5+	5+	2+	4+	2+	+
Ziprasidone	4+	5+	+	2+	2+	+

Behavioral

Extrapyramidal symptoms

Basal ganglia neurons sustain motor behaviors which are modified by antipsychotic medication. These motor behaviors are referred to as extrapyramidal symptoms because, unlike cortical neurons, basal ganglia neurons do not send their axons in the pyramidal tract system. EPS includes parkinsonism, akathisia, dystonia and tardive dyskinesia (TD). Unfortunately, not all publications make this distinction and often EPSs are lumped together.

Parkinsonism

Parkinsonism was observed in patients following the introduction of chlorpromazine in the 1950s and thereafter with most antipsychotics. The core features consist of bradykinesia, tremor and rigidity. These are attributed to the antidopaminergic activity of antipsychotics on D₂ receptors, located on neurons in the basal ganglia.

Parkinsonism usually appears within a week or two upon initiating or increasing the dosage of an antipsychotic.

Initially it was thought that increasing antipsychotic dosage until parkinsonism appeared was essential to achieve antipsychotic response. The antipsychotic clozapine disproved this theory, as therapeutic response was possible without the presence of parkinsonism. The person who coined the term atypical antipsychotic to describe this observation with clozapine should have asked for a patent. Parkinsonism is believed to result from a dopamine and acetylcholine imbalance within the basal ganglia. Cholinergic neurons within the striatum are inhibited by dopamine released by axons originating from neurons located in the substantia nigra. When D₂ receptors are blocked by an antipsychotic, cholinergic neurons are disinhibited. They increase both their firing activity and the release of acetylcholine. Anticholinergic medication is therefore recommended to counteract parkinsonism. Antipsychotics with inherent anticholinergic activity such as chlorpromazine, olanzapine and clozapine will create less parkinsonism than haloperidol or flupenthixol, which have very little anticholinergic activity. Also, it is generally recognized that AAs cause less parkinsonism even when devoid of anticholinergic activity such as risperidone. Blockade of serotonin 5-HT₂ receptors seems to cause disinhibition of dopaminergic neurons, thus counterbalancing D₂ blockade in the basal ganglia.

A meta-analysis indicates that 11–57% of patients treated with AAs required antiparkinsonian medication compared to 36–81% treated with a CAs [11]. This is an indirect indication that patients treated with AAs, compared to CAs, have less but are not devoided of parkinsonism. In an extensive review, it was shown that anticholinergic medications were used more often in bipolar patients compared to schizophrenics [12]. The same authors concluded that in schizophrenic patients, EPS occurs more often with ziprasidone compared to other AAs. From the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, olanzapine patients had less parkinsonism and it was better tolerated than other AAs. Significant EPS, determined by the AIMS (Abnormal Involuntary Movement Scale), was found in 13–16% of patients treated with AAs compared to 17% with the CA perphenazine. The incidence of EPS did not differ significantly between perphenazine and the AAs over the 18-month follow-up; however more patients discontinued perphenazine (8%) than AAs (2–4%) as a result of EPS. Bipolar patients, especially in depression, seem more vulnerable to having acute antipsychotic-induced movement disorders with AAs than patients with schizophrenia [12]. In bipolar, the risk may be higher with aripiprazole, ziprasidone and risperidone in mania, and with quetiapine in depression [12]. Compared to other AAs, clozapine and quetiapine have been recommended in patients at high risk of parkinsonism [13].

Prophylactic use of anticholinergic medication should be considered with high potency CAs even though minimal evidence exists to support this recommendation. Drugs selective for M₁ receptors, located on striatal neurons, are preferred to minimize cardiac side effects which are associated with M₂ muscarinic receptors. Biperiden, followed by procyclidine, trihexyphenidyl and benztropine are among the more selective medication with M₁ anticholinergic activity.

Tardive dyskinesia

TD is an abnormal involuntary movement disorder. It can affect all muscles but predominantly those in the oro-facial area. It is associated with poor quality of life, non-adherence to treatment and increased morbidity and mortality [14, 15]. In the first five years of treatment, the annual incidence rate of TD with CAs is estimated at 5% in the adult population [16, 17] and is closer to 25–30% in the elderly [18–20]. Higher risk of TD has been reported in patients with affective disorder, high dosage of antipsychotic and increasing age [21]. There is yet no explanation for the increased risk of TD in bipolar, but the observation that lithium may have a protective effect suggests that intracellular mechanism implicating calcium metabolism or the enzyme glycogen synthase kinase 3-beta (GSK-3 β) activity may be involved [22]. Acute parkinsonism and akathisia are predictive of future development of TD during treatment with CAs [19, 23, 24].

Correll and Schenk [25] analyzed 12 prospective open or double-blind label studies published since 2004. These authors calculated that the rates of TD with AAs were higher in studies published after, compared to before, 2004. The difference in incidence of TD between AAs and CAs was also smaller after 2004. Potential reasons for this last observation may be the inclusion of longer duration studies with AAs and the usage of mid-potency CAs that were moderately dosed compared to previous studies with haloperidol. In the adult population, the annualized TD incidence was 3.0% with AAs compared to 7.7% with CAs, while in the elderly the incidence rate was 5.2% for both AAs and CAs [25]. The difference in TD rate caused by CAs and AAs in the elderly remains debatable when compared to other studies [18–20, 26]. In a naturalistic cross-sectional study [27], no difference in TD among patients receiving AAs versus CAs for less than five years was observed. The main difference was observed with patients treated with CAs for more than five years. However, risperidone represented 65% of the sample of AAs. Considering the number of published case reports of TD with risperidone which surpasses other AAs, it may be unfair to generalize de Leon results to all AAs.

Evaluation for TD should be done every six months using the AIMS. When present, one should re-evaluate the indication of an antipsychotic and avoid off-label indications. Several options should be considered in the presence of TD and the decision is essentially based on the clinical evaluation and the severity of the symptoms. When possible, decreasing the dosage of the antipsychotic will minimize further exacerbation of TD, although it may initially unmask more abnormal movements. Lowering the anticholinergic dose may also decrease the severity of TD. Administering the antipsychotic during the daytime will mask or suppress dyskinetic movements which may contribute to stigmatization or interferes with the patient's daily activity such as swallowing. Similarly, benzodiazepines given in the daytime can alleviate TD movement accentuated by anxiety. If TD becomes problematic, one should consider switching to clozapine [28], olanzapine [29] or quetiapine [30]. In a 26-week double-blind cross-over study, vitamin B₆ 600 mg twice daily was effective in reducing symptoms of TD [31]. Megadoses of vitamin E do not ameliorate TD, although they may prevent deterioration [32]. In a 1-year single-blind study, gabapentin

has shown a 35% improvement in the AIMS rating scale [33]. Tetrabenazine is a catecholamine depletor used for the treatment of a variety of movement disorders. It has shown some benefit for the treatment of TD at dosages varying between 25 and 75 mg daily [34]. However, tetrabenazine blocks D₂ receptors and partly masks or suppresses TD in the same manner as antipsychotics. Also, tetrabenazine has adverse events similar to those seen with antipsychotics such as parkinsonism and neuroleptic malignant syndrome (NMS). Long-term trials with this drug are needed to confirm its prolonged efficacy as a treatment option.

At present, it seems safe to say that the risk of TD may be less with some AAs. However, new TD studies need to establish whether long-term treatment with AAs makes a difference. Furthermore, we should not assume that all AAs are equivalent in risk for TD because they differ among themselves in their pharmacological properties.

Dystonia

Dystonia is a sustained involuntary muscle contraction. Twisting and torquating movements have been observed [35]. Acute dystonia occurs within the first few days after initiating a treatment with an antipsychotic. Gender is not considered a risk factor although some studies have found a higher incidence rate among younger males. The most frequent acute dystonic reactions are torticollis (30%), forced jaw closure (15%), oculogyric crises (6%) and opisthotonos (3.5%). The most dangerous acute dystonia involves laryngeal and pharyngeal muscles, which can lead to severe distress and ultimately death by asphyxiation and choking, respectively [36]. A number of anecdotal case reports of acute dystonias with AAs have been reported [37]. The incidence seems less with AAs compared to CAs [38], but few systematic studies on this subject have been published. Anticholinergic medications are recommended prophylactically [39] and, when present, acute dystonia will resolve rapidly following intramuscular administration of an anticholinergic medication or a benzodiazepine.

Tardive dystonia manifests itself several months or years later. It often involves group muscles of the neck and thoracic areas which can be exacerbated following dosage reduction of the antipsychotic. Incidence of the disorder varies between 2 and 36% and the risk increases with higher binding affinity to D₂ and higher dosage antipsychotics. This disorder has a limited response to anticholinergic medication. Switching to clozapine may help in a number of selected cases. When the symptoms are localized to a small group of muscles (i.e. lingual dystonia) botulinum can be an option for treatment although injections usually need to be repeated every three months [40]. Finally, deep brain stimulation (globus pallidus, subthalamic nucleus) may be successful in more refractory and debilitating cases, but the frequency and duration of this therapeutic approach needs to be documented by long-term controlled studies [41, 42].

Akathisia

Akathisia is described as a subjective restlessness and patients feel the need to move or walk to decrease a sense of anxiety or dysphoria. In severe cases, distress is such that it may increase the risk of suicide. It can either be acute (symptoms

begin within six weeks after starting an antipsychotic), chronic (symptoms persist more than three months) or tardive (symptoms begin more than three months after starting the medication). Tardive akathisia may last many months to years even after complete cessation of an antipsychotic. Withdrawal akathisia occurs when the medication is decreased or discontinued and may be masked by increasing the dose of an antipsychotic [43]. The incidence rate of acute akathisia is estimated at 20–30% with CAs [44] and the pathophysiology seems to involve the blockade of D₂ receptors although it also occurs, to a lesser extent, with the antidepressants selective serotonin reuptake inhibitors (SSRIs). Sometimes it can be mistaken for restless leg syndrome [45]. Antipsychotics with either anticholinergic or anti-5HT₂ activity have lower rates of akathisia. In this respect, AAs are compared to haloperidol, which has neither of these pharmacological characteristics and produces lower rates of akathisia in the range of 5–9%. Interestingly, incidence of akathisia with perphenazine is the same as with AAs in the CATIE study [1]. The risk of akathisia may be higher with aripiprazole than other AAs in bipolar patients, mainly in the depressive state [12]. Furthermore, very little information is available about AAs regarding chronic, tardive and withdrawal akathisia.

Acute akathisia may respond to propranolol, benzodiazepines (preferably with a long half-life such clonazepam or diazepam) or an anticholinergic [46]. However, the most appropriate first step would be to decrease the dosage of the offending agent and perhaps change to an antipsychotic with a lower affinity to D₂ receptors, such as clozapine and quetiapine, or to an antipsychotic with anticholinergic and/or anti 5-HT₂ activity.

Pharmacological treatments proposed for EPS are summarized in Table 17.3.

Table 17.3 Efficacy of different classes of medication for motor adverse events induced by antipsychotics.

Class of medication	Parkinsonism	Akathisia	Acute dystonia	Tardive dystonia	Tardive dyskinesia
Anticholinergic	+++	+	+++	+	Worsen
Benzodiazepines	+	+++	+++	++	++
Clonidine	–	–	–	++	++
Propranolol	–	+++	–	–	–
Tetrabenazine	Worsen	–	–	+	++
Vitamin B ₆	++	++	–	–	++
Vitamin E	–	–	–	–	+

Sleep and sedation

Sleep disorders are known to occur with many psychiatric disorders, most notably with depression, mania and schizophrenia. A number of antipsychotics exert a sedative effect by blocking predominantly histamine receptors and secondarily cholinergic, α_1 -adrenergic and 5-HT_{2A} serotonergic receptors. While antipsychotics are sometimes used for their therapeutic effect on sleep-wake function and a possible, but

still controversial, effect on sleep-architecture [47, 48], they can also cause daytime sedation and difficulties falling or staying asleep.

Studies assessing sleep-related side effects during antipsychotic trials show that almost all cause daytime sedation. Daytime sedation can be mistaken for cognitive impairment and negative symptoms [49]. There is a great variability in the sedating effect between different agents that depends on their pharmacokinetic effects, dosage, half-life and metabolic profile. For example, the weight gain associated with some antipsychotics can lead to night-time food cravings and to sleep apnea, which is associated with daytime sleepiness [50]. Somnolence or daytime sedation are more prevalent with clozapine (52%) followed by chlorpromazine (33%), risperidone (30%), olanzapine (29%), haloperidol (23%), ziprasidone and quetiapine (16%) and aripiprazole (12%) [48, 50]. Tolerance to daytime sedation may occur few days after drug introduction or dosage augmentation. Sedation and somnolence contribute to impaired functioning, decreased quality of life, non-compliance and falls in the elderly. It is important to rule out hypothyroidism, eliminate other sedating agents such as benzodiazepines, adjust the dosage, the schedule of intake of the offending drug and sometimes consider a substitution to a less sedating antipsychotic. If a patient presents with daytime sedation and weight gain, headaches and snoring, it is important to screen for sleep apnea and to treat it if present. If all these efforts are insufficient, some suggest adding modafinil, bupropion or caffeine, although this is very controversial since it might worsen psychotic symptoms [49].

Difficulties falling or staying asleep have also been reported with antipsychotics. Those with a 5HT_{1A} agonist activity (e.g. aripiprazole) are thought to be more commonly involved. Also, drugs with strong D₂ antagonism can provoke night-time equivalents of EPS such as nocturnal akathisia, restless leg syndrome and periodic leg movements (nocturnal myoclonus that can be diagnosed clinically or during polysomnogram). This disruption of night-time sleep can exacerbate the daytime sleepiness and shift the circadian rhythm forward. It has been reported that clozapine is the drug less associated with insomnia or sleep disruption, with only 4% of patients reporting this side effect. Haloperidol (25%), aripiprazole (24%) and thioridazine (23%) have the highest rates [50]. Thus, if antipsychotic-induced insomnia or sleep-disruption is present, nocturnal EPS should be excluded.

Sexual dysfunction

Sexual dysfunction is now being recognized as a very inconvenient side effect amongst a population who was once thought to be much less sexually active. It may lead to non-adherence more often than in patients who experience sedation or vegetative side effects [51].

The scope of sexual undesirable effects is vast and may include interest and erectile dysfunction, anorgasmia and ejaculatory disturbances. The variety of manifestations of sexual dysfunctions is attributed to binding affinity of antipsychotics on various receptors in the central and autonomic nervous systems. The cause is first and foremost attributable to the elevation of prolactin that results from dopamine blockade in the central nervous system. Cholinergic, α -adrenergic as well as calcium-channel blockade have all been postulated to play a role in

antipsychotic-mediated sexual dysfunction [52]. Serotonin may have a protective or deleterious role, depending on the receptor stimulated. One must account for the fact that drug-naïve patients with schizophrenia also have sexual dysfunction. Numerous other factors may be involved, many of which are present simultaneously in patients (see Table 17.4).

Table 17.4 Factors contributing to sexual dysfunction in a population with schizophrenia.

Social difficulties secondary to social withdrawal of various causes
Negative symptoms
Depressive symptoms
Adverse pharmacological effects: sedation, weight gain, metabolic disturbances
Alcohol and drug misuse
Medical comorbidities: diabetes, coronary heart disease, vasculopathies.

Point prevalence of sexual dysfunction in patients with schizophrenia taking antipsychotics is roughly estimated to be 20–70% [53]. In comparison studies, this number may vary with the antipsychotic being taken [54]. Quetiapine and clozapine are recognized as comparatively less influential on sexual function. Antipsychotics with high affinity to D₂ receptors (risperidone, haloperidol and others) have more impact because of their tendency to increase prolactin. Nonetheless, a recent review has not been able to establish clear advantages of one drug over another [55]. More studies are needed concerning ziprasidone and aripiprazole. Aripiprazole, with innate partial D₂ agonism and a resultant decrease in prolactin, seems to have an impact on sexual function [56]. With any antipsychotic, sexual side effects can be presumed dose dependent.

Clear and simple interventions are proposed to diminish these undesirable effects [57]. First, a lower dosage or an antipsychotic with a tendency to cause less hyperprolactinemia or treating hyperprolactinemia with dopamine agonists, such as with cabergoline [58], should be tried. These interventions are all to be measured against the impact of possible deterioration of psychotic symptoms. Bethanechol, a cholinergic agent, cyproheptadine, yohimbine and amantadine have had some mention in the treatment of sexual side effects [52]. Lastly, many authors bring up the use of sildenafil for treating erectile dysfunction. Although these interventions are theoretically reasonable, no specific one has been proven better in terms of clinical value.

Mania

Close to 60 case reports have been published between 1994 and 2008 describing manic or hypomanic symptoms after initiating a treatment with an AA [59–62]. Symptoms appear a few days up to four weeks after initiating treatment. In published cases, patients had no prior history of mood disturbances and many had been treated for schizophrenia for a number of years. Emergence of manic symptoms has not yet

been reported with clozapine. It has been proposed that manic symptoms are caused by an increased dopamine release in the frontal cortex via blockade of 5-HT₂ receptors. Also, some antipsychotics or their metabolites (e.g. N-desalkylquetiapine) may inhibit neuronal reuptake of norepinephrine and/or serotonin [63] and facilitate a manic-switch in a similar manner as antidepressants. Nevertheless, this adverse event is not a contraindication to treat bipolar patients with AAs, but physicians should be aware that manic symptoms may, for a few patients, be induced or exacerbated by the medication.

Obsessive-compulsive symptoms

Emergence or exacerbation of obsessive-compulsive symptoms (OCSs) has been estimated as between 3 and 12% in schizophrenic patients treated with AAs. OCS may appear within 1–4 weeks of treatment, but longer treatment with olanzapine and clozapine has been associated with higher OCS scores [64, 65]. Nevertheless, careful interpretation of these longer follow-ups is needed considering that OCS is highly prevalent in schizophrenia [66]. Most AAs have been associated with OCS [65, 67] but prevalence appears much higher with clozapine and may reach 20–35% of patients in long-term studies [67, 68]. When patients are disabled by OCS, it is recommended to decrease the dose of the AA or change to another AA or a CA. SSRIs have been used successfully to treat OCS but physicians should be aware of possible pharmacokinetic and pharmacodynamic interactions with an antipsychotic. Clomipramine is not recommended with olanzapine or clozapine because it may increase anticholinergic adverse events. Paradoxically, although OCS may be an adverse event of AAs, they have been used successfully as adjunct medication to treat obsessive-compulsive disorders (OCD) or decrease OCS when using lower doses [69].

Medical and biochemical

Metabolic

The number of publications on metabolic adverse events with antipsychotics probably outweighs publications on efficacy of antipsychotics. This adverse event has condemned psychiatrists for the next generation to assume their responsibility as medical doctors. Awareness of the metabolic syndrome is essential as it will be a major cause of morbidity and mortality in psychiatric patients. There are several ‘official’ definitions of the metabolic syndrome but the variants are minimal. Table 17.5 describes the criteria proposed by the World Health Organization.

The prevalence of the metabolic syndrome is estimated to be between 20 and 25% in the general population and doubles in patients with a major psychiatric disease [70]. In first episode schizophrenic patients, the odds of developing a metabolic syndrome was threefold in patients who had started on AAs, compared to CAs. This difference was no longer significant when clozapine and olanzapine patients were excluded from analysis. Finally, nearly one out of three patients met criteria of a metabolic syndrome after 3 years of treatment with an AA [56]. These findings are

Table 17.5 The World Health Organization criteria for metabolic syndrome.

Signs of insulin resistance characterized either by impaired fasting blood glucose, impaired glucose tolerance or a diagnosis of type 2 diabetes.
Two of the following criteria:
High blood pressure (>140/90 or on antihypertensive medication)
Fasting plasma triglycerides >150 mg/dl (1.7 mmol/l)
HDL cholesterol <35 mg/dl (0.9 mmol/l) for men and <39 mg/dl (1.0 mmol/l) for women
Body mass index >30 (BMI = body weight in kilograms/(height in meters) ²) and/or waist : hip ratio >0.9 in men and >0.85 in women
Urinary albumin excretion rate >20 µg/min or albumin : creatinine ratio >30 mg/g

important considering that individuals with a metabolic syndrome have a 2.4–3.6 increased risk of mortality from a cardiovascular event [71]. When a metabolic syndrome is present and non-pharmacologic approach proved insufficient to relieve the problem, the physician must decide if the therapeutic advantage of the antipsychotic outweighs the metabolic syndrome. Otherwise, antipsychotic substitution is indicated.

Weight gain

Weight gain is highly prevalent among patients treated with antipsychotics and may lead to pharmacological non-compliance and relapse thereafter [72, 73]. Furthermore, obesity is associated with a number of diseases such as cardiovascular problems, diabetes mellitus and possibly cancer [74]. Antagonism of serotonin 5-HT_{2C} and histamine H₁ receptors is strongly associated with an increase risk of weight gain, with some contribution when 5-HT_{1C}, D₂ and/or 5-HT_{1A} receptors are blocked [9, 75]. Neuroendocrinal mechanisms involved in feeding or metabolic regulation include numerous peptides with leptin (binds to hypothalamic nucleus to regulate satiety), ghrelin (appetite-stimulating peptide synthesized in the stomach) and orexins (weight-regulating peptide released by the hypothalamus) and their physiological activity is modified by AAs [75, 76].

Among AAs, the most significant weight gain is reported with olanzapine and clozapine and is a result of their high affinities for 5-HT_{2C} and H₁ receptors. Ziprasidone and aripiprazole have little affinity to those receptors and are associated with minimal weight gain [77–79]. A meta-analysis of 81 studies showed an increase of 4.0 and 4.5 kg over a period of 10 weeks with olanzapine and clozapine respectively [80]. Figure 17.1 shows graphically the estimated mean weight change at 10 weeks with a variety of CAs and AAs. Pooling data from 51 trials with olanzapine, risperidone and haloperidol [81] compared weight gain in first episode psychosis, in chronic patients, in the first and after nine months of treatment. They found that for all three antipsychotics, weight gain was more significant in first episode psychosis and even more so if the treatment lasted for more than nine months (see Table 17.6). In all subgroups of patients those treated with olanzapine had the most weight gain followed by risperidone and then haloperidol. Weight gain profile differs

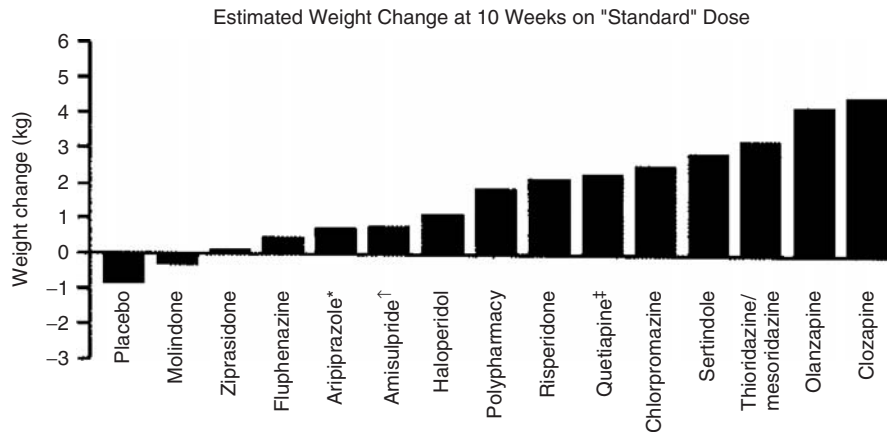


Figure 17.1 Estimated weight change at 10 weeks on ‘standard’ dose. (Source: From Newcomer [78].)

Table 17.6 Weight gain with olanzapine, risperidone and haloperidol in first episode psychosis and chronic patients in relation to the duration of treatment.

	Olanzapine (kg)	Risperidone (kg)	Haloperidol (kg)
First episode psychosis (less than 9 months of treatment)	7.1–9.2	4.0–5.6	2.6–3.8
First episode psychosis (more than 9 months of treatment)	10.2–15.4	6.6–8.9	4.0–9.7
Chronic patients (less than 9 months of treatment)	1.8–5.4	1.0–2.3	0.01–1.4
Chronic patients (more than 9 months of treatment)	2.0–6.2	0.04–3.9	–0.07–0.4

Source: Modified from Alvarez-Jiménez *et al.* [81].

among antipsychotics. For instance, olanzapine and clozapine are associated with a rapid increase in weight compare to risperidone which is more gradual. Proportion of patients who increased their weight by more than 7% is a measure considered more appropriate than mean weight gain because of the variability of this adverse event among patients. In long-term studies, olanzapine demonstrates more than 30–40% of patients with >7% weight gain compared to 7–17% with other antipsychotics [1, 81].

Diabetes

It is generally recognized that the incidence of diabetes is increased twofold in patients with schizophrenia and bipolar disorder, males being more at risk [78, 82]. Other risk factors include age, obesity and a family history of diabetes. In addition, CAs and AAs with binding affinities to 5-HT_{2C}, M₃ and H₁ receptors can worsen blood glycemia or even cause diabetes mellitus [9]. Among AAs, olanzapine

and clozapine are considered the most diabetogenic while the risk is minimal with aripiprazole and ziprasidone [1, 78, 83]. Several cases of diabetic ketoacidosis have been observed less than three months after initiating treatment with olanzapine, clozapine and quetiapine and death occurred among 10–30% of the reported cases [78, 84]. In a 14-week trial, new diabetes developed in 14–21% of patients treated with olanzapine, risperidone or quetiapine compared to 4% with haloperidol [85]. In a 10-year follow-up study 43% of patients treated with clozapine developed diabetes, African and Hispanic Americans being more at risk than Caucasians [86].

Dyslipidemia

Unlike obesity and diabetes, it is unknown whether major psychiatric disorders comprise an inherent risk for hyperlipidemia. However, hyperlipidemia is often but not necessarily associated with obesity. Elevated cholesterol, low-density lipoprotein (LDL) cholesterol and mostly triglyceride levels have been observed with antipsychotic use. However, hyperlipidemia may be more a consequence of weight gain rather than a direct adverse effect of antipsychotics [87]. The risk to induce hyperlipidemia with AAs is highest in patients treated with olanzapine and clozapine, modest to minimal with risperidone and quetiapine and minimal with aripiprazole and ziprasidone [1, 78, 88]. Changes in the lipid profile have been observed as early as six weeks after treatment with olanzapine [89]. Studies looking at lipid levels with CAs are limited, but high potency antipsychotics such as haloperidol appear to carry a much lower risk than low-potency antipsychotics such as chlorpromazine and thioridazine [88].

Metabolic monitoring

Several guidelines have been proposed for monitoring metabolic parameters in patients treated with an antipsychotic [90]. However, there are no studies demonstrating the cost-effectiveness of these guidelines. When establishing guidelines, the following parameters should be taken into consideration: (i) the relative risk of an individual for a metabolic disorder according to personal and family history; (ii) the association of major psychiatric disorder with a specific metabolic disease (e.g. diabetes in schizophrenia) and (iii) the increase risk of an antipsychotic to cause a metabolic disorder (e.g. diabetes and hyperlipidemia with clozapine and olanzapine). The frequency of monitoring should also take into consideration the seriousness of the adverse event (e.g. ketoacidosis in diabetes) and the period for which the risk remains. Finally, CATIE and other long-term studies demonstrated that 60–75% of patients will change or discontinue their treatment within 12–18 months and the frequency of monitoring may change with a new drug. Psychiatrists should do the monitoring unless the patient has a family physician or an internist familiar with metabolic adverse events of antipsychotics. Recommendations based on the American Diabetes Association (ADA) and American Psychiatric Association (APA) Consensus for monitoring patients on AAs is considered a minimum requirement to detect a metabolic anomaly (Table 17.7). Patients with additional risk factors should be monitored more frequently.

Table 17.7 Recommendations based on the American Diabetes Association and American Psychiatric Association (ADA/APA) consensus for monitoring patients on AA.

	ADA/APA Consensus Guidelines ^{a,b}						
	Base	At 4 wk	At 8 wk	At 12 wk	Every 3 mo	Annually	Every 5 yr
Medical history ^b	X						
Weight (BMI)	X	X	X	X	X	X	
Waist							
Circumference	X						
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipids ^a	X			X			X

^aMore frequent monitoring may be warranted if patient has risk factors.
^bPersonal and family history of obesity, diabetes, hypertension and cardiovascular disease.

Treatment

In view of these findings, patients with a metabolic syndrome are at high risk for cardiovascular events because they often present with other risk factors such as smoking and a sedentary lifestyle [88, 91]. Patients should be informed of the metabolic syndrome and non-pharmacological strategies initiated early to prevent weight gain. Diet, nutritional assistance, physical exercise and cognitive-behavioral therapy are effective treatment for weight reduction and should be preferred to pharmacological management [92]. A supervised exercise and weight control program appears to be highly beneficial to prevent weight increase, hyperlipidemia and glucose intolerance in patients treated for 12–18 months with an AA [93]. Several types of pharmacological management of AA-induced weight gain have been reported statistically efficacious compared to placebo as weight-attenuating agents [76, 94]. However, the weight modulating effect is modest and general use of pharmacological interventions for weight management is not recommended as an early intervention. Furthermore, adding a medication increases the risk of adverse events, drug interactions and poorer pharmacological adherence.

Patients with AA-induced diabetes appear to respond to glucose-lowering agents, but no study has been published to support this approach or compare treatment efficacy against idiopathic diabetic patients. Rare cases of insulin-resistant patients have been reported [95]. In the case of hyperlipidemia, lipid lowering medication (LLM) such as a statin can reduce triglyceride levels, total cholesterol and the LDL portion of cholesterol [96, 97]. In the general population, pharmacological treatment with a LLM has been demonstrated to decrease the risk of cardiac events by decreasing total cholesterol and triglyceride levels [98], but this evaluation has not yet been carried out in AA-treated patients. In patients treated with clozapine, combining low-dose clozapine to fluvoxamine reduces the level of triglyceride level by reducing the hyperlipidogenic metabolite nor-clozapine [99]. However, very careful monitoring for clozapine toxicity is necessary because of pharmacokinetic interactions between the two drugs.

Cardiovascular

Cardiovascular side effects of antipsychotics were first described in the 1960s when case reports of sudden death in young adults without known heart problems occurred after intra-muscular injections of CAs. Today, it is estimated that 40–45% of natural deaths in patients with schizophrenia are due to a cardiovascular disease [100]. Cardiovascular mortality risk is twofold greater in patients with schizophrenia than in the general population [101]. We present here the most common and most severe cardiovascular side effects of antipsychotics.

Orthostatic hypotension, blood pressure and pulse variations

Antipsychotics exert cardiovascular effects by blocking the α_1 -adrenoreceptors. This can cause vasodilatation and postural hypotension. Together, with vagal nerve suppression secondary to the anticholinergic muscarinic M_2 activity of antipsychotics, it may result in heart rate variations. This may be a predisposing factor to induce arrhythmias and a higher risk of mortality.

Orthostatic hypotension is one of the most frequent vascular effects of antipsychotics. It occurs more frequently with clozapine and risperidone but all antipsychotics with an anti- α_1 activity can cause it (Table 17.2). It is frequently observed in the early stages of treatment initiation, or when dosage is increased. Orthostatic hypotension is defined as an abnormal decrease of >20 mmHg in systolic blood pressure or >10 mmHg in diastolic blood pressure when a person stands up. Diagnosis can be made by taking the blood pressure at 0, 1, 2 and 5 minutes after a patient goes from a lying down position to sitting and standing up, and is usually accompanied by an increase in the pulse rate. The most frequent symptom is dizziness, but orthostatic hypotension can also be responsible for falls and syncope. The reporting rates for AAs vary from 1.3 to 4.7% [101]. When present, orthostatic hypotension usually resolves within 4–6 weeks after initiation of treatment or dosage augmentation. If symptomatic, treatment is first non-pharmacological: rising slowly from a lying or sitting position, increasing fluid and salt intake, using support stockings, tilting the head of the bed at night and dividing the dose of the offending drug. In exceptional cases, when the patient is very symptomatic and all other treatment options have failed, fludrocortisone or ephedrine can be tried [102].

Sinus tachycardia is diagnosed when the heart rate is over 100 bpm. It has been reported in 25% of clozapine, 7% of quetiapine, 5% of risperidone, 5% of sertindole, 5% of olanzapine and 2% of ziprasidone users. It is usually dose-dependent and happens more often in male and younger patients [100]. If the patient is symptomatic, a lower dose or slow titration can help relieve the symptoms. β -blockers may also be helpful [102] although they may exacerbate a hyperlipidemia. On the other hand, sinus bradycardia is diagnosed when the heart rate is lower than 60 bpm but usually becomes symptomatic only with heart rates under 50 bpm. It has rarely been reported with risperidone, olanzapine and ziprasidone. If asymptomatic, treatment might not be required. When symptomatic, patients usually present with weakness, lethargy and a tendency to fall. One should first revise the patient's medication to look for a lowering heart rate effect of combined drugs (e.g. SSRIs, β -blockers and calcium-channel

blockers) and, second, consider reducing if possible the dosage of the offending antipsychotic.

Henderson *et al.* in their 2004 retrospective chart review of 82 patients found that at 5 years, 40% of clozapine-treated patients had systolic pressure in the range of hypertension (>140 mmHg) and 60% had diastolic pressure in the range of hypertension (>90 mmHg). Among these patients, only 27% received treatment for their hypertension. Since it is one major risk factor for cardiovascular disease, hypertension should be monitored at baseline, 12 weeks after initiation of treatment and at least every year thereafter. It should always be treated by non-pharmacological methods (physical exercise, weight reduction and salt restricted diet) and pharmacological methods only if needed.

QT interval and arrhythmias

The QT interval (in milliseconds from the Q spike to the T wave) calculated by an electrocardiogram (ECG), represents the duration of depolarization and repolarization of myocytes. Since the QT interval varies with heart rate, a rate-corrected QT interval is used in clinical settings (QTc). A prolonged interval usually results from delayed repolarization which may allow for ventricular ectopic beats that can lead to *torsade de pointes* (TdP), a polymorphic ventricular arrhythmia, that can progress to ventricular fibrillation and sudden death. It is generally accepted that QTc intervals <440 ms are normal; 440–460 ms in men and 440–470 ms in women are considered borderline; and >500 ms are considered to represent a substantial risk factor for TdP. Prolonged QTc has many etiologies and was reported with the use of almost all antipsychotics. These are thought to prolong the QT interval by blocking the delayed potassium rectifier channel (I_{kr}) in the myocytes, which prolongs repolarization. The association between I_{kr} blockade, QT prolongation and TdP is modulated by multiple factors such as sodium and calcium channel effects of certain drugs that mitigate their effects on potassium channels or an intrinsic activity that prevents ventricular ectopic beats. Also, QTc can vary due to diurnal effects, electrolyte imbalance, autonomic fluctuations, ECG acquisition technique, gender (androgen-driven differences) and intra- and inter-observer variability [103]. The degree of the prolongation of the QT interval is greater with thioridazine (35 ms), followed by amisulpride, sertindole and ziprasidone which are associated with a modest increase of the QT interval (less than 30 ms) [100]. Because of its cardiac side effects, thioridazine was discontinued in a number of countries in 2005. The QT prolongation is not due to a class effect and is not clearly dose dependent. So far, aripiprazole has not been associated with an increase of the QT interval [101]. A list of other offending agents is available on the university of Arizona web site (www.torsades.org).

When studying individuals with psychotropic-induced TdP, it was determined [104] that the most common risk factors prior to treatment initiation were female gender (71.4%) followed by advanced heart disease (34.2%), concomitant use of more than one psychotropic drug or another agent that might prolong QT interval (30.8%), high doses of offending drug (27.1%), a family history of long-QT syndrome, a previous episode of drug-induced TdP or an obviously prolonged QT interval on the

baseline ECG (18.5%) and hypokalemia (14.2%). Altogether, 98.6% of patients had a least one (gender being overrepresented) and 73% had two or more easily identified risk factors for TdP prior to psychotropic drug initiation. It is still noteworthy that a personal and family history taking, baseline ECG and blood-sampling potassium (and magnesium) levels can reveal most risk factors among psychiatric patients [104, 105].

Prolonged QTc interval is usually asymptomatic. Similarly, TdP can be asymptomatic and self-limited. However, it can progress to tachycardia, syncope, seizure-like activity and fatal arrhythmia. Patients with borderline QTc results before treatment initiation should have repeated ECG after the first dose of an antipsychotic agent and at steady state. For those with prolonged QTc, the dose should be decreased or the drug replaced by another. If the QTc is over 500 ms, the offending drug should be replaced with an antipsychotic with less or without known QT prolongation or TdP. Patients should be told to be aware of dizziness or syncope, mostly during periods of diarrhea or emesis since these conditions can produce hypokalemia.

Myocarditis

Myocarditis is an inflammatory process affecting the myocardium. It is generally due to viral infections, but can also have a toxic etiology. It is often associated with pericarditis. Myocarditis was reported with the use of risperidone, olanzapine, ziprasidone and clozapine, the strongest association being with the latter. Although the physiopathology of antipsychotic-induced myocarditis is not well understood, it is thought to be secondary to a type 1, immunoglobulin E (IgE)-mediated, hypersensitivity reaction. In their review, [106] found an absolute risk of myocarditis in clozapine-treated patients ranging from 0.015 to 0.188%; 65% were male and the median age of patients was 36 years. Clozapine dosage ranged from 50 to 725 mg daily (with the exception of one case of acute clozapine intoxication) and a median duration of treatment before the onset of myocarditis of three weeks. Of all the patients who developed myocarditis, 71% did so within the first month of treatment, 90% within two months and 51% died. The most common symptoms at the time of presentation were fever (48%), dyspnea (35%), flu-like illness (30%), chest pain (22%) and fatigue (17%). In the same review, the most common test findings were left ventricular hypokinesis and/or reduced ejection fraction on echocardiogram (48%), ECG abnormalities (35%) (in particular T-wave changes or flattening), peripheral eosinophilia (35%), elevated creatine kinase (CK) levels (22%), pericardial effusion (17%) and symptoms or signs of heart failure (13%).

Cardiomyopathy is an ensemble of disorders that affect the functioning of the heart muscle. The dilated cardiomyopathy (DCM) is the most common form and has a poor outcome, 50% of patients dying within five years of diagnosis [106]. The risk of having it is fivefold increased among clozapine users compared to the general population. DCM is characterized by ventricular dilatation, contractile dysfunction and sometimes symptoms of congestive heart failure (shortness of breath, peripheral edema, fatigue). There are asymptomatic cases and atypical presentations such as panic attacks. Clozapine-related cardiomyopathy is not well understood, but some suggest a direct cardiotoxic

effect of clozapine while others suggest that DCM evolves from myocarditis. In a review [106], patients with clozapine-related cardiomyopathy: had a median age of 34 years; were 78% male; a median duration of treatment of nine months; and clozapine dosage ranging from 200 to 500 mg daily. Sudden or unexpected death occurred in 22% of patients.

Because of the high degree of morbidity and mortality associated with myocarditis and cardiomyopathy and, since the signs of those two pathologies are inconsistent and non-specific, clinicians must maintain a high level of suspicion. They might consider a cardiology consultation prior to treatment for patients with a family history of cardiac disease or for patients with chest pain, myocardial infarction, heart failure, arrhythmia or syncope. Those with a known structural cardiovascular disease should have an echocardiography prior to treatment initiation for eventual comparison if necessary. Patients should be informed and questioned about cardiovascular symptoms within the first month of treatment.

When myocarditis is suspected, an ECG and cardiac enzymes (creatine kinase-muscle, brain (CK-MB), troponin I and troponin T) should be obtained urgently. If abnormal, the clozapine or offending agent must be stopped, an echocardiography and a cardiology consultation rapidly obtained and the patient closely monitored. Definite diagnosis is usually made by myocardial biopsy, but contrast media-enhanced magnetic resonance imaging has proved to be useful. Supportive treatment is recommended while adjunctive use of corticosteroids is still controversial. Usually, symptoms of myocarditis resolve or substantially improve after withdrawal of the offending agent, but recurrences of symptoms on rechallenge are the rule. Only one case-report describes a patient who successfully resumed clozapine without recurrence of myocarditis. In the case of DCM, there are cases that resolved or improved after clozapine withdrawal. When DCM is diagnosed, the risks and benefits of treatment continuation must be evaluated. If the decision is made to continue the offending drug, a cardiology consultation should be obtained and echocardiography done every 3 months in order to assess the left ventricular size and function. It is recommended to discontinue clozapine or the offending agent if the left ventricular ejection fraction (LVEF) declines at least 15% from baseline to a level of 45% or lower, in order to minimize the risk of heart failure [106]. That being said, there is one case report [107] of a 34 year-old man with clozapine-related cardiomyopathy who resumed clozapine, with the adjunction of carvedilol and captopril, in order to prevent further cardiac deterioration. His cardiac condition was monitored every 2 months and thereafter every 3 months without recurrence of cardiomyopathy over a 5-year follow-up period.

Neuroendocrine

In this section, we will discuss antipsychotic effects on prolactinemia, bone mineral density (BMD) and water osmosis.

Hyperprolactinemia

Prolactin is a hormone secreted by the anterior pituitary gland. Its secretion is primarily regulated by dopamine: the 'prolactin inhibiting factor' or PIF.

Hyperprolactinemia is defined as a serum prolactin level higher than 25 $\mu\text{g/l}$ (normal: 10–25 $\mu\text{g/l}$). It is not always symptomatic. There are different causes of hyperprolactinemia (Table 17.8), one of them being antipsychotic use. Antipsychotics are not equal in their capacity to cause hyperprolactinemia: potent D_2 blockers such as haloperidol, risperidone (and its active metabolite paliperidone) and amisulpride are associated with the most important increases of prolactin serum levels, whereas olanzapine and ziprasidone are less likely to do so. Clozapine and quetiapine have not been associated with symptomatic or sustained elevations of prolactin levels [109]. Aripiprazole, a dopamine partial agonist, has minimal effects on prolactin and is sometimes even associated with decreased levels of prolactin [110].

Table 17.8 Underlying causes of hyperprolactinemia [108].

	Cause
Physiological	Pregnancy Nursing Stress Exercise Sleep
Pathological	Pituitary disorders – for example micro- or macroprolactinoma, acromegaly Hypothalamic disorders – for example craniopharyngioma, pituitary stalk section, glioma
Pharmacological	Antipsychotics (risperidone, amisulpride and typicals) Antidepressants (SSRIs, clomipramine) Antimetetics Antihypertensives Estrogens Verapamil Protease inhibitors
Other	Chronic renal failure Idiopathic hyperprolactinaemia

Source: From Montejo [110].

Treatment with some CAs and risperidone has been shown to increase serum prolactin levels 5–10 times above that of healthy control subjects, with a dose-dependent association and a significant gender difference. Cross-sectional studies have shown prevalence rates of hyperprolactinemia up to 42% in men and 75% in women with schizophrenia [110].

Symptoms and complications of hyperprolactinemia are multiple (Table 17.9). Symptoms emergence usually depends on the rapidity and degree of increase in prolactin levels. The most obvious are gynecomastia (1–2% of patients), galactorrhea (10–90% in women depending on the antipsychotic used and its dosage; rare in men), acne, hirsutism and menstrual abnormalities in women [109]. Sexual dysfunction, hematological, reduced BMD and immunological side effects are more insidious complications of hyperprolactinemia. Hyperprolactinemia is also associated with an increased risk of breast cancer, endometrial and pituitary tumors, mostly benign.

Table 17.9 Possible direct and indirect consequences of hyperprolactinemia [111, 112].

	Symptom
Direct	Amenorrhea
	Galactorrhea
	Gynecomastia
Indirect	Infertility
	Menstrual abnormalities
	Sexual dysfunction: libido decreased; erectile dysfunction
	Acne/hirsutism in women
	Reduced bone mineral density (fractures)
	Breast and endometrial cancer
	Increase of cardiovascular risk ^a

^aSun *et al.* [113]
Source: From Montejo [110].

A retrospective study found a 16% increase in the incidence of breast cancer in women exposed to antipsychotics, with large cumulative doses being associated with the highest risk [114]. Another case-control study found that antipsychotic-induced hyperprolactinemia is associated with an increase of 5.4 of the risk of endometrial cancer [110]. These seemingly alarming numbers should be considered very cautiously since they do not take into account the prevalence of these tumors in the general population, do not specify over what period of time the increased incidence or higher risk occurred and, in particular, are not controlled for other risk factors which the patients had to develop those tumors (hormonal use, age, smoking, age of menarche and menopause etc.). Finally, risperidone (followed by haloperidol, ziprasidone and olanzapine) has the highest adjusted reporting ratio for pituitary tumors [109, 115].

Considering the prevalence of hyperprolactinemia and its complications, and knowing that patients will under-report these sometimes embarrassing symptoms (sexual dysfunction and galactorrhea, for example), clinicians should inquire about symptoms of hyperprolactinemia when an antipsychotic is started and yearly after. It is not recommended to systematically measure prolactin levels before or after antipsychotic initiation, in view that the majority of patients will either be asymptomatic or change or discontinue their antipsychotic during the next year. This being said, a patient who needs a long-term treatment and who is stable on high-D₂ affinity antipsychotics at moderate to high dosage (e.g. haloperidol and risperidone), a fasting morning serum prolactin level should be obtained. If elevated and the patient is asymptomatic, there is no urgency to intervene but the clinician should eventually reduce the antipsychotic and monitor for the emergence of side effects. If hyperprolactinemia is symptomatic, one should first consider decreasing the dosage of the incriminating agent or switch medication to a less prolactin-elevating antipsychotic. A control prolactinemia should be obtained one month after these adjustments. If prolactin levels are still high, the clinician has to rule out other causes of hyperprolactinemia and consider carrying out a magnetic resonance imaging (MRI) scan to verify if a pituitary tumor is present. Antipsychotic-induced

prolactin increases usually range from 25 to 200 $\mu\text{g/l}$, whereas elevations over 200 $\mu\text{g/l}$ usually signal a prolactin-secreting pituitary adenoma [110].

There are some rare cases where a patient with a symptomatic hyperprolactinemia cannot switch antipsychotic. In that case, some authors suggest adding a combined oral contraceptive to menopausal women with symptoms of estrogen deficiency; this has the advantage of minimizing BMD loss [116]. However, the benefits of adding an oral contraceptive should outweigh the risks associated to these drugs. Others suggest adding a dopamine receptor agonist (such as bromocriptine, amantadine or cabergoline) to reverse hyperprolactinemia and enhance BMD, but this might exacerbate psychotic symptoms. In one study, 20 women treated with risperidone who were experiencing mild to moderate hyperprolactinemia accepted a treatment with either bromocriptine or Peony-Glycyrrhiza Decoction (PGD), a herbal medicine with antispasmodic properties. The results showed that PGD was as effective as bromocriptine to decrease prolactin with a significantly greater improvement of adverse effects without exacerbating psychosis [116]. Finally, when all other options have failed, some clinicians might consider adding aripiprazole to potent D_2 blockers such as haloperidol, since a study showed that this combination normalized prolactin levels in 88.5% of 55 patients after an 8-week trial compared to 3.6% with placebo [115]. For all the above suggestions, risks and benefits of treatment should be assessed and discussed with the patient and prolactin levels monitored at 1- and 6-month intervals. Prolactin level monitoring should then be obtained when symptoms appear or multiple risk factors of hyperprolactinemia and its complications are present.

Bone mineral density

BMD reduction and osteoporosis are multifactorial but are also long-term complications of antipsychotics use that might result from chronic hyperprolactinemia. Since prolactin inhibits the release of hypothalamic gonadotropin-releasing hormone (GnRH) and thus decreases gonadotropins (luteinizing hormone or LH and follicle-stimulating hormone or FSH), hyperprolactinemia then causes a decrease in estrogen and testosterone levels. This decrease in sex steroid levels might be responsible for menstrual abnormalities, infertility or subfertility and decreased BMD seen with chronic use of prolactin-raising antipsychotics. A study of 55 patients who were treated with a prolactin-raising antipsychotic for over 10 years showed that 57% of males and 32% of females (all post-menopausal) had age-significant reduced BMD. Medication dose and low testosterone levels (in males) were correlated to the bone loss [116]. Another study of 38 women showed that 65% of the prolactin-raising group compared to 17% of the olanzapine group had low BMD, while 95% of those who had low BMD had also hyperprolactinémie [117].

SIADH

Water and electrolyte balances are mainly regulated by the hormone vasopressin (also called antidiuretic hormone or ADH). ADH stimulates reabsorption of free water in the kidney when hyperosmolality, hypotension or decreased plasma volume are detected. When ADH is released in the absence of appropriate osmotic and

non-osmotic stimuli, hyponatremia and serum hypo-osmolality are the result [118]. This condition is called the syndrome of inappropriate secretion of antidiuretic hormone or SIADH. It is often undiagnosed and can cause serious neurological damage and death. Antipsychotic-induced SIADH is thought to be the result of 5HT₂ and 5HT_{1c} stimulating activity on central ADH secretion while D₂-agonism seems to potentiate the kidney response to ADH [119]. There are 10 case reports of SIADH induced by AAs, namely aripiprazole, quetiapine, clozapine, risperidone, olanzapine or ziprasidone. With aripiprazole, SIADH-associated hyponatremia appeared within the first four days of medication initiation. For the other antipsychotics, onset time varied between 7 and 50 days [119]. Symptoms include agitation, confusion and delirium, and can evolve to hypotonic encephalopathy and seizures with natremia <120 mEq/l. If hyponatremia worsens, cerebral herniation secondary to cerebral edema and respiratory arrest might develop [118].

The different etiologies and pathophysiologies of hyponatremia are outwith the scope of this chapter. Nevertheless, hyponatremia caused by SIADH should be distinguished from electrolytic imbalance induced by primary or secondary polydipsia (also called potomania) which is highly prevalent in patients with chronic psychosis. Table 17.10 summarizes features to help the clinician differentiate between both conditions. It is estimated that 25% of patients suffering from schizophrenia have either primary or secondary polydipsia but not all will present hyponatremia [118]. Polydipsia has been attributed to dry mouth, positive, negative, cognitive and disorganization symptoms, nicotine, diabetes, tumors, lithium and other drugs side effects [120, 121]. Initial clinical signs of polydipsia may include polyuria, nycturia and enuresis. Usually, hyponatremia secondary to polydipsia develops gradually over months or years of treatment. Symptoms are therefore more insidious than with SIADH. As the hyponatremia progresses, minor cognitive and behavioral symptoms appear. With sodium levels under 125 mEq/l, the patient might suffer from nausea, vomiting, irritability, anxiety, lethargy, confusion and muscle cramps. Other symptoms such as impaired response to stimuli, hallucinations and bizarre behaviors can also appear. This chronic type of water intoxication is characterized by serum sodium levels between 115 and 132 mEq/l and is associated with an increased risk of falls secondary to gait disturbances.

In patients with hyponatremia, we recommend morning and late afternoon serum and urinary electrolytes and osmolality. Significant differences in results of these measurements are seen in polydipsia but not with SIADH (see Table 17.10). Renal function, blood glucose and thyroid function will help to eliminate other causes of hyponatremia. Rapid-onset hyponatremia secondary to SIADH is a medical emergency and rapid intervention to normalize sodium levels is necessary. Chronic hyponatremia secondary to polydipsia can be slowly corrected by fluid restriction only and removal of the underlying cause when possible. There is some evidence that clozapine and quetiapine can improve polydipsic behaviors and normalize serum sodium levels [120].

Table 17.10 Hyponatremia: SIADH vs primary polydipsia.

Diagnosis	Polydipsia	Polyuria	Onset of hypernatremia	Daily weight gain	Serum sodium (mEq/l)	Urinary osmolality (mOsm/l)	Urinary osmolality (mOsm/l)
Normal	None	None	Normal	Minimal	135–145	300–800	300–800
Primary polydipsia	Yes	Yes (secondary to polydipsia)	Slow (months to years)	Yes 2–3 kg	<135	Very low	Very low
SIADH	None	None	Rapid (days to weeks)	Minimal	<135	Very high compared to plasma	Very high compared to plasma

Seizures

The propensity of a drug to elicit seizures in a given individual depends upon a number of factors such as individual or family history of epilepsy, medical and neurological comorbidities, history of head trauma and polypharmacy. Psychotic disorders, depression and obsessive-compulsive disorder are also associated with reduced seizure threshold [122].

Antipsychotics differ in their potential to elicit seizures. The literature identifies chlorpromazine and clozapine as having the greatest risk [123]. Olanzapine, risperidone, quetiapine and ziprasidone generally have comparable risk. Aripiprazole may confer lower risk [124]. A review by Hedges *et al.* reports overall risk for seizures associated with CAs to vary between 0.5 and 0.9% (with the exception of chlorpromazine, the figure for which seems to be higher). The reasons for differences among antipsychotics still remain unclear but are suspected to be associated with their affinity for different receptors in the brain. The overall risk of seizure induction with antipsychotics is not so alarming when one takes into account that the yearly incidence rate of a first seizure in the general population is around 0.8% [125]. The type of seizure most frequently observed is generalized, tonic-clonic but other types, such as myoclonic and also atonic seizures may occur [126].

Documented electroencephalographic (EEG) changes associated with antipsychotics include general slowing of background activity, increase in paroxysmal theta or delta activity and the development of epileptiform discharges [127]. Clozapine has relatively frequent associated EEG changes, in up to 47% of patients [128]. Nonetheless, the clinical significance of these changes is not well defined and is not predictive of seizures [126].

Risk varies with dosage and blood-level of the antipsychotic. For example, there is a gradation for seizure incidence associated with clozapine according to dose: the incidence is 1% with doses less than 300 mg/day, 2.7% between 300 mg/day and 599 mg/day and 4.4% with doses higher than 599 mg/day [129].

Basic recommendations to prevent seizures associated with antipsychotics are to increase doses slowly and to use a minimal, efficacious dose. Increasing clozapine by more than 100 mg per week exposes a patient to more risk for convulsions. There is no need to avoid a particular drug in patients with epilepsy, or to rule out the use of a certain drug forever if new seizure phenomenon occurs. Naturally, individual risks vs benefits need to be weighed. We recommend that each patient be investigated neurologically immediately after seizures. It would be wise to withhold the antipsychotic being used until careful investigation has been completed. Afterwards, if judged necessary, the drug can be reintroduced at a lower dose if possible. The plasmatic level of drugs may be monitored, especially in cases of suspected metabolic interactions. Antiepileptic drugs may be indicated, especially when aggressive behavior or associated mood disorders are present. Valproic acid is recommended in patients treated with clozapine if they have had previous seizures, with or without clozapine if myoclonic jerks are present or if they have had brain trauma or other neurological abnormalities. Prophylaxis with valproate is recommended when doses of clozapine exceed 550 mg/day. There are case reports of treatment of clozapine-related seizures with gabapentin and topiramate. Carbamazepine is avoided, as it confers an

additional risk of blood dyscrasias. Phenytoin is also avoided for its numerous drug interactions.

Neuroleptic malignant syndrome

NMS is a rarely occurring idiosyncratic reaction to antipsychotics. Its incidence has diminished since its original description in 1967 and is now thought to be around 0.02% [130]. Although potentially fatal, the syndrome's mortality rate is estimated at 10–20% but it has decreased over time [131].

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) has elaborated descriptive research criteria which define NMS (Table 17.11). They encompass signs and symptoms of autonomic instability and altered level of consciousness. Elevated temperature and muscle rigidity are the pivotal signs to which must be added at least two of the other 10 criteria of non-specific laboratory findings, signs or symptoms. Muscle rigidity may not necessarily be present in some cases of NMS caused by AAs [132]. Differential diagnosis of neuroleptic syndrome is summarized in Table 17.12.

Table 17.11 Research criteria for neuroleptic malignant syndrome (DSM-IV-TR).

The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
Two (or more) of the following:
Diaphoresis
Dysphagia
Tremor
Incontinence
Changes in level of consciousness ranging from confusion to coma
Mutism
Tachycardia
Elevated or labile blood pressure
Leukocytosis
Laboratory evidence of muscle injury (e.g. elevated creatinine phosphokinase or CPK)
The symptoms in Criteria A and B are not due to another substance (e.g. phencyclidine) or a neurological or other general medical condition (e.g. viral encephalitis).
The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g. mood disorder with catatonic features).

The insidious changes associated with NMS must take place after recent initiation of an antipsychotic, as two-thirds of cases occur within the first week. Rarely does the syndrome occur after a month unless there was a recent dose augmentation or an additional antipsychotic added.

Pathophysiology of NMS remains unclear but the best hypothesis involves the diminished level of dopaminergic activity in the central nervous system (CNS), more specifically in the nigrostriatal pathway. Supporting this hypothesis is that individual drug's potency to block D₂ receptors seems linked to their individual risk for the syndrome. Additionally, dopamine's main metabolite, homovanillic acid, is

Table 17.12 Differential diagnosis of neuroleptic syndrome.

<ul style="list-style-type: none">• Benign extrapyramidal signs• Malignant hyperthermia• Serotonin syndrome• Delirium• Drug intoxication (more specifically hallucinogens, ecstasy and stimulants)• Drug withdrawal (more specifically from alcohol and sedatives)• Catatonia associated with mental illness such as affective disorders or schizophrenia• Systemic or CNS infections• CNS anatomical lesions

diminished in cerebral spinal fluid of acutely ill patients with NMS [130]. Virtually all antidopaminergic drugs have case reports of NMS.

As for risk factors, there is no formal consensus on what concerns innate patient characteristics such as gender, age or race. Treatment factors on the other hand, are recognized as having considerable importance. Pharmacological characteristics increasing risk for NMS include high D₂-affinity, parenteral administration, high dosage and rapid titration. Variable factors such as dehydration, previous catatonic state, severe exhaustion and underlying CNS abnormalities are recognized as contributing factors [131].

Untreated NMS is self-limited in the vast majority of cases, considering there is prompt withdrawal of all antidopaminergic agents. This is the undisputable first action to take. The syndrome's average duration after this stage lasts up to two weeks [133]. Supportive therapy is generally sufficient. It includes aggressive volume correction, antipyretic measures and prevention and treatment of possible complications. Complications include rhabdomyolysis and secondary renal dysfunction, aspiration pneumonia and deterioration of cardio-respiratory function. Benzodiazepines have some evidence of improving clinical course. Dopaminergic agonists such as bromocriptine remain controversial. Dopamine agonists may hasten recovery but carry the risk of potential dangerous effects such as rebound symptoms or unwanted secondary effects. Muscle relaxants such as dantrolene may have a role in extreme cases where severe muscle rigidity is a problem but may not yet be considered evidence-based [134]. There are many reports on the use of electroconvulsive therapy, which is generally regarded as efficacious but reserved for extreme or resistant cases. Reintroduction of antipsychotics brings about recurrence of the syndrome in as high as in one-third of cases. If inevitable, one should reinstitute treatment only 2 weeks after recovery and choose an antipsychotic with less D₂-affinity.

There have been a few reports of a rise in muscular-type creatine kinase (CK-MM) secondary to antipsychotic use. This complication is to be distinguished from known causes of CK elevation, notably muscle injury, NMS, acute psychosis and delirium. CK-MM due to antipsychotics seems to occur within the first days of treatment [135]. The mechanism responsible for CK elevation remains unspecified but direct muscle toxicity is suspected. Olanzapine may be more likely as a cause than other antipsychotics. It has been suggested that CK levels should be monitored to prevent renal failure [136], but no precise guidelines exist for this. The levels may normalize

without discontinuation of treatment, but careful follow-up is required when the phenomenon is observed.

Hepatic

Both CAs and AAs may disturb liver function tests (LFTs) as reflected by elevations in the hepatic aminotransferases alanine aminotransferase (ALT) and aspartate aminotransferase (AST). There are probably individual differences among the antipsychotics in their likelihood to induce abnormal LFTs [137]. Although mild elevation in LFTs may occur in as much as 50% of patients taking antipsychotics, serious liver damage has rarely been reported [138]. Most cases are asymptomatic, mild (less than threefold) and transient (<1 month) even when the drug is continued. Symptomatic changes can include hepatitis or jaundice from cholestasis and severe hepatic damage may manifest itself by neurocognitive changes. There has been at least one fatal case of hepatotoxicity presumably caused by clozapine [139]. Liver cell damage affects the metabolism of many other drugs.

Pathophysiology may imply direct hepatic cell damage or immuno-allergic reactions [140]. Amisulpride has hepatic metabolism of minor significance but has also been associated with a moderate rise in aminotransferases which may suggest that indirect mechanisms may be playing a role [141]. One example of a possible indirect, toxic hepatic effect of antipsychotics may involve leptin, a cytokine which was found to induce inflammation in the liver. Leptin levels rise secondary to increased food intake but also in response to some antipsychotics.

Elevation of aminotransferases related to AAs is thought to be unrelated to dose. Other risk factors may include high plasmatic concentration of the antipsychotic, older age, alcoholism, simultaneous drug-abuse, obesity and history of hepatic disorder [142]. Some drugs may also multiply the risk, notably antiepileptic drugs such as valproic acid.

To date, there is no consensus on specific recommendations for the follow-up of liver enzymes during antipsychotic treatment. The clinician needs to rely on his judgment of risk assessment based on concurring factors elevating this risk. It is customary to assess liver function before initiating treatment and to repeat this at one and three months, thereafter annually. However, the delay for hepatic injury varies considerably in the literature, from 1 week to 17 months [143]. The decision to discontinue treatment is probably judicious when a persistent (>1 month) threefold rise occurs. It also depends on the disadvantages or advantages of a possible switch and the feasibility to maintain supervision of liver function.

Hematological

Blood dyscrasia is an adverse effect known to occur with most if not all antipsychotics. However, hematological monitoring is regulated only for clozapine because of the frequency and severity in decreasing white blood cell (WBC) count. Incidence is estimated to be 10 times more frequent than compared to other antipsychotics. This adverse effect has limited clozapine use and is a reason for discontinuation in patients otherwise known as responders.

In the first year of treatment, the cumulative incidence of agranulocytosis (neutrophil count $<0.5 \times 10^9/l$) and neutropenia (neutrophil count $<3.0 \times 10^9/l$) varies between 0.58–0.8% and 2.3–8.5%, respectively [144–147]. However, 53–89% of the cases of agranulocytosis occur between the first 6–18 weeks of treatment [145, 146]. Because this major adverse effect can lead to major health problems or death due to severe infections, most countries require weekly monitoring of WBC count during the first 18–26 weeks and thereafter bimonthly or monthly throughout clozapine treatment. Race, notably Black and Asian ethnicity, increasing age [144, 145] and gender [144] have been reported to represent additional risk factors. The disorder is reversible if clozapine is withdrawn.

Agranulocytosis and neutropenia has been observed within a few days or few weeks after adding a number of drugs, namely some antibiotics, valproic acid, antidepressants or another antipsychotic to clozapine-treated patients. Late-onset neutropenia, even after years of treatment with clozapine, can occur with or without the addition of concomitant medication and suggest that WBC monitoring should be maintained throughout treatment. In patients who have developed agranulocytosis or neutropenia, rechallenge with clozapine will be tolerated in 62% of the patients without recurrent blood dyscrasia [148]. Anecdotal cases have reported an increase of WBC after adding lithium [149]. Nevertheless, this strategy is not always efficacious and is not recommended unless the response to clozapine is significant. Subcutaneous injections of filgrastim (granulocyte-colony stimulating factor or G-CSF) can be administered daily on a short-term basis to hasten marrow recovery thus reducing the risk of infections in severe agranulocytosis.

Thrombocytopenia [150] and thrombocytosis [151] have been reported and one should consider stopping clozapine if platelet count is lower than $100\,000/\mu l$ or above $450\,000/\mu l$. Eosinophilia with clozapine requires the vigilance of the physician, because it may precede neutropenia but foremost myocarditis. When anomalies of other blood cells line are detected, it is necessary to look for other physical signs and symptoms and pursue a medical investigation.

Anticholinergic side effects

Anticholinergic side effects of antipsychotics are related to their muscarinic antagonistic activity. Here, we will review the main anticholinergic side effects, with an emphasis on constipation, urinary retention and delirium and review the risk factors and general treatment.

Constipation

Constipation is a very common side effect of antipsychotics but only clozapine and quetiapine have published case reports describing it. It occurs in 14–60% of clozapine and 8% of quetiapine users. One case series [152] of five patients linked quetiapine and constipation, with a possible dose-response relationship. Important constipation appeared at dosage 1000 mg and over (one patient taking 700 mg). Clozapine has been associated with more severe cases of constipation and a clozapine-induced

gastrointestinal hypomotility (CIGH) syndrome that ranges from esophageal immobility and dysphagia to ileus, intestinal obstruction, bowel ischemia, megacolon and colon perforation. A recent analysis of 102 cases of CIGH [153] included patients with a median age of 42 years old, two-third male, clozapine dose ranging from 12.5 to 1000 mg/day (mean = 428 mg/day) and duration of treatment ranging from 3 days to 15 years. The prevalence of potentially life-threatening CIGH is estimated at around 3 cases per 1000 patients exposed to clozapine. In that series, 27% of patients died from CIGH. The syndrome developed within the first month of treatment in 20% and within the first year in 50% of all patients. It is noteworthy that 20% of patients received a concomitant anticholinergic drug and 14% another drug that could cause constipation. The more frequent symptoms of CIGH were abdominal pain (73%), abdominal distension (55%), vomiting (55%), constipation (45%), diarrhea (32%) and nausea (23%), but 32% of patients presented in an already septic shock state (tachycardia and hypotension).

Prevention of antipsychotic-induced constipation comprises high-fiber diet, adequate fluid intake and exercise. If a patient complains of constipation, stool softeners and bulk-forming laxatives should be prescribed [102] and the bowel function monitored. Clinicians should avoid combining constipating drugs, particularly those with anticholinergic activity. Clozapine should be temporarily reduced or gradually discontinued and referral to a specialist considered when multiple signs of CIGH (e.g. pain, vomiting, obstruction or septic shock) are present. It is not clear if a rechallenge can be considered or not after a severe CIGH [154].

Urinary Retention

Anticholinergic drugs are known to be associated with urinary hesitancy or retention. This can result in secondary overflow incontinence, enuresis and an increased risk of urinary tract infections and even sepsis [102]. Although those side effects are rarer with AAs, there are some case reports linking urinary hesitation or retention to risperidone, quetiapine, olanzapine (dose-dependent relationship) and more frequently with ziprasidone [155]. It seems that the stimulation of the α_1 -adrenergic receptor may be partly responsible for this.

When faced with antipsychotic-induced urinary hesitancy or retention, the clinician should rule out urinary infections and structural defects, minimize the dose of the offending agent and eliminate as much as possible the combination with other anticholinergic or α_1 -adrenergic active drugs. In the case of incontinence or enuresis, monitoring fluid intake, voiding before going to bed and in the middle of the night and limiting diuretic use (including caffeine and alcohol) can be useful. Switching to another antipsychotic should be considered before opting for a trial with ephedrine, intranasal desmopressin or oxybutynin [102].

Other peripheral side effects

Dry mouth or xerostomia [156], dilated pupils, blurred vision, decreased sweating and tachycardia are all possible peripheral anticholinergic side effects of antipsychotics. Table 17.13 summarizes their potential complications.

Table 17.13 Peripheral anticholinergic side effects of antipsychotic agents.

Peripheral effects	Potential medical complications
Decreased salivation	Dental caries, ulceration of gums and buccal mucosa
Decreased bronchial secretions	Mucous plugging of small airways in patients with asthma or bronchitis
Decreased sweating	Hyperthermia
Increased pupil size	Photophobia, precipitation of acute narrow angle glaucoma
Inhibition of accommodation	Blurred vision, especially when reading small print
Increased heart rate	Angina, myocardial infarction
Difficulty urinating	Bladder distention, urinary retention
Decreased gastrointestinal motility	Constipation

Source: Table from Lieberman [154].

Central side effects

While AAs became popular because of their potential to improve cognitive functioning in patients suffering from schizophrenia, there is some evidence that they may sometimes worsen it because of their central anticholinergic activity. The same is true about CAs. Central anticholinergic side effects range from impaired concentration and attention deficits to confusion, memory impairment and delirium. Although antipsychotics are successfully used to treat delirium, sometimes they provoke or worsen it. Anticholinergic delirium is characterized by confusion, disorientation and hot and dry skin, dry mucous membranes, dilated pupils, absence of bowel sounds and tachycardia [154]. Some case-reports link olanzapine, and clozapine to delirium [102]. Most include elderly patients or those with CNS disease, terminally ill patients and those suffering from dementia. One open-label study of olanzapine for delirium in patients with cancer reported a worsening of delirium in some patients (all were over 80 years of age) [157]. Clozapine-induced delirium has been estimated to range from 2.1 to 10%, with some case reports in otherwise healthy middle-aged (e.g. 44 years of age) schizophrenic patients [158].

Finally, it should be emphasized that anticholinergic side effects of antipsychotics, whether central or peripheral, can sometimes be benign but sometimes very disabling, contribute to falls and rarely be fatal. Vulnerable populations are the elderly, those with CNS diseases, those with medical conditions that could be worsened by anticholinergic drugs (e.g. narrow angle glaucoma, prostatic benign hypertrophy, Crohn disease etc.) and those with polypharmacy. The general management of anticholinergic side effects includes reducing the dose of the offending drug, decreasing the rate of dose titration, minimizing polypharmacy and sometimes switching antipsychotics when possible and specific treatment for the specific complication. This being said, one should always be careful in the process of reducing the dosage of a drug with an anticholinergic activity because of a possible anticholinergic rebound.

Stroke and thromboembolism

Cases of thromboembolism have been reported early after the introduction of chlorpromazine. Subsequent field studies in the late 1950s and 1960s suggested an incidence rate close to 3%, pulmonary embolism being the most frequently reported vascular event [159]. Among patients younger than 60 years, increased risk has been observed with lower potency CAs such as chlorpromazine and thioridazine compared to haloperidol [160]. A retrospective studies on nursing home residents indicate that patients treated with an AA are 2–3 times more at risk of being hospitalized for venous thromboembolism compared to a treatment with CAs or any other medication [161]. Hospitalizations started early within 30–60 days after initiating a treatment with an AA. Higher risk of mortality due to pulmonary embolism in patients aged less than 54 have been reported with clozapine [162]. In a medicalegal autopsy series, fatal pulmonary embolism was overrepresented among patients treated with lower potency CAs and even more so with AAs [163]. Odds ratio varied from 2.39 for lower potency CAs to 6.9 for AAs. The risk was much lower with high potency CAs.

In a recent study, both CAs and AAs increased the incidence of first-ever stroke in elderly patients [164]. For most patients the interval between initiation of treatment and stroke varied from 26 to 120 days. Risk factors included older age (>80), gender (male), severity of a chronic disease, medical co-morbidities and concurrent treatment with an anticoagulant medication.

It is proposed that antipsychotics, and more so lower potency CAs and AAs, increases platelets aggregation by acting on platelets 5-HT₂ receptors. Other factors such as polypharmacy, venous stasis exacerbated by excessive sedation and physical restraint, raised levels of antiphospholipid antibodies and homocysteinemia are possible confounders [159, 161].

Mortality

There is increasing evidence that higher all-cause mortality is observe in elderly patients with dementia treated with an antipsychotic. In 2005, the FDA asked that drug manufacturers add a ‘black box’ warning to inform physicians of the increased mortality risk with AAs. This decision was based on a meta-analysis of 17 double-blind randomized placebo-controlled trials showing a 1.7 times greater mortality with AAs than with placebo. Compared to no treatment or other psychotropic drugs, recent studies have confirmed higher mortality with antipsychotics and the risk may even be higher than initially reported [165–167]. Higher mortality is documented within the first 30 days and remains higher throughout the following 12 months of treatment. It is unclear if the risk is higher with AAs compared to CAs, but a combination of both classes seems to increase the risk [165]. These finding are extremely relevant considering that antipsychotics have not always yielded significant therapeutic benefits or, at the most modest, in relieving psychosis or behavioral disturbances in demented patients [168, 169]. A white paper by the American College of Neuropsychopharmacology (ACNP) recommends using the lowest dosages and targeting symptoms that are persistent or recurrent and cause significant functional disruption [170].

Mortality attributed to antipsychotics has not been reported nor systematically studied in other psychiatric disorders. In one study, polypharmacy with antipsychotics was suspected to increase mortality in schizophrenia [171]. Clozapine appears to decrease mortality mostly by decreasing suicide rates but increases mortality for less common causes such as respiratory disorders and pulmonary embolism [162]. Sudden death with clozapine may be higher than with other antipsychotics [172].

Immunology

Over the past decade, several findings have suggested a role for the immune system in the pathogenesis of major psychiatric disorders [173]. Several immune markers indicate an inflammatory state in many psychiatric patients. Cytokines are small proteins or peptides with a role as humoral mediators of infection and inflammation. They are secreted by several cell types, notably WBCs, and in the brain by microglia and astrocytes. AA drugs decrease the synthesis of pro-inflammatory cytokines and promote the synthesis of anti-inflammatory cytokines compared to haloperidol, which has very little effect on immune parameters [174]. In a retrospective study, clozapine was shown to be associated with an increase use of antibiotics in patients with normal WBC count [175]. It was proposed that the increase in number of infections was caused by the interaction of clozapine on cytokines secretion. Also, as previously mentioned, immune-like reactions may be responsible for myocarditis and other organ-specific related reactions.

Rare adverse events

Among rare adverse effects seen with antipsychotics are various cutaneous reactions, hypersalivation, pancreatitis, pigmentary retinopathies and cataracts.

Non-specific skin rashes occur in approximately 5% of individuals taking antipsychotics. Exanthematous eruptions, skin pigmentation changes, photosensitivity, urticaria and pruritus are among the most frequent cutaneous adverse effects. Only a very small percentage of these pose important risk [176]. Photosensitivity has mostly been reported with chlorpromazine. It is generally thought wise to replace the agent in any case of eruption, although the question of risk versus benefit always remains.

Hypersalivation, otherwise known as sialorrhea, may be caused by antipsychotics (more frequently so with clozapine). It can lead to stigmatization or other unfortunate effects such as nausea. The pathophysiological basis is unclear but may involve overproduction of saliva or impaired swallowing which results in overflow. Sialogogues are either muscarinic agonists, peripheral alpha-2 adrenoreceptor antagonists or centrally acting agents that reduce adrenergic tone [177]. Pharmacological treatment of medication-induced sialorrhea aims to decrease amounts of saliva. There exists a variety of possible pharmacological interventions, none of which have been found superior to the others [178]. They include: reduction of cholinergic tone, either systemically with oral anticholinergics, or locally with sublingual ipratropium spray, or increasing adrenergic tone, for instance with a clonidine patch. Botulinum

injections into the parotid gland have recently been used successfully to treat refractory cases, which require to be repeated every 3–4 months.

The literature does not agree on whether there is an increased incidence of pancreatitis with AAs or CAs. One study reports increased risk with clozapine, olanzapine, risperidone and lastly, haloperidol, in decreasing order [179]. Another demonstrated increased risk of hospitalization for acute pancreatitis in low-potency CAs (relative risk or RR 1.6) only, versus current or former use of an AA (RR 0.6 and 0.3 respectively) [180].

Although there have been several hypotheses for the possible retinotoxic effects of thioridazine, an actual mechanism for an iatrogenic form of retinitis pigmentosa remains unfounded. However, clinicians must remain vigilant of this rare adverse reaction with any antipsychotic treatment [181]. Cataracts have been a concern mainly with phenothiazines and do not seem to occur as much in patients taking AAs [182]. Cataract occurrence in canines, which were given considerable doses of quetiapine, brought about recommendations for periodic ocular exams in individuals on long-term treatment with AAs. It was more recently concluded that cataracts secondary to quetiapine are unlikely, and that biannual ophthalmic examinations are simply unnecessary [183]. There have been a few case reports of cataracts in patients on olanzapine and ziprasidone but again, no known causal link has been elucidated [184].

17.3 Discontinuation symptoms

Antipsychotics bind to several receptors but discontinuation symptoms have been attributed essentially to dopaminergic and cholinergic rebound activity. Withdrawal symptoms in response to a sudden drop in anticholinergic activity encompass gastrointestinal symptoms, headache, mild agitation, anxiety, insomnia, akathisia and parkinsonism. Symptoms occur from days 7–10 after discontinuation of an antipsychotic. Buckley *et al.* and Seppala *et al.* [185, 186] found that patients who discontinue an anticholinergic antipsychotic were less likely to deteriorate if they continue other anticholinergic medication such as a tricyclic antidepressant or an antiparkinsonian.

When antipsychotics are discontinued abruptly, patients are exposed to a rebound or supersensitivity psychosis. This phenomenon is attributed to the sudden release of dopamine in response to prolonged antidopaminergic activity. The phenomenon was initially brought to the attention of clinicians when clozapine had to be suddenly ceased due to agranulocytosis [187]. The switch to an antipsychotic with partial dopaminergic agonism or with a longer half-life before achieving a steady state may also give rise to rebound symptoms. Theoretically, rebound psychosis may also occur when a new drug with weak receptor occupancy replaces a drug that had resulted in important up-regulation of that receptor.

Discontinuation symptoms seem to occur more often but not exclusively with clozapine compared to other antipsychotics. A very large variety of symptoms have been reported upon rapid discontinuation of clozapine such as: headaches, nausea, vomiting, diarrhea, agitation, delirium, stupor, catatonia, auditory hallucinations and

suicidal ideation. Quick deterioration of half of the patients was measured after clozapine withdrawal [186]. Furthermore, patients with Parkinson's disease and psychosis having discontinued their antipsychotic, either quetiapine or clozapine, experienced rebound psychoses almost without exception [188]. In addition to this, discontinuation of clozapine may lead to a deterioration in the quality of subsequent remission and result in the need for higher dosages than in patients who continued treatment uninterrupted [189]. We therefore emphasize the need for active reinforcement of compliance in patients taking antipsychotics, particularly clozapine, and psychoeducation on the need for continued treatment and gradual cessation.

17.4 Conclusion

Antipsychotics have now been used for over 50 years. They have benefited patients that would otherwise have been disabled by their symptoms and it has improved their quality of life. Clinicians may now choose among a greater number of drugs to treat patients with efficiency. Nevertheless, adverse events are still present with newer drugs and they continue to be of some concern. Using antipsychotics for off-labeled indications is to be done with extreme prudence because of unknown risk of adverse events. To increase adherence to treatment, physicians should inform patients on frequently encountered adverse events. When present, adverse events should be addressed rapidly so that dosage changes or even a drug substitution can be discussed before the patient discontinues their medication. AAs were thought initially to be superior and produce less adverse events than CAs. However, adverse events caused by AAs are now better identified due to several independent clinical studies. Some researchers have even stated that, compared to CAs, AAs do not represent major gains in effectiveness or tolerability [190].

Sufficient data has been gathered over the past decade on the pharmacological profile and clinical adverse events to recognize that AAs differ among themselves and they represent, like CAs, a heterogeneous group of drugs. For these reasons, it seems misleading to continue regrouping antipsychotics into two classes; a pharmacological classification is desirable.

It remains puzzling that frequently encountered adverse events such as weight gain, diabetes and hyperlipidemia, which have become such an issue with AAs, were undetected in pre-clinical trials. One can imagine that low incidence but potentially dangerous adverse events can go undetected for long periods of time after a drug is commercialized. Postmarketing surveillance, single case reports and independent clinical trials therefore remain extremely important to ensure patients' safety.

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18

Meta Musings on Methodology

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Abstract

Clinical trials are the gold standard methodology used to evaluate treatment efficacy. Federal agencies invoke strict regulations that lead to increasingly standardized approaches to conducting trials. The author argues that this standardized approach may stifle the creative development of new research and ultimately reduce the production and availability of medications available to the public. Assumptions regarding clinical trial methodology are presented along with benefits and limitations inherent in each.

Key Words

Clinical trials; History; Methodology; Placebo response; Missing data; Meta-analysis

18.1 Brief history of the clinical trial

The idea of clinical trials in medicine, at least upon the grand scale, is a product of the second half of the twentieth century.

Clinical trials to test therapeutic hypotheses, especially about the efficacy of medications, were not the accepted norm until as recent as the 1970s. Of course, the concept already had its advocates. One of the most articulate for it in America was the National Institutes of Health (NIH) administrator, Thomas Chalmers [1]. Indeed, however, the official biological research community harbored great skepticism, even hostility to the idea that large-scale trials would be worthy of the additional time, effort and expense they would require. When political support from above forced the NIH and related Institutes to consider funding clinical trials, the negative, internal within-the-bureaucracy response to the Nixon administration's pressure was even vituperative.

The central reason for the opposition was about funding. The NIH feared that, rather than appropriating additional funds to pay for clinical trials, the Federal government would force the Institutes to shift monies in their existing budgets to support such an initiative. One might say that there is a distinguished American tradition of trying to do more with already limited resources.

At the time that clinical trials emerged as a significant scientific and political issue, the NIH funded studies in human beings that typically involved a double digit number of volunteer subjects (ss). Arguably, these experiments may have been designed to do the most with the least cost. Some of them involved fewer than 20 ss because, with tight designs, this might be sufficient to demonstrate treatment differences at a $p > 0.05$.

Advocates of the more extensive trials eventually carried the day. Their arguments for cooperative sizeable studies included the following points.

- The smaller studies were all well and good. Ideally, all clinical trials should be vetted on a much more modest scale. Only in this way can potential pitfalls of design be detected, which the best of theoreticians could never have imagined.
- However, smaller n 's have their limitations. Let us suppose that $n = 20$. Let us further suppose that half of the group are on placebo, randomly assigned. Even if the small study displays statistically significant differences from placebo, small alterations in outcome, from a single digit number of ss, could dramatically affect the outcome or even reverse the results.
- By contrast, they speculated that in larger trials the results would be relatively impervious to systematic errors.
- By the same token, small differences in groups which might be important in the greater understanding of biochemical mechanisms (such as risks to human subjects) would more likely be detected if the samples were larger and more representative of the population of interest.

These disputes are hardly trivial. For many years, standard practice in the face of *Streptococcus B* infections was to treat with a full course of Penicillin (and later, other such antibiotics). It turns out that this practice rested largely, if not exclusively, upon a single experiment conducted by Ramelkamp at Western Reserve in the 1950s [2]. The result was clear-cut. It showed that:

- 1 the antibiotic did, in fact, overcome most infections within two weeks;
- 2 the fate of the placebo recipients was, on average, that the infections continued to rage.

Since we now think that longer-term negative sequelae of *Streptococcus B* infections can be devastating, including rheumatic fever, this paper had a profound and lasting impact upon clinical practice.

Louis Weinstein made the point in the 1960s that the ready adoption of immediate treatment as the benchmark for such infections had now made it impossible to replicate, confirm or expand upon the original experiment [3, 4]. If more work had gone into the original results before they were published, our confidence in the result would be much stronger.

Ironically, what was considered heretical in 1970s has now long since become the gold standard for approval of medications as clinical treatments, certainly by the Food and Drug Administration (FDA) and even by the NIH. In addition to this, the ground rules for conducting such trials have grown increasingly rigid and formulaic. On the one hand, this approach leads to greater standardization and clearer expectations on the part of the regulators and the pharmaceutical companies. Whether it leads to (i) greater confidence in the outcomes of licensure of medications or (ii) promotion of creative new treatments, which might be improvements on existing benchmark regimens, remains to be seen.

Some readers will undoubtedly object that when the results of experiments seem to be clear, and the result of non-treatment may be devastating, experiments should be discontinued and publication be immediate. This may be framed as an ethical issue. Whatever one's beliefs about the ethics involved, there is no reason to think that this is why Ramelkamp published the data when he did. Nor had these matters been thought through in the ethical sphere at the time the experiment was conducted.

Lest this point be considered an academic quibble, let it be understood that the American FDA often requires pharmaceutical companies to include a placebo arm in clinical trials. In fact, this is even true where the efficacy of other active, possible comparator treatments has already been accepted by the same regulatory agency.

18.2 Criticisms of assumptions about clinical trials methodology

What are the assumptions made regarding clinical trials (with particular reference to psychiatry and neurology) and how are they translated into practice?

All subjects are equal

Trials are meant to induct volunteers whose diagnostic condition and health status are as similar as possible (or where differences are at least reliably measurable). Where restrictions are imposed, these are clear and readily identifiable. For example, these typically include age and sex.

On the other hand, they most commonly do not take into account race, ethnicity or geographical distribution. Often they also finesse matters of socioeconomic status (SES). It is as if, for most purposes, these factors are unimportant or that diseases are Equal Opportunity Oppressors which, for the most part, level everyone in much the same manner. (We already know, through many years of epidemiological study, that SES has profound effects upon the prevalence and severity of many diseases, for example: tuberculosis.) [5].

Bigger is better

As noted above, one of the most critical rationales for conducting clinical trials at all is that some significant effects can only be detected by substantially enlarging the sample size. Typically, at least in psychiatry, this means going from double to low triple digits in total numbers.

When numbers get into three digits, the temptation to use more complex methods of analysis grows. Until recently, however, tradition has frowned upon succumbing to such seductive irregularities. Instead, the most complex analysis generally considered standard is one of the more common multivariate analyses. The same may, perhaps, be said of unusual design methods. For example, when was the last time you read about an own-control model in a paper about a clinical trial? Notwithstanding that there are many such wrinkles in study design taught in graduate school, widely recognized as legitimate among reputable statisticians, they generally do not seem to have made much headway in penetrating the world of clinical trials.

Everybody everywhere is doing everything the same way

In order for larger samples to have greater power, it must be the case that standardization in methodologies of execution is rigorous at all sites. This proves to be a major challenge. First of all, independent professionals often feel they know better how to improve upon the stated design than the protocol might allow. The more frequently such deviations occur, the more invalid that the assumption of standardization becomes.

The most reasonable approach to controlling for likeness is a combination of training and oversight. The FDA encourages 'training' in order to ensure everyone understands the scales being administered and renders them as similarly as possible. Latterly, in a number of trials, raters are being examined by review of electronic tapes. At technologically advanced university centers, some more sophisticated programs actually re-check raters at monthly or even weekly intervals. They may ask all raters to attend a seminar to achieve a consensus about the 'right' questions and how to interpret the answers.

In psychiatry, many instruments are essentially structured interviews. Structured interviews are by nature far more complex. The same interviewer in the same situation may ask questions differently at a certain juncture during the interview. This can send the questioning down a totally different pathway from previously. Some standard structured interviews try to compensate for this problem via complex algorithms which, theoretically, will ultimately lead reliably to the same conclusions.

Double blind is the summum bonum of effectiveness

A very high percentage of clinical trials conforms to the model that the assignment of subjects to one of the arms of the study is beyond the control or knowledge of the participants or the researchers conducting the study. In recent times, this may be accomplished by a random number generator at a central site in order to further isolate subjects and researchers from access to the assignment codes.

Double blind also assumes that the people in the field cannot accurately detect whether active medication is being used by observing the effects upon the patient, especially unwanted side effects. Much has been written about this particular subject. For the moment, let us just say that the occurrence of significant compromise of the blind is dependent upon both the nature of the disease condition being tested and upon the effects of the drug.

Less attention has perhaps been paid as to how the study design itself may have impact on the threshold of detection. A double-blind trial typically compares an active medication with placebo (although other comparators are possible and sometimes employed). Where the placebo-response rate is high, the differential between active treatment and placebo may prove to be correspondingly small. Examples of this may be found in a variety of trials for treating anxiety disorders. General Anxiety Disorder (GAD) trials are notorious for attracting patient volunteers who may have high responder rates to placebo – possibly as high as 50% of the study population in some trials conducted in primary care practices.

At these rates, in order to display a significant difference between true responders and placebo response, the size of the sample needs to be so large as sometimes to be prohibitive (in the hundreds). What is more, at the conclusion of such a study it may appear as if the marginal advantage of active medication is really rather modest. To make matters worse, placebo responders may also be more sensitive to physical concerns. Hence, their reported rates of side effects may be correspondingly elevated, not to say outlandish.

Considering all these obstacles, it is a wonder that any medication passes the tests for effectiveness even when it works perfectly well in practice.

Significance at the $p > 0.05$ level against placebo

Significance at the $p > 0.05$ level against placebo is the gold standard for whether a medication is effective or not. The notion that the statistics can be wrong 1 out of 20 times and the result sufficiently good is the convention. Statisticians have noted that the choice is arbitrary. Depending upon the purpose for which the statistic is employed, greater or lesser standards may prove more rational. For example, if there are few safe and effective treatments for a given disease or condition, even marginal differences may be important to detect. This was the case in the early days of medication treatments for Alzheimer's disease. Cognex was approved at a time when it could safely be said to be an 'orphan drug', that is one for which there was no known established alternative treatment. It is hardly used any more, mainly because its side effect profile was so adverse. As many as 30–40% of the elderly (the patient population) could not tolerate it at a reasonable dose. The less tolerable a medication is, the more difficult it is to tell how effective it may be (since the dropout rate from studies is also likely to be large).

At the opposite pole, there are medications where the standard needs to be 100% effectiveness. This is the case, for instance, with contraceptives. (In actual fact, no contraceptive method is 100% effective. The difference between a 5% and a less-than-1% failure rate is enormously important.)

Last observation carried forward

'Last observation carried forward' (LOCF) is the accepted method for dealing with dropouts and lost data. As far as we can tell, this is about the only (certainly the predominate) way in which missing data is taken into account in clinical trials. In this set of assumptions, whatever was happening last in a time series is assumed to be predictive of what would have happened ultimately. Usually this means accepting the last data point as the endpoint of outcome.

Most statisticians would probably agree that ultimately there is no satisfactory method for compensating for lost data. Hence, one must decide which compromises are the most acceptable. The limitations of LOCF, including the following, are multiple.

- Adverse events are quite common in clinical trials. In fact, a very substantial sub-group (in some trials the majority) of patients experience some form of adverse events which are mostly minor, short-lived and usually quite clearly unrelated to the study. Life has its real events, and they are co-terminus with the study.
- The vast majority of adverse events resolve within the time period of the study. If followed after the official termination date, another minor (but substantial) group also resolve any adverse events without important consequences.
- The putative reason for cataloguing all events is that, in large enough samples, some subtle and unobvious consequences might be revealed. But isn't the major reason for conducting trials to determine possible negative consequences of the treatment?

Unfortunately, this kind of conservative reasoning can lead to errors of commitment: if it is thought that a drug's effects might be adverse, caution should err on the side of assuming the worst. If one is wearing the hat of a Federal regulator, this makes good (political) sense. Better to be above criticism than be condemned for failures of omission. However, errors of commitment also mean that treatments which are fresh and different may also be delayed or rejected for the wrong reasons.

18.3 Thoughts on alternative study designs

A variety of well-known study designs might address some of the limitations and weaknesses of present day clinical trials methodology.

'Own control' designs

These are treatment trials in which the patient volunteer serves as her/his own comparator. They require a minimum of two different time conditions during a trial,

for example at least one for each alternative treatment method. In such a model, efficacy and safety are measured separately under as similar conditions as possible and compared to each other.

Incidentally, the double-blind condition does not need to be compromised, any more so than it would be in the standard clinical trial methodology. What is more complex is the requirement to keep the differing conditions as separate and distinct as possible.

The potential power of 'own control' designs may also be greater, so that smaller sample sizes may also provide satisfactory answers to the study questions [6].

As well as the subtlety challenge, other limitations of this type of design include the mirror image of the standard design: namely, smaller sample sizes may be less representative of larger populations (although they also allow a thorough diagnosis in screening). In addition, if an adverse event occurs in the first phase of the study, how should one react? Supposing that this continues so that the comparator phase is compromised, then how one take the missing data into account? No answer to this question is totally satisfactory, but the problem is not obviously any worse than that of the standard method.

Analysis of (some) relatively objective study measures

Timed trials already examine whatever objective measures they can along the way at appropriate intervals, many at each patient visit. Under the standard method, these data are not generally examined until the dataset has been submitted, still blind, in 'final' form to the FDA.

More recently, some trials have undertaken to subject the ongoing to at least limited analysis at particular interim time points. If care is taken, this can be done with appropriate 'fire walls' among the collectors of data (the so-called field investigators), the recipients of the data at a central site and the interim analysts. Relative objectivity can therefore be made as stringent as possible.

Such interim analysis has the potential to check whether the longer, larger trial is actually on the right course. If not, sometimes it allows for appropriate design or implementation corrections which can ultimately rescue the trial. In such cases, where the result is already so strong that the trend to the outcome (good or bad) seems very likely, the trial can also be aborted at an early stage if necessary. (This is the counter to the historical argument about the rheumatic fever trial referred to above.)

Making use of meta-analyses

Meta-analysis is a relative newcomer to science and statistics. The unifying concept is that, with appropriate cautions, examinations of a cumulative set of studies of the same subject can begin to address some questions in a manner at least analogous to those of the standard clinical trial.

The criticisms of meta-analysis are many and sometimes offensive [7, 8] and include the following.

- The choice of inclusions/exclusions of studies may be capricious and arbitrary. How broadly the net is cast may well determine the outcome, rather than the nature of the study questions themselves.
- There is no consensus about appropriate statistical approaches to analyzing the data (although there are certainly methodologies described in the literature) [9].
- Characteristics of subjects and interventions may be so disparate as to make comparisons a mockery. This criticism is almost impossible to refute in entirety since, by definition, the studies collected were carried out under very different circumstances with usually little or no effort at comparability.

All these points have a degree of validity. However, to reject the general concept entirely is nihilistic. Meta-analysis, at the very least, can

- 1 suggest what directions more extensive trials might take;
- 2 underscore difficulties in methodology which need to be addressed in larger trials;
- 3 highlight potential toxicity or adverse events from particular treatments; and
- 4 redirect efforts to other approaches which might be more productive.

18.4 Conclusion: standardization can be stultifying

We have come a long way from the hostile rejection which clinical trials evoked in the 1960s. Arguably, hostile rejection has evolved into a set of cookbooks for bureaucrats, who review clinical trials with a very standard set of assumptions and approaches.

This standardization is well and good for certain purposes. It also makes for increased employment in the world of pharmaceutical companies, the sprawling industry of clinical trial intermediary firms and Federal reviewers. But does standardization produce sound, creative research? And does it ultimately serve the public good?

We have argued that the institution of standard methods for clinical trials has probably proved to be vastly superior to the seat-of-the-pants approach to new treatments earlier in the twentieth century. However, we seem to have reached the point where we may have gone vastly overboard in the rigidity of methodology for clinical trials. No good can come of this.

At the very least, some more open discussion about methodologies is appropriate. The public has a stake in such matters and accordingly should be represented in such discussions. In the early days of AIDS trials, AIDS activists virtually battered down the doors of the NIH to have their say; Fauci and others responded [10–12]. Many would say that these debates, often acrimonious, may have resulted in more balanced approaches to promising treatments. However, AIDS is a very special case;

many other diseases are not so immediately life-threatening. Alternatively, the public advocates of other conditions have been less aggressive and vocal.

In any event, democracy thrives upon discussion. For the most part, we make decisions by consensus. Where matters are unsettled, such discussions can be substantial and even aggressive. Without them, however, progress can unwittingly stall. The production of new, safe and effective treatments for disease has been a major priority of healthcare around the world. Clinical trials deserve periodic re-examination for their relevance, contribution and plasticity.

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Note: Abbreviations used in the index: ADHD = attention-deficit hyperactivity disorder;
SUDs = substance use disorders. Page numbers in *italic* refer to tables.

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