Milestones in Drug Therapy
Michael J. Parnham
Jacques Bruinvels
Series Editors

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy

Carlos A. Zarate Jr.
Husseini K. Manji
Editors

Birkhäuser

Milestones in Drug Therapy
MDT

Series Editors

Prof. Dr. Michael J. Parnham PhD
Director of Preclinical Discovery
Centre of Excellence in Macrolide Drug Discovery
GlaxoSmithKline Research Centre Zagreb Ltd.
Prilaz baruna Filipovića 29
HR-10000 Zagreb
Croatia

Prof. Dr. J. Bruinvels
Sweelincklaan 75
NL-3723 JC Bilthoven
The Netherlands

Bipolar Depression:
Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy

Edited by Carlos A. Zarate Jr. and Husseini K. Manji

Birkhäuser
Basel · Boston · Berlin

Editors
Carlos A. Zarate
Mood Disorders Research Unit
Laboratory of Molecular Pathophysiology
National Institute of Mental Health
Mark O. Hatfield Clinical Research Center
Unit 7SE, Rm. 7-3445
10 Center Drive
Bethesda, Maryland 20892
USA

Husseini K. Manji
Laboratory of Molecular Pathophysiology
National Institute of Mental Health
Porter Neuroscience Research Center
Building 35, Room 1C-917
36 Convent Drive, MSC 3711
Bethesda, Maryland 20892
USA

Library of Congress Control Number: 2008935771

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the internet at http://dnb.ddb.de

ISBN: 978-3-7643-8566-8 Birkhäuser Verlag AG, Basel – Boston – Berlin

ISBN 978-3-7643-8566-8 e-ISBN 978-3-7643-8567-5

9 8 7 6 5 4 3 2 1 www. birkhauser.ch

Contents

Section C: Acute and long-term treatment of bipolar disorder

Section D: Treatment of bipolar disorder in special populations

List of contributors

John L. Beyer, Duke University Medical Center, Durham, NC 27710, USA; e-mail: beyer001@mc.duke.edu

Joseph R. Calabrese, Department of Psychiatry, Bipolar Disorder Research Center in Mood Disorders Program, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106, USA; e-mail: joseph.calabrese@uhhospitals.org

Wayne C. Drevets, Section on Neuroimaging in Mood and Anxiety Disorders, NIH/NIMH DIRP, 15K North Dr., Bethesda, MD 20892, USA

Wallace C. Duncan, Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, Maryland 20892, USA

Robert L. Findling, Department of Psychiatry, University Hospitals Case Medical Center, 10524 Euclid Avenue, Cleveland, Ohio 44106, USA; e-mail: robert.findling@uhhospitals.org

Kathryn Fletcher, School of Psychiatry, University of New South Wales, Sydney, NSW 2031, Australia; e-mail: k.fletcher@unsw.edu.au

Keming Gao, Department of Psychiatry, Bipolar Disorder Research Center in Mood Disorders Program, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106, USA; e-mail: keming.gao@uhhospitals.org

David E. Kemp, Department of Psychiatry, Bipolar Disorder Research Center in Mood Disorders Program, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106, USA; e-mail: kemp.david@gmail.com

K. Ranga R. Krishnan, Duke University Medical Center, Durham, NC 27710, USA

Hannah G. Lund, Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, USA

Husseini K. Manji, Laboratory of Molecular Pathophysiology, National Institute of Mental Health, Porter Neuroscience Research Center, Building 35, Room 1C-917, 36 Convent Drive, MSC 3711, Bethesda, Maryland 20892, USA; e-mail: manjih@mail.nih.gov

Andreas Marneros, Klinik und Poliklinik für Psychiatrie, Psychotherapie und Psychosomatik, Martin-Luther-Universität Halle-Wittenberg, 06097 Halle, Germany; e-mail: andreas.marneros@medizin.uni-halle.de

Francis J. McMahon, Unit on the Genetic Basis of Mood and Anxiety Disorders, Mood & Anxiety Disorders Program, National Institute of

Mental Health, National Institutes of Health, Dept. of Health & Human Services, Bethesda, MD 20892, USA

Gordon B. Parker, Black Dog Institute, Prince of Wales Hospital, Sydney, NSW 2031, Australia; e-mail: g.parker@unsw.edu.au

Jennifer L. Payne, Johns Hopkins School of Medicine, 550 N. Broadway, Suite 305, Baltimore, MD 21205, USA; e-mail: jpayne5@jhmi.edu

Zoltán Rihmer, Department of Clinical and Theoretical Mental Health, and Department of Psychiatry and Psychotherapy, Semmelweis Medical University, Kútvölgyi Clinical Centre, Kútvölgyi út 4, 1125 Budapest, Hungary; e-mail: rihmerz@kut.sote.hu

Patricia Roy, Johns Hopkins School of Medicine, 550 N. Broadway, Suite 305, Baltimore, MD 21205, USA; e-mail: proy3@jhmi.edu

Gary S. Sachs, Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, USA; e-mail: sachsg@aol.com

Harold A. Sackeim, 4 Grant's Path, Poughquag, NY 12570, USA; e-mail: has1@columbia.edu

Jonathan Savitz, Section on Neuroimaging in Mood and Anxiety Disorders, NIH/NIMH DIRP, 15K North Dr., Bethesda, MD 20892, USA; e-mail: savitzj@mail.nih.gov

Thomas G. Schulze, Unit on the Genetic Basis of Mood and Anxiety Disorders, Mood & Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Dept. of Health & Human Services, Bethesda, MD 20892, USA; e-mail: schulzet@mail.nih.gov

Louisa G. Sylvia, Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, USA

Mauricio Tohen, Lilly Research Laboratories, Indianapolis IN 46285; McLean Hospital, Harvard Medical School, Belmont MA 02184, USA; e-mail: m.tohen@lilly.com

Tamas Treuer, Lilly Hungaria Kft., Madacs Imre u. 13–14, 1075 Budapest, Hungary; e-mail: treuert@lilly.com

Jun-Feng Wang, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1; e-mail: junfengw@exchange.ubc.ca

L. Trevor Young, Department of Psychiatry, University of British Columbia 2255 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1; e-mail: trevor.young@ubc.ca

Carlos A. Zarate, Mood Disorders Research Unit, Laboratory of Molecular Pathophysiology, National Institute of Mental Health, Mark O. Hatfield Clinical Research Center, Unit 7SE, Rm. 7-3445, 10 Center Drive, Bethesda, Maryland 20892, USA; e-mail: zaratec@mail.nih.gov

Acknowledgements

The editors gratefully acknowledge the contributions of our book project coordinator, Ioline Henter. Her editing abilities, organizational assistance, and attention to detail were integral to the preparation of this volume. We also wish to acknowledge the support of Detlef Klüber and his colleagues at Birkhäuser Publishing, who accepted our delays with good-natured patience, and whose professionalism made them a pleasure to work with. Our thanks also go out to the research staff of the 7 Southeast Unit and the Outpatient Clinic at the National Institute of Mental Health (NIMH-NIH).

Foreword

Bipolar disorder is a major public health problem, a reality reflected in its position as the sixth leading cause of disability worldwide in 15 to 44-year olds – the age range most associated with the onset of the disorder. Two-thirds of this disability can be traced to the depressive phase of the disorder. While it is beyond question that treatments for the depressive phase of bipolar disorder represent the major unmet need for patients with bipolar disorder and their clinicians alike, it is striking how out of balance the medication development for this disorder has been. With one exception, every drug developed for bipolar disorder has entered the market as a treatment for acute mania, so that we now have nearly a dozen agents proven to work for this indication.

What proven treatments do we have for bipolar depression? There are two with FDA indications for the acute treatment of bipolar depression, but only one of them is a drug, the other being a combination of two drugs marketed in a single pill. The one monotherapy that has been proven to the satisfaction of regulatory agencies is quetiapine, and yet, in spite of its ability to separate from placebo in its effect on core depressive symptoms, the size of the overall quetiapine effect in bipolar depression comes substantially from its ability to improve sleep and reduce anxiety.

What about monotherapies that can prevent or attenuate new episodes of depression when used as maintenance treatments? One agent – lamotrigine – is effective in reducing the time to intervention for new episodes of depression among patients with bipolar disorder studied following remission from acute mania or acute depression; in addition, the older maintenance data on lithium suggest that that drug has at least a moderate ability to prevent or attenuate depressive episodes. Placebo-controlled "maintenance" studies of olanzapine and aripiprazole monotherapy show that the great bulk of the difference between drug and placebo occurs in the continuation phase of treatment, i.e. in the first few months after a manic episode (primarily by preventing relapse back into the index manic episode). However, the ability of any atypical antipsychotic to prevent or attenuate new episodes of depression has not yet been established.

What about the host of "traditional" antidepressants – both the older tricyclic and MAO inhibitor classes and the newer "second-generation" SSRIs, SNRIs, bupropion and a few others? None of these "traditional" antidepressants has ever been FDA-approved for bipolar depression. Indeed, in all of the numerous large studies conducted in the process of registering these drugs as antidepressants, patients with bipolar disorder were excluded. And recent large randomized studies of patients with bipolar disorder in the depressive phase

(by the NIMH STEP program and the Stanley Bipolar Network) have shown little, if any, benefit to adjunctive traditional antidepressants when compared with mood stabilizers alone.

From the above, it should be obvious that I believe that a book focusing on bipolar depression can bring much needed additional attention to this underdeveloped area. Drs. Manji and Zarate have pulled together an impressive international array of major leaders from a broad swath of inter-related disciplines, from clinical phenomenology to basic molecular and cellular neurobiology, genetics, neuroimaging, and circadian physiology.

Starting the book with chapters on phenotype underscores the Editors' belief, which I share, that a careful examination of clinical phenomenology is the foundation required for the development of rational neurobiological and genetic hypotheses of bipolar disorder. Of course the ultimate test of any neurobiological observation is whether it can lead us to new and more refined treatments, especially, in this context, pharmacological agents. While that remains to be seen, several promising leads are explored herein, especially in a chapter the Editors wrote devoted to novel therapeutics.

As with any edited book, the challenge for both the Editors and the readers is to be able to extract integrated themes, drawing on insights from all the diverse chapters. With the help that the Editors have provided for the reader, this integration and synthesis is both achievable and welcome.

Dr. Frederick K. Goodwin
Research Professor of Psychiatry and Behavioral Sciences
Director, Center on Neuroscience, Medical Progress, and Society
George Washington University Medical Center
Washington, DC, USA

Section A:
Bipolar depression: Clinical phenotype and course of illness

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

The history of bipolar disorders

Andreas Marneros

Department of Psychiatry and Psychotherapy, Martin Luther University Halle-Wittenberg, Germany

Abstract

Bipolar disorders have a long history. Depression and mania are mankind's oldest known mental disorders, and they were the first mental disorders conceptualised by Hippocrates as a part of medicine. Mania and depression as part of one and the same disease – what we today call bipolar disorder – was first described by the famous Greek physician of the first century AD, Aretaeus of Cappadocia.

The next decisive step in the development of our conceptualisation of bipolar disorders was done by two French psychiatrists, Falret (1851) and Baillarger (1854), who described them as separate entities. At the end of the 19th century, Emil Kraepelin subsumed all kinds of mood disorders – both unipolar and bipolar – under the umbrella of manic-depressive insanity. But there was also strong opposition against the very influential opinions of Kraepelin, especially by the so-called Wernicke-Kleist-Leonhard school (Karl Kleist coined the term 'bipolar'), which subclassified bipolar disorders into distinct entities. In 1966, Angst and Perris showed that unipolar and bipolar disorders are autonomous. That was also the start of a very rapid development of concepts, research, and general knowledge about bipolar disorders. Subgroups like cyclothymia, hypomania, and mixed states were identified or re-identified. Another innovation was the development of a bipolar spectrum disorder concept. An overlap of bipolar and schizophrenic spectra can be postulated which is certainly genetically determined, and which gives rise to states like bipolar schizoaffective disorders or acute polymorphic disorders.

Origins: from Homer to Aretaeus

Depression and mania are the oldest known mental disorders of mankind. Depression was the first mental disorder diagnosed by a physician – not by a priest or magician – at least according to Homer. If we accept that the mental disorder of Ajax in the Iliad, which led to his suicide, was an agitated depression, then Podaleirios – the mythic founder of internal medicine and, together with his brother Machaon the surgeon (both were sons of Asklepios), doctors of the Trojan war – diagnosed the 'madness' of Ajax by examining him physically, especially by looking in his eyes.

Independent of the mythic traditions, depression (melancholia) and mania are two of the earliest human disorders scientifically described by Hippocrates and the Hippocratic physicians. Hippocrates assumed a biological basis – namely disturbances or damages of the brain – for depression and mania, but also for hallucinations, delusions, anxiety, etc. [1]: "We suffer all those …

through the brain when it is ill …"[1] (Hippocrates, *On the Sacred Disease*). Although melancholia and mania were known to Greek physicians and philosophers long before, Hippocrates (460–337 BC) was the first to systematically describe them in a scientific way. His book *On the Sacred Disease* could be seen as the beginning not only of scientific medicine in general, but also of psychiatry; he disconnected mental and physical diseases from mysticism, God, and punishment and connected them to physiological processes and to the environment. Mental functions or states like emotions, thinking, perception, volition, and behaviour were – according to Hippocrates – also linked to the brain. Hippocrates based his theories and opinions on the materialistic views of Pythagoras and his scholars, especially Alcmaeon, but also Empedocles. The views of Alcmaeon of Crotona, who may have been the first Greek philosopher and scientist to experiment with animal brains (perhaps at the same time as another great Greek philosopher, Anaxagoras), obviously had a great influence on Hippocrates (see also [2]). Hippocrates was strongly interested in the branch of medical science that about 2200 years later (in 1808 AD) would be named 'psychiatry' by Johann Christian Reil [3], and he was the first to classify mental disorders (into melancholia, mania, hypomania, and paranoia). Together with his fellows (the so-called Hippocratic physicians) he also described organic and toxic deliria, postpartum psychoses, and phobias, and he made the first attempt to describe personalities (choleric, phlegmatic, sanguine, and melancholic personalities) [1, 2].

The term *melancholia* (Greek; 'black bile'; melas = black, cholé = bile) is older than Hippocrates and is based on biological assumptions like that of Alcmaeon, who postulated that the origin of mental disorders was a disturbed interaction of body fluids and the brain, but Hippocrates systematised these views. As a basic characteristic of melancholia, he assumed a long lasting anxiety or fear (Greek: phobos) and moodiness (Greek: dysthymia). Later, Hippocrates as well as Aristotle distinguished between the disease 'melancholia' (Greek: nosos melancholiké) and the corresponding personality type (Greek: typos melancholicós). Whereas the first is a disease, the second is a personality type.

In contrast to the etymology of *melancholia,* that of *mania* is not clear. Even in Homer's time it was associated with several different meanings. The Roman physician Caelius Aurelianus gave at least seven possible etymologies of the Greek word in his book *On Acute Diseases* (translated by Drabkin in 1950). In the classical Greek era four main meanings of the word *mania* were described: 1) a reaction to an event with the meaning of rage, anger, or excitation, e.g., in Homer's Iliad, 2) a biologically defined disease (Hippocrates, Aretaeus of Cappadocia), 3) a divine state (Socrates, Plato), 4) a kind of temperament, especially in its mild form, e.g., hypomania (Hippocrates) [1].

[1] All translations from the Greek by the author of the present paper.

The birth of bipolar disorders

The first to describe mania and melancholia as a bipolar disorder was the Greek physician Aretaeus of Cappadocia in the first century AD. Some of his contemporary physicians had similar views (e.g., Caelius Aurelianus, who himself believed that mania and melancholia did not belong together, but nevertheless cited the contrary views of Apollonius). Aretaeus of Cappadocia was a Greek physician who lived in Alexandria, Egypt in the first century AD. He was the most prominent representative of the 'Eclectics' school of philosophy and was strongly influenced by Hippocrates. In his books *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases* he had several chapters on mental disorders like melancholia, mania, phrenitis, and others. He depicts the symptomatology of melancholia as follows: "The symptoms [of melancholia] are not unclear: [the melancholics] either are quiet or dysphoric, sad or apathetic; additionally they could be angry without reason and suddenly awake with panic." In the book *On the Causes and Symptoms of Chronic Diseases* the symptoms of mania were specified as follows: "Some patients with mania are cheerful, they laugh, they play, they dance day and night, they stroll in the market, sometimes with a garland on their heads, as if they had been winner in a game: these patients do not bring worries to their relatives. But others fly into a rage. … The manifestations of mania are countless. Some manics, who are intelligent and well educated, deal with astronomy, although they never have studied it; they deal with philosophy, which they had studied autodidactically; they consider poetry as a gift of muses."

Some authors have claimed that the concept of mania and melancholia as described by Hippocrates, Aretaeus, and other ancient Greek physicians differed from modern concepts. That is not correct. Rather, the classical concepts of melancholia and mania were broader than the modern concepts, but their core is the same [1].

Aretaeus considered melancholia and mania as two manifestations of one and the same disease: "… I think that melancholia is the beginning and a part of mania. … The development of a mania is really a worsening of the disease [melancholia] rather than a change into another disease. … In most of them [melancholics] the sadness disappears after various lengths of time and changes into happiness; the patients then develop a mania."

Resurrection and re-birth of bipolar disorders in modern times

A very long time elapsed between the descriptions of Aretaeus of Cappadocia and new concepts of bipolar disorders. These concepts were put forward 1900 years later by Jean-Pierre Falret [4, 5] and Jules Baillarger [6]. Yet the time between Aretaeus and the two French psychiatrists (Falret and Baillarger) was not empty. Many classical Greek and Roman physicians, such as Asclepiades (who established Greek medicine in Rome), Aurelius Cornelius Celsus (who

translated the most important Greek medical authors into Latin), Soranos of Ephesus, his scholar Caelius Aurelianus, and later Galenos of Pergamos wrote about melancholia, mania, and other mental disorders [1, 2].

Many European authors described (without knowing the work of Aretaeus) the longitudinal association of mania and melancholia, including Willis [7], Morgagni [8], Lorry [9], Heinroth [10], and Griesinger [11, 12] (see also [13, 14]). Then in 1851, Jean-Pierre Falret, a pupil of Esquirol, published a 14-sentence-long statement in the *Gazette des Hôpitaux* ("De la folie circulaire ou forme de maladie mentale caracterisée par l'alternative régulière de la mélancholie"). Falret described for the first time a separate entity, which is characterised by a continuous cycle of depression, mania, and free intervals of varying length and which is different from simple depression. Three years later he completed his concept [5] by defining the sequential change from mania to melancholia and *vice versa* and the interval in between as an independent disease of its own, the 'folie circulaire' [1, 15]. Three years after Falret's first publication, Jules Baillarger [6] described the 'folie à double forme'. Baillarger (arguing very aggressively against Falret) assumed a type of disease in which mania and melancholia change into one another, but the interval is of no importance. In contrast, Falret involved the intervals between the manic and the melancholic episodes in his concept; even episodes of mania and melancholia separated by long intervals belonged together, forming the 'folie circulaire' [1, 15]. The concepts of 'folie circulaire' and 'folie à double forme' found a receptive audience in German-speaking countries [16] as well as in English-speaking countries (as evidenced by publications in *Brain* [17] and in the *American Journal of Insanity* [1, 15, 18]).

At the end of the 19th and beginning of the 20th Centuries it was Emil Kraepelin's fundamental work that strongly influenced psychiatric thinking worldwide. He eliminated the distinction between unipolar and bipolar forms and included all types of mood disorders into the unitary concept of manic-depressive illness, which later proved to be a step back [1, 14, 19–21]. Although Kraepelin himself was non-dogmatic and had severe doubts regarding the validity of his concept [22–24], his followers contributed to some inflexible positions. In his two fundamental works *Die Klinische Stellung der Melancholie* ('The clinical position of melancholia') and the sixth edition of his textbook *Psychiatrie* – both published in 1899 [20, 21] – Kraepelin reported on merging 'circular insanity' and unipolar types as two subtypes of one and the same disorder, namely manic-depressive insanity ('manisch-depressives Irresein'). He wrote: "Unfortunately our textbooks do not help us at all in distinguishing between circular depression and melancholia in cases where the course itself is not informative. The description of melancholic states is absolutely identical to that of circular depression and we can hardly doubt that the most beautiful and exciting descriptions of melancholia are mostly derived from observations of circular cases" [20, p. 328][2]. And some

[2] All translations from the German by the author of the present paper.

pages later: “Apart from our experience that in a whole series of manic episodes a depressive one can occur unexpectedly, and that those cases are immensely rare in which – apart from manic irritability – not the slightest feature of depression is visible, it is absolutely impossible to distinguish these manic fits of circular insanity from periodic mania. But if periodic mania is identical with circular insanity we cannot deny the possibility that also periodic melancholia, or at least some of the cases designated so, must in fact be understood as a kind of circular insanity in which all the episodes take on a depressive hue, just as in periodic mania they all have a manic tinge” [20, p. 333].

In many countries an opposition to Kraepelin’s views arose, but due to his enormous influence this opposition was ignored for many years. Especially the German school of Wernicke, Kleist, and Leonhard delivered subtle descriptions of various affective syndromes, which were assumed to be separate entities. The father of the term ‘bipolar’, Karl Kleist, and his fellow Karl Leonhard, gathered many clinical and family history data to support the distinction between ‘unipolar’ and ‘bipolar’ [25–29].

Unfortunately Kleist’s opinions had no relevant influence on international psychiatry for a long time, at least until 1966, the year of the ‘re-birth’ of bipolar disorders, as Pichot [15] called it. In that year two fundamental studies were published: Jules Angst’s monograph *Zur Ätiologie und Nosologie endogener depressiver Psychosen* (‘On the aetiology and nosology of endogenous depressive psychoses’) [30] and Carlo Perris’s article on *A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses* [31] in a supplement of *Acta Psychiatrica Scandinavica*. The studies of Angst and Perris, which were carried out independently of each other, uncovered very similar findings [32]. They revealed (in summary) that:

1. genetic and peristaltic factors have a synergic impact on the aetiology of ‘endogenous’ depression
2. there is a relationship between female gender and ‘endogenous’ depression; bipolar disorders, however, are equally represented in males and females
3. manic-depressive illness is not homogeneous in a nosological sense. Unipolar depression differs significantly from bipolar disorders in many characteristics
4. unipolar depression has a strong genetic relationship to bipolar disorders.

The work of Angst and Perris, but also that of George Winokur, Paula Clayton, and Theodore Reich [33, 34], showing very similar findings, confirmed some fundamental assumptions of Wernicke, Kleist, and Leonhard and contributed to a real explosion of interest and knowledge in the field of bipolar disorders [14, 35, 36].

Recent developments

In summarising the developments of the last half century it can be pointed out that despite the very dynamic development of biological knowledge about bipolar disorder, which includes genetics and treatment, and which is discussed in various chapters of the present book, the description or re-description of various disorders belonging to a wide bipolar spectrum and their longitudinal course is an essential completion of the concept.

Apart from the classical syndromes of bipolar depression and mania, other special bipolar syndromes were more or less intensely studied: cyclothymia, hypomania, mixed states, bipolar schizoaffective disorder, and other mood disorders or even personality states [37–40].

One of the re-discoveries was that of *cyclothymia*. Cyclothymia is an old and controversial term, first published by Ewald Hecker in 1877 [41], but coined by his teacher Karl Kahlbaum. According to Kahlbaum, 'cyclothymia' refers to the mildest type of bipolar disorders; the term was accepted by Hecker [42] and also by Kraepelin [21]. Ernst Kretschmer [43] described a cyclothymic temperament, and called cyclothymia a "broad constitutional overterm involving health and disease in the same way". The boundaries of cyclothymia as a mood disorder or as a disorder of temperament or personality are not yet clear [37–40].

Another old term, re-discovered in recent years, is *hypomania.* It was, however, first described by Emanuel Mendel in 1881 [44]. Mendel was influenced by Hippocrates, who first described the 'hypomanics' to characterise a type of hyperthymic personality. Mendel wrote: "I recommend (taking under consideration the word used by Hippocrates) to name those types of mania that show a less intense phenomenological picture, 'hypomania'" [44, p. 109]. In recent decades hypomania gained importance through the description of bipolar II disorders by Dunner, Fleiss, and Fieve [45]; through the description of recurrent brief hypomania by Angst [46]; and through its relation to hyperthymic temperament [38]. *Bipolar II disorders*, characterised by episodes of major depression and hypomania, are obviously more frequent than assumed earlier. According to Angst and his co-workers [47] the prevalence of bipolar II disorders amounts to between 5 and 11% of all bipolar disorders, depending on the criteria applied.

In contrast to those mentioned above, the term *rapid cycling* is a modern one. Dunner and Fieve first coined the term in 1974 [48]. Nevertheless, the phenomenon itself was very well known earlier in psychiatry. Emil Kraepelin may have been the first to systematically describe the phenomenon of rapid cycling [21, 49]. The modern term 'rapid cycling', as well as the increasing interest in this phenomenon, has also accrued since the advent of modern, successful psychopharmacological treatments for bipolar disorder. The boundaries between 'rapid cycling' (having at least four cycles in a year) and not 'rapid cycling' (having fewer than four episodes per year) are in fact arbitrary, although Dunner and Fieve found that lithium non-responders tended to

belong to the group of patients who had more than four episodes annually. The subsequent work of Wehr and Goodwin [50] replicated the findings of Dunner and Fieve and additionally anticipated that antidepressant agents could contribute to the manifestation of rapid cycling, a finding that has also been replicated by others [51–53] (see also [54]). The DSM-IV [55] included 'rapid cycling' as a specifier of longitudinal course, but not as a specific mood disorder subtype. The ICD-10 of the World Health Organization [56] does not include any specifier or subgroup 'rapid cycling'.

The *mixed states*, too, have been re-discovered in the 20th century, perhaps under the influence of pharmacotherapy and the recognition of its limitations, especially regarding some sub-groups of bipolar disorders, one of which is the mixed states [35, 57]. The description of mixed states dates back to the very beginning of psychiatry [1], but the German psychiatrist Johann Christian August Heinroth – who was actually the first professor of 'mental medicine' in Europe, perhaps also worldwide – was possibly the first to classify them [10]. He characterised 'mixed states' as a mixture of exaltation and depression (hyper-asthenias) and divided them into three groups, each having four subgroups: 1) 'mixed mood disorders'; 2) 'mixed mental disorders', and 3) 'mixed volition disorders'. The first to conceptualise the mixed states in modern terms were Emil Kraepelin [21] and his pupil Wilhelm Weygandt [58]. Weygandt was also the first to write a book on mixed states in which he concluded: "The co-existence of the main symptoms of both typical episodes of manic-depressive insanity, mostly only of short duration, is extraordinarily frequent; in some cases the mixed states can occupy the entire episode or at least the greater part of its duration; usually the later episodes have the tendency to change to long-lasting mixed states; the course is in many aspects somewhat more chronic than that of the pure manic or depressive episodes, but in other ways the prognosis regarding the recovery of the episode is exactly the same" [58, p. 63].

The renaissance of the study of mixed states began in the USA at the end of the 1970s and the beginning of the 1980s as a consequence of the pharmacological revolution in psychiatry. Initial and relevant contributions were those of Winokur and colleagues [34], Kotin and Goodwin [59], Himmelhoch and colleagues [60, 61], Akiskal and colleagues [62], Akiskal [63–65], Secunda and colleagues [66], Goodwin and Jamison [67], Himmelhoch [68], McElroy and colleagues [69–72], Swann and colleagues [73], and Akiskal and Pinto [74]. Another interesting aspect of the evolution of the mixed states concept is their extension to the group of schizoaffective disorders. But although both ICD-10 and DSM-IV describe a group of 'mixed schizoaffective disorders', there is unfortunately little work on the topic [75, 76]. My colleagues and I have described the frequency, clinical characteristics, and the prognostic value of schizoaffective mixed episodes [35, 77–90]. We have found that mixed states and schizoaffective disorders do not seem to be rare; indeed, approximately 33% of bipolar schizoaffective patients had at least one mixed schizoaffective episode over the long-term course of their illness [57].

One of the most controversial issues of psychiatry concerns *schizoaffective disorders* [91, 92]. Although they seem to be a nosological nuisance for many researchers, they are an everyday reality for every clinician. In this sense they are a challenge for nosologists and other researchers. The nuisance or problem or challenge or reality of the 'intermediate psychotic area' or the 'cases in-between' is even older than the term 'schizoaffective' itself, which was originated by Kasanin in 1933 [14, 91–99], though it may have begun with Karl Kahlbaum [16] and led through Kraepelin's work to the clinical empiricists of the 20th century. The renaissance of schizoaffective disorders also began with the work of Jules Angst in 1966 [30] when he investigated the schizoaffective disorders (under the term 'Mischpsychosen' (mixed psychoses)) as a part of mood disorders. This was an outlier's position not only against the 'zeitgeist', which considered schizoaffective disorders as part of schizophrenia, but was also contrary to the opinion of his teacher Manfred Bleuler, who also assumed they were a part of schizophrenia. Later investigations by Angst and his group [100, 101], by Clayton and colleagues [102], by other members of the Winokur group [103], by Cadoret and colleagues [104], and the voluminous comparative studies of Marneros and co-workers [75, 78–84, 86, 105–111] strongly supported the notion that the relationship between schizoaffective disorder and mood disorders is stronger than the relationship between schizoaffective and schizophrenic disorders.

Schizoaffective disorders can be divided into unipolar and bipolar using the same criteria applied to pure mood disorders. Consequently, bipolar schizoaffective disorders could be assumed to be part of the bipolar spectrum resulting in an overlap of the affective and the schizophrenic spectra [99], and are probably genetically determined [112–114]. Clinical research also provides evidence that the so-called *polymorphic disorders* (acute and transient psychotic disorders) have strong similarities to the bipolar spectrum, building together with schizoaffective disorders a continuum between the bipolar and the schizophrenic spectra [115].

The concept of a spectrum of manic conditions developed by Kretschmer [43] and Eugen Bleuler [116] has undergone various modifications [1, 117]. Over the past decades the group of Jules Angst and Hagop Akiskal provided evidence – based on clinical observations, epidemiological studies, and a sound knowledge of the literature – to establish and enlarge this idea of a continuum [19, 37, 46, 100, 117–122]. The modern concept of a bipolar spectrum includes variations of overlapping temperament, personality, and clinical picture in the affective and schizophrenic spectra [99]. Bipolar schizoaffective disorders, as well as acute and transient psychotic disorders – especially the acute polymorphic psychoses (the so-called 'cycloid psychoses' of Wernicke, Kleist, and Leonhard or the 'Bouffée délirante' of Magnan) – may be the most important clinical manifestations of a genetically determined overlap of schizophrenic and affective spectra [113, 114], as shown in Figure 1.

Finally, the history of the treatment of bipolar disorders is the history of treatment in psychiatry. The physical therapies devised by Greek and Roman

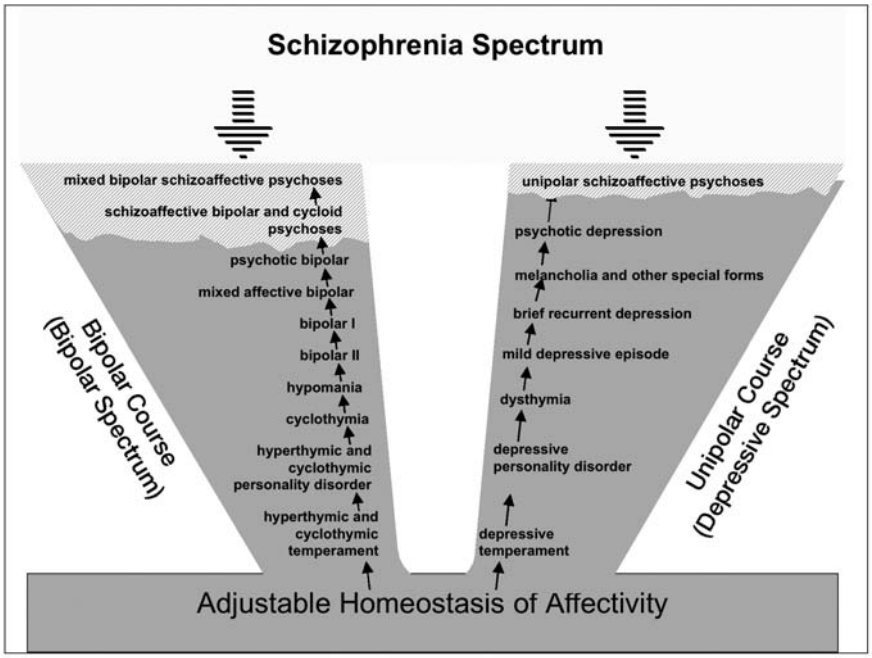


Figure 1. The severity spectrum of mood disorders (adopted from [88]).

physicians were applied with fewer or more modifications up to the end of the 19th century. Phytopharmacotherapy, insulin, cardiazol, electroconvulsive treatment, opium, alcoholic beverages, narcotics (already used by the Greeks), bromides, chloral hydrates, rauwolfia serpentina, and other drugs were still used in the 20th century until the development of modern psychopharmacology [2]. The psychopharmacological revolution in psychiatry began in the second half of the 20th century and had an enormous impact on all areas of psychiatric knowledge. This topic, however, is beyond the scope of this chapter.

References

1 Marneros A, Angst J (2000) Bipolar disorders: roots and evolution. In: A Marneros, J Angst (eds): *Bipolar Disorders*. Kluwer Academic Publishers, Dordrecht, Boston, London, 1–36
2 Alexander F, Selesnick S (1966) *The history of psychiatry*. Harper & Row, New York
3 Marneros A, Pillmann F (2005) *Das Wort Psychiatrie wurde in Halle geboren*. Schattauer, Stuttgart
4 Falret J (1851) De la folie circulaire ou forme de maladie mentale caracterisée par l'alternative régulière de la manie et de la mélancolie. *Bull Acad Natl Med (Paris)*
5 Falret J (1854) Mémoire sur la folie circulaire, forme de maladie mentale caracterisée par la reproduction successive et régulière de l'état maniaque, de l'état mélancholique, et d'un intervalle lucide plus ou moins prolongé. *Bull Acad Natl Med (Paris)* 382–415
6 Baillarger J (1854) De la folie à double forme. *Ann méd psychol* 6

7 Willis T (1676) *De anima brutorum*. Lyon
8 Morgagni JB (1761) *Recherches anatomiques sur le siège et les causes des maladies (translated)*. Destouet, Venice
9 Lorry AC (1765) *De melancholia et morbis melancholis*. Paris
10 Heinroth JCA (1818) *Lehrbuch der Störungen des Seelenlebens oder der Seelenstörung und ihrer Behandlung – aus rationaler Sicht*. Vogel, Leipzig
11 Griesinger W (1845) *Pathologie und Therapie der psychischen Krankheiten*. Krabbe, Stuttgart
12 Griesinger W (1861) *Pathologie und Therapie der psychischen Krankheiten, 2nd edition*. Krabbe, Stuttgart
13 Haugsten TH (1995) Les troubles bipolaires dans l'histoire de la psychiatrie (Kraepelin excepté). In: ML Bourgeois, H Verdoux (eds): *Les troubles bipolaires de l'humeur*. Masson Médicine et Physiotherapie, Paris
14 Marneros A, Angst J (2000) *Bipolar Disorders. 100 Years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, Boston, London
15 Pichot P (1995) The birth of the bipolar disorder. *Eur Psychiatry* 10: 1–10
16 Kahlbaum K (1863) *Die Gruppirung der psychischen Krankheiten und die Eintheilung der Seelenstörungen*. Kafemann, Danzig
17 Foville A (1882) Folie à double forme. *Brain* 5: 288–323
18 Hurd HM (1882) The treatment of periodic insanity. *Am J Insanity* 39: 174–180
19 Angst J (1997) A brief history of bipolar disorder. *J Bipolar Disord* 1: 31–36
20 Kraepelin E (1899) Die klinische Stellung der Melancholie. *Mschr Psychiatr Neurol* 6: 325–335
21 Kraepelin E (1899) *Psychiatry. 6th edition*. Barth, Leipzig
22 Kraepelin E (1920) Die Erscheinungsformen des Irreseins. *Zeitschrift für die gesamte Neurologie und Psychiatrie* 62: 1–29
23 Craddock N, Owen MJ (2007) Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry* 6: 20–27
24 Marneros A (2006) Beyond the Kraepelinian dichotomy: acute and transient psychotic disorders and the necessity for clinical differentiation. *Br J Psychiatry* 189: 1–2
25 Kleist K (1911) Die klinische Stellung der Motilitätspsychosen. *Z Gesamte Neurol Psychiatr* 3: 914–977
26 Kleist K (1926) Über cycloide Degenerationspsychosen, besonders Verwirrtheits – und Motilitätspsychosen. *Zentralblatt für die gesamte Neurologie und Psychiatrie* 44: 655–657
27 Kleist K (1928) Über cycloide, paranoide und epileptoide Psychosen und über die Frage der Degenerationspsychosen. *Schweizer Archiv für Neurologie, Neurochirurgie und Psychiatrie* 23: 3–37
28 Kleist K (1953) Die Gliederung der neuropsychischen Erkrankungen. *Mon Psychiatrie Neurol* 125: 526–554
29 Leonhard K (1957) *Die Aufteilung der endogenen Psychosen*. Akademie-Verlag, Berlin
30 Angst J (1966) *Zur Ätiologie und Nosologie endogener depressiver Psychosen. Eine genetische, soziologische und klinische Studie*. Springer, Berlin, Heidelberg, New York
31 Perris C (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. *Acta Psychiatr Scand* 194 (suppl): 1–89
32 Angst J, Perris C (1968) Zur Nosologie endogener Depressionen. Vergleich der Ergebnisse zweier Untersuchungen. *Arch Psychiatrie Z Neurol* 373–386
33 Winokur G, Clayton P (1967) Family history studies: I. Two types of affective disorders separated according to genetic and clinical factors. In: J Wortis (ed.): *Recent advances in Biological Psychiatry. Vol. 10*. Plenum, New York
34 Winokur G, Clayton PJ, Reich T (1969) *Manic Depressive Illness*. CV Mosby, St Louis
35 Marneros A, Goodwin FK (2005) *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge
36 Goodwin FK, Jamison KR (2007) *Manic-depressive Illness. Bipolar Disorders and Recurrent Depression*. Oxford University Press, Oxford
37 Akiskal HS (1983) Dysthymic and cyclothymic disorders: a paradigm for high risk research. In: JM Davis, JW Maas (eds): *The Affective Disorders*. American Psychiatric Press, Washington, DC, 211–231
38 Akiskal HS, Akiskal K (1992) Cyclothymic, hyperthymic, and depressive temperaments as subaffective variants of mood disorders. In: A Tasman, MB Riba (eds): *Review of Psychiatry 11*. American Psychiatric Press, Washington, DC

39 Akiskal HS, Chen SE, Davis GC, Puzantian VR, Kashgarian M, Bolinger JM (1985) Borderline: an adjective in search of a noun. *J Clin Psychiatry* 46: 41–48
40 Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin F (1995) Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 52: 114–123
41 Hecker E (1877) Zur klinischen Diagnostik und Prognostik der psychischen Krankheiten. *Allg Z Psychiatrie* 33: 602–620
42 Hecker E (1898) Die Cyclothymie, eine cirkuläre Gemüthserkrankung. *Z Prakt Ärzte* 7: 6–15
43 Kretschmer E (1921–1950) *Körperbau und Charakter (1st–21st edition)*. Springer, Berlin
44 Mendel E (1881) *Die Manie*. Urban & Schwarzenberg, Wien, Leipzig
45 Dunner DL, Fleiss JL, Fieve RR (1976) The course of development of mania in patients with recurrent depression. *Am J Psychiatry* 133: 905–908
46 Angst J (1997) Recurrent brief psychiatric syndromes: Hypomania, depression, anxiety and neurasthenia. In: LL Judd, B Saletu, V Filip (eds): *Basic and clinical science of mental and addictive disorders*. Karger, Basel
47 Angst J, Gamma A, Ajdacic V, Eich D, Pezawas L, Rössler W (2005) Recurrent brief depression as an indicator of severe mood disorders. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 109–130
48 Dunner DL, Fieve RR (1974) Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry* 30: 229–233
49 Kraepelin E (1913) *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 3rd volume: Klinische Psychiatrie, 2nd part (8th edition).* Johann Ambrosius Barth, Leipzig
50 Wehr TA, Goodwin F (1979) Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36: 555–559
51 Calabrese JR, Meltzer HY, Markovitz PJ (1991) Clozapine prophylaxis in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 11: 396–397
52 Calabrese JR, Woyshville MJ, Kimmel SE, Rapport DJ (1993) Predictors of valproate response in bipolar rapid cycling. *J Clin Psychopharmacol* 13: 280–283
53 Elhaj O, Calabrese JR (2005) Rapid-cycling bipolar disorder. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 61–87
54 Kilzieh N, Akiskal HS (1999) Rapid-cycling bipolar disorder. An overview of research and clinical experience. *Psychiatr Clin North Am* 22: 585–607
55 APA (1994) *Diagnostic and Statistical Manual of Mental Disorders. 4th edition. (DSM-IV).* American Psychiatric Association, Washington
56 WHO (1991) *ICD-10 Classification of Mental and Behavioural Disorders*. Churchill Livingstone, Edinburgh, London, Melbourne, New York, Tokyo
57 Marneros A, Goodwin FK (2005) Bipolar disorders beyond major depression and euphoric mania. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 1–44
58 Weygandt W (1899) *Über die Mischzustände des manisch-depressiven Irreseins*. JF Lehmann, München
59 Kotin J, Goodwin F (1972) Depression during mania: clinical observations and theoretical observations. *Am J Psychiatry* 129: 55–56
60 Himmelhoch JM, Coble P, Kupfer KJ, Ingenito J (1976) Agitated psychotic depression associated with severe hypomanic episodes: a rare syndrome. *Am J Psychiatry* 133: 765–771
61 Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ (1976) Incidence and significance of mixed affective states in a bipolar population. *Arch Gen Psychiatry* 33: 1062–1066
62 Akiskal HS, Khani MK, Scott-Strauss A (1979) Cyclothymic temperament disorders. *Psychiatr Clin North Am* 2: 527–554
63 Akiskal H (1981) Subaffective disorders: dysthymic, cyclothymic and bipolar II disorders in the "border-line" realm. *Clin North Am* 4: 25–46
64 Akiskal H (1992) The mixed states of bipolar I, II, III. *Clin Neuropsychopharm* 15: 632–633
65 Akiskal H (1997) Overview of chronic depressions and their clinical management. In: H Akiskal, G Cassano (eds): *Dysthymia and the spectrum of chronic depressions*. Guilford Press, New York, 1–34
66 Secunda SK, Swann A, Katz MM, Koslow SH, Croughan J, Chang S (1987) Diagnosis and treat-

ment of mixed mania. *Am J Psychiatry* 144: 96–98
67 Goodwin FK, Jamison KR (1990) *Manic-Depressive Illness*. Oxford University Press, Oxford
68 Himmelhoch JM (1992) The sources of characterologic presentations of mixed bipolar states. *Clin Neuropsychopharm* 15: 630A–631A
69 McElroy SL, Freeman MP, Akiskal H (2000) The mixed bipolar disorder. In: A Marneros, J Angst (eds): *Bipolar Disorders. 100 years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, 63–88
70 McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI, Faedda GL, Swann AC (1992) Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry* 149: 1633–1644
71 McElroy SL, Strakowski SM, Keck PE Jr, Tugrul KL, West SA, Lonczak HS (1995) Differences and similarities in mixed and pure mania. *Compr Psychiatry* 36: 187–194
72 McElroy SL, Strakowski SM, West SA, Keck PE Jr, McConville BJ (1997) Phenomenology of adolescent and adult mania in hospitalized patients with bipolar disorder. *Am J Psychiatry* 154: 44–49
73 Swann A, Secunda SK, Katz MM (1995) Specifity of mixed affective states: clinical comparison of dysphoric mania and agitated depression. *J Clin Psychiatry* 56: 6–10
74 Akiskal HS, Pinto O (2000) The soft bipolar spectrum: footnotes to Kraepelin on the interface of hypomania, temperament and depression. In: A Marneros, J Angst (eds): *Bipolar Disorders. 100 Years after Manic-depressive Insanity*. Kluwer, Dordrecht, Boston, London, 37–62
75 Marneros A, Röttig S, Wenzel A, Blöink R, Brieger P (2005) Schizoaffective mixed states. In: A Marneros, FK Goodwin (eds): *Bipolar Disorders. Mixed States, Rapid Cycling and Atypical Forms*. Cambridge University Press, Cambridge, 187–206
76 Marneros A, Rottig S, Wenzel A, Bloink R, Brieger P (2004) Affective and schizoaffective mixed states. *Eur Arch Psychiatry Clin Neurosci* 254: 76–81
77 Marneros A (1989) *Schizoaffektive Psychosen. Diagnose, Therapie und Prophylaxe*. Springer, Berlin, Heidelberg, New York
78 Marneros A, Deister A, Rohde A (1986) The Cologne Study on schizoaffective disorders and schizophrenia suspecta. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 123–142
79 Marneros A, Deister A, Rohde A, Junemann H, Fimmers R (1988) Long-term course of schizoaffective disorders. Part I: Definitions, methods, frequency of episodes and cycles. *Eur Arch Psychiatry Neurol Sci* 237: 264–275
80 Marneros A, Rohde A, Deister A, Fimmers R, Junemann H (1988) Long-term course of schizoaffective disorders. Part III: Onset, type of episodes and syndrome shift, precipitating factors, suicidality, seasonality, inactivity of illness, and outcome. *Eur Arch Psychiatry Neurol Sci* 237: 283–290
81 Marneros A, Rohde A, Deister A, Junemann H, Fimmers R (1988) Long-term course of schizoaffective disorders. Part II: Length of cycles, episodes, and intervals. *Eur Arch Psychiatry Neurol Sci* 237: 276–282
82 Marneros A, Deister A, Rohde A (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. I. Premorbid and sociodemographic features. *Eur Arch Psychiatry Neurol Sci* 239: 158–163
83 Marneros A, Deister A, Rohde A, Junemann H (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. III. Long-term outcome. *Eur Arch Psychiatry Neurol Sci* 239: 171–176
84 Marneros A, Rohde A, Deister A (1989) Unipolar and bipolar schizoaffective disorders: a comparative study. II. Long-term course. *Eur Arch Psychiatry Neurol Sci* 239: 164–170
85 Marneros A, Andreasen NC, Tsuang MT (1991) *Negative versus Positive Schizophrenia*. Springer, Berlin, Heidelberg, New York
86 Marneros A, Deister A, Rohde A (1991) *Affektive, Schizoaffektive und Schizophrene Psychosen: Eine vergleichende Langzeitstudie*. Springer, Berlin, Heidelberg, New York
87 Marneros A, Deister A, Rohde A (2000) Bipolar schizoaffective disorders. In: A Marneros, J Angst (eds): *Bipolar Disorders: 100 years after manic depressive insanity*. Kluwer Academic Publishers, Dordrecht, 111–126
88 Marneros A (2004) *Das Neue Handbuch der Bipolaren und Depressiven Erkrankungen*. Thieme, Stuttgart, New York
89 Marneros A, Rohde A, Deister A (1996) Bipolar mixed illness. *Eur Neuropsychopharmacol* 6: 9
90 Marneros A, Rohde A, Deister A, Fischer J (1996) Die gemisch-bipolare Erkrankung. *Nervenarzt* 67: 67

91 Maj M (1984) The evolution of some European diagnostic concepts relevant to the category of schizoaffective psychoses. *Psychopathology* 17: 158–167
92 Marneros A, Tsuang MT (1986) *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York
93 Kasanin J (1933) The acute schizoaffective psychoses. *Am J Psychiatry* 13: 97–126
94 Angst J (1986) The course of schizoaffective disorders. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 63–93
95 Perris C (1986) The case for the independence of cycloid psychotic disorder from the schizoaffective disorders. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 272–308
96 Pichot P (1986) A comparison of different national concepts of schizoaffective psychosis. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 8–17
97 Strömgren E (1986) Reactive (psychogenic) psychoses and their relations to schizoaffective psychoses. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 260–271
98 Angst J, Marneros A (2001) Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord* 67: 3–19
99 Marneros A, Akiskal HS (2007) *The Overlap of Affective and Schizophrenic Spectra.* Cambridge University Press, Cambridge
100 Angst J (1990) Recurrent brief depression: a new concept of depression. *Pharmacopsychiatry* 23: 63–66
101 Angst J (1989) Der Verlauf schizoaffektiver Psychosen. In: A Marneros (eds): *Schizoaffektive Psychosen, Diagnose, Therapie und Prophylaxe*. Springer, Berlin, 87–88
102 Clayton P (1968) Family history studies: III – Schizoaffective disorder, clinical and genetic factors – including a one to two year follow-up. *Compr Psychiatry* 9: 31–49
103 Fowler RC, McCabe MS, Cadoret RJ, Winokur G (1972) The validity of good prognosis schizophrenia. *Arch Gen Psychiatry* 26: 182–185
104 Cadoret RJ, Fowler RC, McCabe MS, Winokur G (1974) Evidence for heterogeneity in a group of good-prognosis schizophrenics. *Compr Psychiatry* 15: 443–450
105 Marneros A, Rohde A, Deister A (1986) Features of schizoaffective disorders: The "cases-in-between". In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 143–154
106 Marneros A, Rohde A, Deister A, Risse A (1986) Schizoaffective disorders: The prognostic value of the affective component. In: A Marneros, MT Tsuang (eds): *Schizoaffective Psychoses*. Springer, Berlin, Heidelberg, New York, 155–163
107 Marneros A, Deister A, Rohde A, Steinmeyer EM, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. I. Definitions, methods, psychopathological and social outcome. *Eur Arch Psychiatry Neurol Sci* 238: 118–125
108 Marneros A, Steinmeyer EM, Deister A, Rohde A, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. III. Social consequences. *Eur Arch Psychiatry Neurol Sci* 238: 135–139
109 Steinmeyer EM, Marneros A, Deister A, Rohde A, Junemann H (1989) Long-term outcome of schizoaffective and schizophrenic disorders: a comparative study. II. Causal-analytical investigations. *Eur Arch Psychiatry Neurol Sci* 238: 126–134
110 Marneros A (2007) The paradigma of overlapping affective and schizophrenic spectra: schizoaffective conditions. In: A Marneros, HS Akiskal (eds): *The Overlap of Affective and Schizophrenic Spectra*. Cambridge University Press, Cambridge, 1–24
111 Marneros A, Röttig S, Röttig D, Tscharntke A, Brieger P (2007) The longitudinal polymorphism of bipolar I disorders and its theoretical implications. *J Affective Disord* 107: 117–126
112 Craddock N, O'Donovan MC, Owen MJ (2005) The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet* 42: 193–204
113 Craddock N, O'Donovan MC, Owen MJ (2007) Phenotypic and genetic complexity of psychosis. *Br J Psychiatry* 190: 200–203
114 Kelsoe JR (2007) The overlapping of the spectra: overlapping genes and genetic models. In: A Marneros, HS Akiskal (eds): *The Overlap of Affective and Schizophrenic Spectra*. Cambridge University Press, Cambridge, 25–42
115 Marneros A, Pillmann F (2004) *Acute and Transient Psychoses*. Cambridge University Press,

Cambridge
116 Bleuler E (1922) Die Probleme der Schizoidie und der Syntonie. *Z Gesamte Neurol Psychiatr* 78
117 Akiskal HS (2002) Classification, diagnosis and boundaries of bipolar disorders: a review. In: M Maj, H Akiskal, JJ Lopez-Ibor, N Sartorius (eds): *Bipolar Disorder*. Wiley & Sons, Chichester, 1–52
118 Angst J (1997) Minor and recurrent brief depression. In: HS Akiskal, GB Cassano (eds): *Dysthymia and the spectrum of chronic depression*. Guilford, New York, London
119 Angst J (2008) The affective spectrum and its neglected sub-diagnostic groups. In: A Marneros, D Röttig (eds): *Biogenese und Psychogenese*. Roderer, Regensburg
120 Akiskal HS (1983) Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. *Am J Psychiatry* 140: 11–20
121 Akiskal HS, Mallya G (1987) Criteria for the 'soft' bipolar spectrum: treatment implications. *Psychopharmacol Bull* 23: 68–73
122 Akiskal HS, Djenderedjian AM, Rosenthal RH, Khani MK (1977) Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. *Am J Psychiatry* 134: 1227–1233

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

The clinical diagnosis of bipolar depression

Gordon B. Parker and Kathryn Fletcher

School of Psychiatry, University of New South Wales, and the Black Dog Institute, Prince of Wales Hospital, Sydney, Australia

Abstract

'Bipolar depression' is not a specific type of depression, with most episodes phenotypically weighted to melancholic or psychotic depression. In order to improve our understanding of the etiology and management of bipolar depression, sub-typing heterogeneity should be constrained. A 'top-down' approach to delineate specific sub-typing characteristics is suggested, allowing consideration as to whether 'bipolar depression' differs in expression across bipolar I (BPD I) and II (BPD II) disorders. Current diagnostic systems employ imprecise criteria to differentiate sub-types of BPD, disallowing 'top-down' studies seeking to identify prototypical bipolar depression features.

We describe a categorical 'isomer' model, assisting discrimination between bipolar subtypes and unipolar depressive disorders. In essence, the respective presence or absence of psychotic features differentiates BPD I from BPD II, with a core elevated mood/energy construct delineating BPD from unipolar disorders. Our model allows a 'top-down' approach to clinical diagnosis, *versus* the questionable validity of the bipolar spectrum 'soft signs' approach.

Introduction

'Bipolar depression' is generally defined quite simply – as the depressed phase experienced by an individual who has bipolar disorder (BPD). Thus, the clinical diagnosis generally first requires clarification as to whether an individual has BPD or not. A provisional diagnosis of BPD usually involves the individual describing: (i) clear-cut hypomanic or manic episodes that have a sufficient number of prototypic distinctive features; (ii) a clear onset to their highs – that they can remember a time when mood swings commenced – although we must concede the occasional onset of BPD in childhood; and (iii) that during the 'highs' their usual levels of 'anxiety' disappear as their self-confidence increases in line with the elevated mood state. Thus, by adopting the logic expressed in the first sentence, 'bipolar depression' is effectively the converse depressed state experienced by those with BPD.

However, just as 'depression' is a non-specific term and its clinical expressions can be sub-typed, 'bipolar depression' is not a specific type of depression. Most – but not all – episodes of 'bipolar depression' have a phenotypic picture that is weighted to the melancholic or psychotic depressive picture. Such depressive sub-types have a number of ascriptions, including: (i) having

distinctive symptoms and signs; (ii) having biological determinants that are more relevant than psychosocial determinants; and (iii) that such conditions have more selective responses to physical treatments.

Turning to distinctive symptoms and signs, commonly suggested features [1] include a more severely depressed and non-reactive mood, a depressed state marked by anhedonia and anergia, impaired concentration, psychomotor retardation and/or agitation, appetite and/or weight loss, insomnia (especially early morning wakening), and diurnal variation (with mood and energy worse in the morning). In psychotic depression, psychomotor disturbance is even more severe, mood congruent or incongruent delusions and/or hallucinations are present, and diurnal variation is usually lost, with mood and energy remaining low across the day.

Finally, just as it is a common human experience to develop 'depression' in response to stressors that impact on an individual's self-esteem, those with BPD are not immune to such experiences, and may therefore also develop non-melancholic depressive episodes; in these, the phenotypic picture is marked by the absence of the more specific melancholic features rather than by any class of distinctive features.

If we are to improve our etiological understanding and management of bipolar depression, there is a need to constrain such sub-typing heterogeneity. The remainder of this chapter will consider this key issue – and consider whether there is any *sui generis* bipolar depressive condition or – and more to be expected – distinct over-representation of any type or specific features.

How might we proceed to advance sub-typing of BPD? Theoretically, there are two contrasting ('top down' and 'bottom up') approaches that might lead to delineating any specific sub-typing 'bipolar depressive' characteristics. The former approach would involve studying clearly diagnosed patients with BPD during their depressed phase. The latter might involve studying those with clinical depression and identifying predictors of bipolar status.

Operationalising a 'top down' approach

As noted, while individuals with BPD are not immune to experiencing episodes of 'reactive depression' in response to life's vicissitudes, a 'top down' approach might proceed by selecting groups of individuals with clearly defined BPD, and then identifying the 'characteristic' features experienced by them across multiple depressive episodes. Such an approach emphasises 'characteristic' and 'consistent' features to identify the most prototypic clinical features. As BPD is increasingly sub-divided into bipolar I (BPD I) and bipolar II (BPD II) subtypes, with manic and hypomanic phases respectively, the ideal categorical system would allow consideration as to whether 'bipolar depression' is identical in expression across both bipolar sub-types. This raises the question of how well official classificatory systems (such as the DSM-IV and ICD-10) define and differentiate bipolar sub-types.

The DSM-IV [2] classificatory system has essentially the same criteria for mania and hypomania. Thus, Criterion A for both mania and hypomania involves a "distinct period of abnormally and persistently elevated, expansive, or irritable mood". Criterion B requires three or more (or four or more if the mood is only irritable) of seven listed features. Minimal durations of 7 days for mania and 4 days for hypomania are imposed, although neither of these intervals has been established empirically [3]. If, during the 'high' the individual experiences psychotic features, or if hospitalisation is required, then irrespective of duration, DSM-IV criteria for a manic episode are met. While mania and hypomania require a level of impairment, DSM-IV definitions of 'impairment' are not distinctive across either of the two expressions.

The ICD-10 [4] system contains only one bipolar category ('Bipolar Affective Disorder'), and weights description rather than meeting a set of diagnostic criteria. Hypomania is a non-psychotic state lasting "at least several days", with the associated mood and behavioural changes being more distinctive and persistent than allowed by a diagnosis of 'cyclothymia'. Manic episodes are defined as lasting from 2 weeks to several months and may or may not include psychotic features which, if present, may have mood congruent or mood incongruent characteristics.

Thus, the two categorical diagnostic systems essentially differentiate 'mania' from 'hypomania' by the presence of psychotic features, a longer minimum duration and (in the case of DSM-IV) by hospitalisation. In terms of clinical course, the DSM-IV system characterises BPD I as involving the occurrence of one or more manic episodes or mixed episodes, while BPD II involves at least one hypomanic episode and the occurrence of one or more episodes of major depression. The DSM-IV model essentially positions bipolar depression as 'major depression' – as it effectively does for unipolar depressive conditions. Thus, major depression can exist with or without diagnostic specifiers (e.g., psychotic features, catatonic features, melancholic features, and atypical features), context specifiers (e.g., post-partum onset) and course specifiers (e.g., chronicity, seasonal pattern, or rapid cycling). As major depression is not a specific diagnosis [5] and more an operational strategy to differentiate 'clinical depression' from less substantive depressive disorders, such specifiers are likely to be more salient in determining and quantifying whether 'bipolar depression' is more, or less, likely to be distinctive.

The ICD-10 system [4] adopts a dimensional model for the depressive disorders, operating across severity, persistence, and recurrence parameters. Its so-called 'somatic features' correspond broadly to DSM-IV melancholia criteria, but the Introduction notes that their scientific status is "somewhat questionable", so that such data can be recorded or ignored. Similarly, in light of the imprecise 'criteria' for hypomania ('at least several days') and 'cyclothymia' (where duration and severity criteria are not operationalised), differentiation of BPD from unipolar depressive disorder proves difficult. Thus, the ICD-10 system does not lend itself to 'top down' studies seeking to identify any specific features of bipolar depression.

We have sought to develop a categorical model for BPD and to assist discrimination from unipolar depressive disorders. We first developed [6] a questionnaire (the Mood Swings Survey or MSS), comprising 46 items capturing aspects of 'highs' as generated from a literature review and from clinical experience. In the initial study, 157 depressed outpatients were asked to complete the questionnaire. Of the 101 subjects diagnosed with BPD, 49 received a diagnosis of BPD I by largely respecting DSM-IV criteria of psychosis or hospitalisation (i.e., 61% had had psychotic manic episodes and 37% had been hospitalised when in a mood elevated state), and 52 received a diagnosis of BPD II disorder. BPD I and BPD II groups did not differ by mean age (41 *versus* 37 years), gender, social class, family history of BPD (41% *versus* 38%), nor age of onset of initial elevated mood (24 *versus* 22 years) or initial depression (22 *versus* 20 years). BPD I subjects were significantly more likely, however, to report longer periods of elevated mood.

In completing the MSS, the bipolar groups were asked two probe questions ("Do you ever have mood swings and, as part of such swings, have times when (i) your mood is higher than your usual sense of happiness", and (ii) "Do you feel quite 'wired', 'energised', 'elevated', 'expansive', and possibly 'irritable'?"), and asked to complete the questionnaire for such periods. The probe questions therefore sought to ensure that ratings were for manic or hypomanic episodes rather than merely for periods of happiness. By contrast, the 56 patients with a clinically diagnosed unipolar depressive disorder were asked to complete the same questionnaire (here titled 'Happiness Survey') and invited to think of "times when you are really happy (e.g., your favourite sporting team has won, you're spending a weekend with long-lost friends)". Each questionnaire had identical rating options ('much more than usual', 'somewhat more than usual', and 'no more than usual' scored, 2, 1 and 0, respectively). Items weighted high energy, mood elevation, creativity, disinhibition, mystical experiences, irritation, and anger constructs, but not psychotic features, and therefore sought to measure the core state defining a 'high'.

When questionnaires scores were summed, the 49 BPD I subjects had only marginally higher MSS scores than the 52 BPD II subjects (32.7 *versus* 29.7). The 56 unipolar subjects returned a mean score of 11.2, significantly lower than those with either BPD I or BPD II disorders. We examined the performance of the total score (and later a refined 27-item score) in terms of differentiating BPD and unipolar subjects from each other. Using the total MSS score, ROC analyses established a high level of discrimination (the Area-Under-the-Curve or AUC = 0.93), while at the derived cut-off score of 36 or more, a sensitivity and specificity of 84.3% and 92.6%, respectively, was quantified. Results therefore suggested that the 'core' mood/energy state (quantified by the measure) is likely to differentiate those with BPD from those with unipolar disorder, but not differentiate BPD I from BPD II expressions – again providing support for the MSS to discriminate bipolar from unipolar disorders.

Inspection of individual items indicated that those with BPD were most clearly distinguished from those with unipolar depressive disorders by high

energy and elevated mood items, essentially the converse of melancholic/psychotic depressive states, which (as detailed later) are dominated by psychomotor (including anergic) symptoms and a lowered mood state.

Such data allowed a model to be developed. The core mood/energy construct clearly differentiated bipolar and unipolar disorders, but was insufficient in itself to differentiate BPD I from BPD II conditions. Further, in our initial study, we established that, of those assigned on the basis of being psychotic and/or requiring hospitalisation during a high, 41% had experienced an episode of psychotic depression when depressed. By contrast, none of the BPD II subjects had experienced psychosis during episodes of elevated mood (by definition) and none – the key issue here in developing a model – had experienced psychotic depression when depressed. Such specificity argued for differentiating BPD I and BPD II conditions from each other by the *respective presence or absence of psychotic symptoms.*

Such specificity of psychotic symptoms and the mirror imaging of BPD I and BPD II polar states allows an 'isomer' or 'mirror image' model for distinguishing between BPD I and II disorders, and, of key importance here, having 'top down' potential to inform us about the expression of 'bipolar depression'. In essence, the model (as shown in Fig. 1) recognises that, while the elevated mood/energy state is a core construct of BPD (and shared across both BPD I and BPD II states), it is insufficient to effectively distinguish the two. It is the respective presence or absence of the psychotic 'mantle' that distinguishes BPD I from BPD II. This is a mixed model in that it dimensionalises the core mood/energy construct (increased in 'high' states, decreased in 'depressed' states, and with such changes slightly greater in BPD I subjects than BPD II

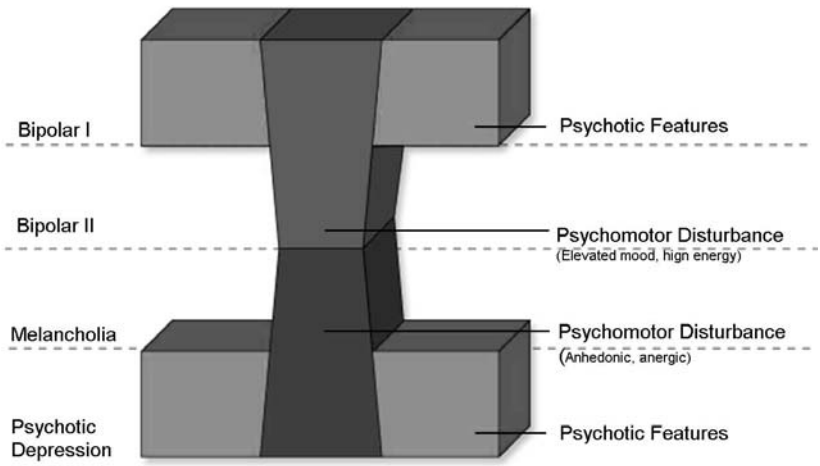


Figure 1. An isomer model capturing psychotic and melancholic depression as mirror images of Bipolar I and Bipolar II disorders, respectively.

subjects), and is categorical in positioning 'psychotic features' as differentiating subtypes of BPD.

The model is also heuristic. It presupposes that those with BPD II oscillate within a narrower band than those with BPD I. While we had previously produced data [7] indicating that those with BPD were highly likely to experience melancholic or psychotic depression when depressed, the isomer model allows more refined hypotheses. It suggests that those with BPD II oscillate between non-psychotic hypomanic and melancholic episodes, while those with BPD I experience psychotic manic episodes and have either psychotic or melancholic episodes when depressed. The model not only allows causal hypotheses to be pursued but provides a platform for testing the relative utility of quite differing drug treatments (antidepressants, mood stabilisers, and antipsychotic drugs) for BPD I and BPD II. Of key relevance here, the model allows comparisons to be made of 'bipolar depression' as experienced by those with differing BPD I and BPD II, as well as comparison to the depression experienced by those with unipolar depression.

Operationalising a 'bottom up' approach

The 'bottom up' approach involves assessing individuals or groups during the depressed phase and considering whether any of the clinical features are indicative or markers of BPD. This approach has also been applied in the absence of the individual reporting clear cut 'highs', particularly by those who model BPD as a non-categorical 'spectrum condition'. As reviewed by Phelps [8], proponents of the dimensional spectrum model allow the existence of some degree of bipolarity even in the absence of clear-cut hypomanic or manic episodes. For example, Ghaemi and colleagues [9] described a number of bipolar 'soft signs' effectively suggesting or allowing a diagnosis of BPD to be suspected on the basis of either (a) the *depressive features*, e.g., having four or more features of major depression; early onset (younger than 25 years) of first episode of major depression; 'atypical' symptoms such as hypersomnia and hyperphagia; or psychotic episodes when depressed; (b) *illness course variables*, e.g., brief episodes of major depression of less than 3 months; and (c) *associated variables*, e.g., a first-degree relative having a diagnosis of BPD; the individual having a hyperthymic personality style; onset of depression in the post-partum period; antidepressant-induced 'highs'; progressive loss of efficacy of an antidepressant (the 'poop out' phenomenon); and three or more unsuccessful antidepressant trials.

Ghaemi and colleagues [9] also provided an algorithm for defining 'bipolar spectrum disorder'. In addition to (i) at least one major depressive episode and no "spontaneous hypomanic or manic episodes" individuals should have either (a) a first-degree relative with a history of BPD or (b) antidepressant-induced manic or hypomanic switching, or, if neither of those features are present, at least 6 of 9 other criteria (essentially those listed in the previous paragraph).

Such a spectrum model is clearly problematic in risking 'over-diagnosis' of false positive bipolar states. As BPD is generally defined as an oscillating state with clearly defined highs and lows, a diagnosis of BPD in the absence of any hypomanic or manic episodes – and merely on the basis of 'soft signs' or proxy features – appears counter-intuitive, and risks intuitive rather than fact-based diagnostic practice. For example, one of those 'soft signs' (a 'hyperthymic' personality style) is worthy of contemplation. As detailed by Jamison [10], it is possible to have a personality style of 'exuberance' without necessitating a diagnosis of BPD. Just as Freud once observed that a cigar can simply be a cigar, sometimes exuberance is simply exuberance, and categorically independent of any 'hypomanic' or 'manic' status. To the extent that BPD is associated with any specific depressive phenotypic picture, then applying a dimensional spectrum model may confound delineation and description of bipolar depression.

An overview of previous studies of bipolar depression

While many individual studies exist that principally focus on differences in particular symptoms or illness correlates, consistency in findings is relatively low. We will first consider possible explanations for such issues before giving an overview of the general findings.

In any attempt to define 'bipolar depression' there are three immediate problems. First, it could be defined, as indicated in the 'top down' section, by studying those with BPD during the depressed phase. However, this descriptive approach is only of modest value as it lacks specificity. The more substantive second problem is whether bipolar depression is 'different' or 'distinctive' from unipolar depression, and the issue here is in considering and studying the appropriate reference group. Let us consider the limitations to any comparison with 'major depression' or 'clinical depression'. As noted earlier, neither represents a pure clinical depressive type, with each effectively capturing heterogeneous depressive conditions, caused (across individuals) by quite differing biological, psychological, and social factors, and subsequently expressed in quite variegated clinical feature patterns. If 'bipolar depression' is a pure type (say ubiquitously 'melancholic') and a sample of those with bipolar depression were compared to those with 'major depression' (with melancholic and non-melancholic constituent representation), then we might expect differentiation from the comparison group. If, by contrast, the comparison group was limited to those with a (unipolar) melancholic depressive episode, few or no differences might be expected. Differences then can be created or obviated by choice of comparison group.

The third problem is that it is unlikely that 'bipolar depression' is a homogenous entity. Based on the isomer noted earlier, we might expect that a sample of those with bipolar depression would include some with psychotic depression, a considerable proportion with melancholic depression, and some with non-melancholic disorders. The extent to which these three differing sub-types

were represented within the bipolar depression sample would also influence comparison with any reference group.

Turning to the literature, this key issue of whether 'bipolar depression' represents a pure type has rarely been considered. We reported [11] an analysis examining whether 'melancholia' was the characteristic sub-type, based on three large data sets of unipolar and patients with BPD recruited over a 15-year period. 'Melancholia' was defined using several diagnostic systems. When comparing BPD and unipolar subjects, the former group were significantly more likely to be diagnosed as having a melancholic depression by DSM-IV criteria (69% *versus* 37%), by the CORE measure [1] (59% *versus* 33%), and by clinical definition (70% *versus* 29%). We undertook logistic regression analyses examining a large number of clinical features, and found that observable psychomotor disturbance (particularly retardation) and pathological guilt were the only two significantly overrepresented features in those with BPD during the depressed phase. Results of these analyses confirm an over-representation of melancholia in the depressed phase of BPD and, via the over-representation of pathological guilt, suggest that psychotic depression is also likely to be represented.

In considering more fine-focused studies, it is more useful to consider an overview report rather than individual studies. One of the most comprehensive reviews was undertaken by Mitchell and colleagues [12] as part of the *International Society for Bipolar Disorders Guidelines Taskforce on Bipolar Depression*. As does much of the literature on BPD, this review focuses on BPD I, and it may be quite unwise to assume that what holds for BPD I can be extrapolated to BPD II. Nevertheless, the review is likely to be the definitive reference for a period. In terms of illness course, the authors suggest that depression is somewhat more likely to be the first state experienced by those initially experiencing BPD. Second, those with BPD tend to experience more depressive episodes over a lifetime than those with a unipolar depressive disorder; however the severity of depression does not appear to differ.

In terms of the depressive sub-type, the authors note an earlier paper that addressed the methodological concern noted early in this section – effectively the need to compare 'apples with apples'. Thus, if bipolar depression is most commonly melancholic in 'type', then those with bipolar depression should be matched in terms of depressive sub-type representation rather than compared with those within a broader diagnostic group (for instance, those with major depression). Mitchell and colleagues [13] compared 39 bipolar depressed patients with 39 unipolar depressed patients, matched for age, sex, and the presence or absence of melancholia as defined by the DSM-IV system. While the groups did not differ in terms of depression severity, those with BPD were more likely to have had a psychotic depressive episode in the past. During the current episode they were more likely to report anhedonia, persistence of depressed mood, and hypersomnia, but less anxiety. In terms of psychomotor disturbance, they did not differ in agitation severity but scored significantly higher on the measure of retardation.

Mitchell and colleagues [12] closely reviewed several other relevant studies and tabulated data (from a large number of studies) on potentially differential clinical features, co-morbid features, course of illness, and family history variables. Of the set of more than 20 clinical features, several were suggested as possibly more likely in those with BPD, including worthlessness, psychotic features, social withdrawal, hyperphagia and hypersomnia, and mood lability. Co-morbid anxiety states and alcohol use were suggested as overrepresented, as was a family history of BPD.

Mitchell and colleagues [12] examined some 40 candidate markers of bipolarity and proposed a 'probabilistic' model for considering a diagnosis of bipolar I depression in an individual experiencing a major depressive episode with no clear prior episodes of mania. In essence, they argued that those with bipolar depression would be more likely to report 'atypical depressive symptoms' (e.g., leaden paralysis, hypersomnia, hyperphagia) while those with unipolar depression would be more likely to report initial insomnia or general insomnia, and appetite and weight loss. Further, they suggested that those with bipolar depression would be more likely than those with unipolar depression to report: i) psychomotor retardation (activity levels in those with unipolar depression would be less likely to be abnormal); ii) psychotic features and/or pathological guilt (whereas those with unipolar depression would be more likely to report somatic complaints); and iii) lability of mood or manic symptoms. Drawing on their literature review, their probabilistic model argued that those with BPD would be more likely to have a positive family history of BPD, to have an early onset of their first depressive episode, and to have had multiple prior episodes of depression, while those with unipolar depression would be more likely to report depressive episodes lasting 6 months or longer.

Most measures assessing depressive phenomenology rate symptoms in terms of their severity (whether self-reported or observer-rated). We have recently completed a study in which patients attending our Depression Clinic were asked to rate their most recent and/or severe depressive episode in terms of its characteristic features. While these results will be reported elsewhere, we will review here the findings of relevance to this chapter.

We examined the most characteristic symptoms as nominated by those with (i) bipolar depression (n = 123), (ii) unipolar melancholia (n = 86), and (iii) unipolar non- melancholic depression (n = 142). The BPD/unipolar and melancholic/non-melancholic decisions were generated by careful clinical assessment. In this analysis, we did not differentiate between BPD I and BPD II. When the rank order of the 32 symptoms (returned by the unipolar melancholic and unipolar non-melancholic groups respectively) was compared, analyses indicated that bipolar patients' prioritising of characteristic symptoms was slightly closer to those with unipolar melancholia than to unipolar non-melancholic depression. Those with bipolar depression were somewhat more likely to report psychomotor disturbance (i.e., difficulty doing basic things like getting out of bed, feeling somewhat paralysed), and somewhat less likely to report irritability and anger than those with unipolar non-melancholic depres-

sion. Other differences between BPD and unipolar non-melancholic subjects included the former as more likely to report diurnal variation in mood (i.e., depressed mood worse in the morning), and concentration difficulties (i.e., brain feeling foggy, thinking slowed).

A synthesis and some speculation

Findings regarding bipolar depression, and in particular as reviewed by Mitchell and colleagues [12], suggest that those with BPD (compared to those with unipolar depression) are more likely to have a family history of BPD, somewhat briefer episodes of depression, and to report depressive symptoms that are generally compatible with melancholic and psychotic depression. That review concluded, however, that rather than report classic 'endogeneity symptoms' such as appetite/weight loss and insomnia (especially early morning wakening) those with BPD are more likely to report the so-called 'atypical features' of hyperphagia and hypersomnia.

Such over-representation of 'atypical depressive features' in those with BPD has long been recognised [14, 15]. However, such features – while common in younger subjects with bipolar depression – are also more common in younger subjects with unipolar melancholia. In one study [16], we focused on the relative proportion of those experiencing hypersomnia *versus* early morning wakening across three differing depressive sub-types (BPD, unipolar melancholia, and unipolar non-melancholic depression) and four age bands (<25 years, 26–35 years, 36–45 years and 46–55 years). Hypersomnia rates decreased as age increased in those with bipolar depression (i.e., 75%, 70%, 43% and 46%) and in those with unipolar melancholia (i.e., 60%, 44%, 43% and 30%) but not in the non-melancholic group (i.e., 76%, 61%, 57% and 66%). Hypersomnia (during depression) has been viewed as an adaptive homeostatic response restoring slow wave sleep during stress [17], and may therefore characterise a general coping response. However, as age increases, those with melancholic depression (whether experiencing a unipolar or bipolar course) may experience more noradrenergic neurotransmission perturbation with age, influencing HPA activity and thus contributing to a differing sleep pattern – the more classic endogeneity feature of early morning wakening. Similarly, we have speculated [15] that hyperphagia may be a general coping response, albeit more commonly reported by those with 'atypical depression', exerting a 'comforting' effect via release of endorphins and multiple other chemical compounds. As they age, those with bipolar depression and unipolar melancholia appear more likely to report the endogeneity symptoms of appetite and weight loss, and again this may reflect the impact of age on contributory monaminergic systems.

Concluding comments

We suggest that the clinical diagnosis of bipolar depression be weighted to a 'top down' approach, in light of many questions about the validity of the bipolar spectrum 'soft signs' approach. This would require ensuring that the individual meets appropriate diagnostic criteria for BPD I or BPD II in terms of their manic or hypomanic episodes respectively, and that they are assessed in relation to characteristic depressive episodes. While bipolar depression appears more weighted to the psychotic and melancholic clinical phenotype, there is the suggestion that so-called atypical features such as hypersomnia and hyperphagia may be over-represented, particularly in younger individuals.

We have detailed an 'isomer model' which suggests that bipolar depression should be studied separately in those with manic and hypomanic episodes, and provided data indicating that, while those with BPD I are at some risk of developing psychotic depression and those with BPD II are likely to develop melancholic episodes, those with BPD II are unlikely to develop psychotic depression.

Acknowledgements
Supported by Program Grant 222708 from the National Health and Medical Research Council of Australia and an Infrastructure Grant from NSW Health.

References

1 Parker G, Hadzi-Pavlovic D (eds): (1996) *Melancholia: A disorder of movement and mood*. Cambridge University Press, New York
2 American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders*, 4th edn. (DSM-IV). APA, Washington DC
3 Parker G, Manicavasagar V (eds): (2005) *Modelling and managing the depressive disorders*. Cambridge University Press, Cambridge
4 World Health Organization (1992) *International statistical classification of diseases and related health problems*. Tenth revision (ICD-10). WHO, Geneva
5 Parker G (2005) Beyond major depression. *Psychol Med* 35: 467–474
6 Parker G, Hadzi-Pavlovic D, Tully L (2006) Distinguishing bipolar and unipolar disorders: An isomer model. *J Affect Disord* 96: 67–73
7 Mitchell P, Sengoz A (1996) Phenotypic expression of melancholia contrasted for those with bipolar and unipolar illness courses. In: G Parker, D Hadzi-Pavlovic (eds): *Melancholia: A disorder of movement and mood.* Cambridge University Press, New York, 172–178
8 Phelps J (2008) The bipolar spectrum. In: G Parker (ed.): *Bipolar II disorder. Modelling, measuring and managing*. Cambridge University Press, Cambridge, 15–45
9 Ghaemi SN, Ko JY, Goodwin FK (2002) 'Cade's disease' and beyond: Misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry* 47: 125–143
10 Jamison KR (2005) *Exuberance: The passion for life.* Vintage Books, USA
11 Parker G, Roy K, Wilhelm K, Mitchell P, Hadzi-Pavlovic D (2000) The nature of bipolar depression: implications for the definition of melancholia. *J Affect Disord* 59: 217–224
12 Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RMA (2008) Diagnostic guidelines for bipolar I depression: A probabilistic approach. *Bipolar Disord* 10: 144–152
13 Mitchell P, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS (2001) The clinical features of bipolar depression: A comparison with matched major depressive disorder patients. *J Clin Psychiatry* 62: 212–216
14 Paykel ES, Rowan PR, Parker RR, Bhat AV (1982) Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Arch Gen Psychiatry* 39: 1041–1049

15 Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadzi-Pavlovic D (2002) Atypical depression: A reappraisal. *Am J Psychiatry* 159: 1470–1479
16 Parker G, Malhi G, Hadzi-Pavlovic D, Parker K (2006) Sleeping in? The impact of age and depressive sub-type on hypersomnia. *J Affect Disord* 90: 73–76
17 Thase ME, Frank E, Kornstein SG, Yonkers KA (2000) Gender differences in response to treatments of depression. In: E Frank (ed.): *Gender and its effects on psychopathology*. American Psychiatric Press, Washington DC, 103–129

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Course and outcome of bipolar disorder – focusing on depressive aspects

Tamas Treuer[1] and Mauricio Tohen[2]

[1] *Area Medical Center Vienna, Eli Lilly & Company, Budapest, Hungary*
[2] *Lilly Research Laboratories, Indianapolis, and McLean Hospital, Harvard Medical School, Belmont, USA*

Abstract

The prognosis of an illness is perhaps relatively more valuable in psychiatry than in other therapeutic areas, because the lack of a laboratory-based diagnostic test and poor biological markers in mental disorders limit outcome predictions based mostly on the information from the psychiatric interview and examination. This is particularly true in bipolar disorder. In this chapter the authors summarize the main factors predicting course and outcome in bipolar disorder with a focus on depressive symptoms. The natural course, the impact of first episode, the impact of depressive phase, cycle length, onset, age, gender, type of illness, personality traits and temperament, co-morbidity, family history, life events, and outcome features will be reviewed. Conceptual models and their prognostic value will be discussed as well.

Introduction

The prognosis of an illness is perhaps relatively more valuable in psychiatry than in other therapeutic areas, particularly because the lack of a laboratory-based diagnostic test and poor biological markers in mental disorders limit outcome predictions based mostly on the information gathered during the psychiatric interview and examination. Furthermore, clinical features are not always reliably available, and their impact is not always clear in assessing the outcome in the case of an individual patient. The assessment is further complicated by the fact that bipolar disorder in general represents a dimensional condition within a full spectrum of mood disorders [1].

Although there is agreement among researchers that bipolar spectrum disorders are severe, chronic, and lifelong conditions, and that breakthrough depression usually presents higher risks for long-term treatment than mania, there are several methodological issues in the study of the natural course of bipolar disorder [2]. Despite a considerable amount of research, the course and outcome of bipolar disorder still remain highly unpredictable. Likewise, it is difficult to determine the effect of treatment on the natural course of bipolar disorder that, despite treatment, still involves multiple relapses and impaired psychosocial functioning [3].

While identifying and treating the illness early in its time course may be associated with a better prognosis, there are several barriers to early identification; the delay from the first episode of illness to a diagnosis of bipolar disorder is approximately 10 years [4]. This delay poses a threat for the effectiveness of early treatment intervention, especially because data suggest that beginning lithium therapy within the first 10 years of illness may provide better outcomes than beginning prophylaxis later in life for patients with bipolar disorder [5]. Furthermore, a history of multiple previous episodes may be associated with poor response to lithium [6, 7], although these findings are limited by the lack of a comparator and the inclusion of subjects who had previously failed to respond to lithium. Similarly, long-term divalproex [8], non-pharmacological therapies [9], and maintenance therapy with olanzapine [10] have been found to be less effective in preventing relapses in patients with a high number of previous episodes.

The very high degree of co-morbidity and treatment resistance in outpatients with bipolar disorder highlights the need to develop new treatment approaches, much earlier illness recognition, diagnosis, and intervention in an attempt to reverse or prevent this illness burden [11]. Although full symptomatic remission does not guarantee functional recovery [12–14], it may have a favorable impact on long-term prognosis.

In this chapter we will summarize the main factors predicting course and outcome in bipolar disorder with a focus on depressive symptoms. The natural course, the impact of the first episode, the impact of the depressive phase, cycle length, age of onset, age, gender, type of illness, personality traits and temperament, co-morbidity, family history, life events, and outcome features will be reviewed. Conceptual models such as staging and outcome dimensions and their prognostic value will also be discussed.

Natural course

Researchers agree that bipolar spectrum disorders are severe chronic conditions, and should be considered lifelong disabilities [11], regardless of the impact of modern treatment on the natural course of the illness. It is uncertain how modern treatment interventions can significantly influence the natural course of the illness. High diagnostic instability is considered a feature of bipolar disorder, and a recent naturalistic study found a high prevalence of misdiagnosis and diagnostic shift from other psychiatric disorders to bipolar disorder [15]. More than half of severe mood disorders become bipolar disorder, and the risk of depression developing into bipolar disorder is lifelong [15, 16].

The decade-long McLean-Harvard First Episode Project has systematically followed large numbers of patients with DSM-IV bipolar or psychotic disorders from their first hospitalization. The project's findings indicate that the course of Bipolar I disorder is much less favorable than had been formerly believed, despite modern clinical treatment with mood-stabilizing and other

pharmchologic agents. Full functional recovery from initial episodes was uncommon, and full symptomatic recovery was much slower than early syndromal recovery; most early morbidity was depressive-dysphoric, as reported in mid-course, and initial depression or mixed-states predicted more later depressive episodes and overall morbidity, whereas initial mania or psychosis predicted later mania and a better prognosis [17].

Naturalistic and long-term studies showed that patients with bipolar disorder develop persistent impairment: patients experienced some degree of disability during the majority of long-term follow-up including 19–23% of the time with moderate and 7–9% of the time with severe overall impairment [18]. One study found that Bipolar I patients were completely unable to carry out work role functions during 30% of assessed months, which was significantly more than for unipolar major depression or Bipolar II patients (21% and 20%, respectively). Neuropsychological impairment persists during euthymic states, but it is confounded partly by mild affective symptoms in remitted patients. The clinical representations of these persistent alterations are related to the degree of disability [19].

The recurrence risk of bipolar disorders is about twice that of unipolar depression. Furthermore, recovery is more frequent among unipolar than among bipolar patients, although 5-year remission rates were found to be independent of the number of episodes [16]. There appears to be a constant risk of recurrence over the life-span up to the age of 70 or more, even 30 to 40 years after onset [20]. The long-term course usually causes significant handicaps and problems in the lives of patients, and in many cases leads to disability [21].

Illness recurrence and the course of syndromal and functional recovery

Most of the evidence from both the pre-lithium and modern eras suggests that the index episode tends to predict the polarity of the subsequent major mood episode: a manic index episode tends to predict a manic relapse, whereas a depressive index episode predicts a depressive relapse [22]; indexed mixed episodes have been found to predict relapse into a depressive episode [14]. The presence of at least two manic/hypomanic symptoms in the index episode is associated with a higher rate of family history of Bipolar I disorder, a higher score for suicidal thoughts during the episode, a longer duration of the episode, and a higher affective morbidity during the observation period [23].

Within 4 years of first lifetime hospitalization for mania, prospective data show that most subjects achieved syndromal recovery by 2 years, but 28% remained symptomatic, only 43% achieved functional recovery, and 57% switched phases or had new illness episodes after achieving recovery [24]. In this study, factors associated with a shorter time to syndromal recovery for 50% of the subjects were female sex, shorter index hospitalization, and lower initial depression ratings. The 43% who achieved functional recovery were more often older and had shorter index hospitalizations. Within 2 years of syn-

dromal recovery, 40% experienced a new episode of mania (20%) or depression (20%), and 19% switched phases without recovery. Predictors of manic recurrence were initial mood-incongruent psychotic features, lower premorbid occupational status, and initial manic presentation. Predictors of depression onset were higher occupational status, initial mixed presentation, and any co-morbidity [24].

Targeting residual symptoms in maintenance treatment may represent an opportunity to reduce risk of recurrence of bipolar disorder. Another 2-year follow-up study of the clinical features associated with the risk of recurrence in patients with bipolar disorder receiving treatment found that 58% of patients subsequently achieved recovery [25]. During up to 2 years of follow-up, half of these individuals experienced recurrences, with more than twice as many developing depressive episodes *versus* manic, hypomanic, or mixed episodes. Residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence [25]. Another recent report [26] suggests that it is not just chronic subsyndromal symptoms that predict shorter time to a new episode, but rather their emergence, particularly the emergence of depressive symptoms.

Although most bipolar adolescents experience syndromic recovery following their first hospitalization, rates of symptomatic and functional recovery are much lower [12, 13, 27]. Few studies have examined the clinical, neuropsychological, and pharmacological factors involved in the functional outcome of bipolar disorder. The variable that appears to best predict psychosocial functioning in bipolar patients is verbal memory; low-functioning patients are cognitively more impaired than highly functioning patients on verbal recall and executive functions [28]. Few studies have examined whether co-morbid personality disorders and other clinical factors can predict functional morbidity in bipolar disorder. Residual depression predicts poorer residential and social/leisure outcomes independent of personality disorders or maladaptive traits [29].

The mortality of patients with bipolar disorder is considerably higher than that of the general population. At least 25–50% of patients with bipolar disorder attempt suicide at least once in their lives [30]. Polarity of patients' first reported mood episode suggests that depression-prone subtypes have a greater probability of suicidal acts [31]. Patients with mood disorders in general have a higher risk of death by suicide (15–30%) than healthy people, however Bipolar II patients may be more likely to attempt suicide than Bipolar I patients. Co-morbid anxiety disorders may also elevate risk for suicidal ideation and attempts [32]. The rates of mixed depression among bipolar and non-bipolar depressive suicide attempters is much higher than previously reported among non-suicidal Bipolar II and unipolar depressive outpatients, suggesting that suicide attempters come mainly from mixed depressives who

have predominantly Bipolar II disorder [33]. Recent findings show that while modest changes in severity of depression are associated with statistically and clinically significant changes in functional impairment and disability in patients with bipolar disorder, changes in severity of mania or hypomania are not consistently associated with differences in functioning [34].

Dimensions of outcome and staging models

Berk and colleagues have suggested a staging model to predict outcome (Stage 0–Stage 5) [35]. Staging models are widely used in clinical medicine, and offer an insight into the progressive nature of many disorders. According to Berk, bipolar disorder begins with an at-risk, asymptomatic period, then patients begin to exhibit mild or non-specific symptoms that usually progress to manifest the range of prodromal patterns that have been described in the literature. The first threshold episode may then be followed by a first relapse, and subsequently followed by a pattern of periods of euthymia and recurrences. Some patients may have syndromal or symptomatic recovery, while others may have an unremitting or treatment refractory course. It is possible that all these stages require specific therapeutic interventions, and the impact of comorbidity, specific treatment, personality, adherence, and response to therapy could differ in each stage. Additional research is needed to clarify the usefulness of Berk's staging model to complement existing and proposed classifications of bipolar disorder, with an emphasis on a longitudinal dimension instead of a merely cross-sectional view.

The impact of treatment on the course of illness

The delay from the first episode of illness to a diagnosis of bipolar disorder is approximately 10 years, a circumstance that is at odds with the notion that early treatment intervention may contribute to a better prognosis. Studies have shown that bipolar disorder outcome worsens as the number of manic episodes increases [6], suggesting that prevention of recurrent episodes early during the disorder could improve long-term prognosis.

The initial prodrome of bipolar disorder has received very little attention to date and there are no prodromal features that clearly distinguish between patients who go on to develop bipolar disorder and those who develop schizophrenia [36]. Several authors point out that pharmacological treatment of the early phase of bipolar disorders lacks specific guidelines [37]. Knowledge is limited on how to identify prodromal bipolar from unipolar depression, but even mania is frequently misdiagnosed. This is key because the outcome of mania is not as good as was formerly believed [38].

Although the impact of different treatment options for bipolar disorder is discussed elsewhere in this book, it is worth noting that few effective treat-

ments exist for acute bipolar depression. Furthermore, the effectiveness and safety of specific treatments such as standard antidepressant agents for depressive episodes associated with bipolar disorder have not been well studied. Because episodes of depression are the most frequent cause of disability among patients with bipolar disorder, it is important to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania and therefore changing the course and outcome of the disorder. A recent double-blind controlled trial showed that the use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch [39]. It is also important to determine the benefits of the continued use of a typical antipsychotic agent following remission from an acute manic episode. Studies show that there are no short-term benefits with the continued use of a typical antipsychotic after achieving remission from an episode of acute mania. In fact, its continued use is associated with detrimental effects including relapse into depression [40].

Finally, a recent report suggested that early-stage (but not intermediate-or later-stage) patients had a significantly lower rate of relapse/recurrence of manic/mixed episodes with some treatments but not with others [10]. Subsyndromal symptoms are common during maintenance treatment and appear to be associated with relapse into an episode of the same polarity [26, 41]. Co-morbid anxiety symptoms in patients with bipolar depression have a negative impact on treatment outcome, so treatment interventions should focus on reducing both depressive and anxiety symptoms in these patients [42].

Predictive factors affecting prognosis

Age at onset and gender

The average age of onset of a first manic episode is 21 years, but onset may occur at any age from childhood to old age. Childhood-onset bipolar disorder usually has a poorer prognosis, and it is associated with long delays to first treatment, averaging more than 16 years. Patients with childhood or adolescent onset retrospectively report more episodes, more co-morbidities, and rapid cycling; prospectively, they demonstrate more severe mania, depression, and fewer days well [43].

Data have consistently shown that 70–100% of children and adolescents with bipolar disorder will eventually recover from their index episode, however, despite ongoing treatment, up to 80% will experience recurrences after recovery [44]. Bipolar disorder has a considerable effect on the normal psychosocial development of the child and increases the risk for academic, social, and interpersonal (family, peers, work) problems, as well as for health care utilization. Some studies suggest that approximately 30% of preadolescents with

major depressive disorder experience a manic episode and manifest bipolar disorder within 5 years [45].

Mania in the elderly appears to be a heterogeneous disorder. In elderly patients with first-episode mania who were followed for three to 10 years, men had a higher risk of mortality, and compared to patients with multiple episodes of mania, elderly patients with first-episode mania were twice as likely to have a co-morbid neurological disorder [46].

Previous findings suggest that men have a significantly earlier onset of first-episode mania and bipolar disorder associated with childhood antisocial behavior; women have more depressive episodes than manic episodes and higher incidence rates of Bipolar II disorder throughout adult life, except for early life, and a greater likelihood of rapid cycling [47]. More men than women report mania at the onset of Bipolar I disorder, and men also have higher rates of co-morbid alcohol abuse/dependence, cannabis abuse/dependence, pathological gambling, and conduct disorder [48]. Women report higher rates of co-morbid eating disorders, weight change, appetite change, and middle insomnia during depressive episodes [48]. However, no gender differences appear to exist between male and female subjects in time to remission from the index episode, number of recurrences, and time spent with any clinical or subclinical mood symptom over a 48-week period, at least when similar treatment strategies are adopted [49].

Type of onset, type of disorder

The length of untreated individual illness episodes in bipolar disorder varies from several weeks to several months, and depends on the type of episode. There are significant differences in time to recovery in patients with bipolar disorder by episode subtype [47, 50]. Based on a median follow-up of 18 months, the life-table estimate of the probability of remaining ill for at least 1 year was 7% for the pure manic patients compared with 32% in patients who entered the study with episodes that were mixed or cycling. Purely depressed patients had a 22% probability of remaining ill, approximating rates found in patients without bipolar disorder who have episodes of depression. However the duration of individual episodes also depends on response to treatment, and 15–30% of patients with mood disorders suffer from persisting alterations of personality or social interaction, or from persisting symptoms. Rapid-cycling and mixed states are associated with a poorer prognosis and non-response to anti-manic agents. Risk factors for rapid cycling include biologic rhythm dysregulation, antidepressant or stimulant use, hypothyroidism, and premenstrual and postpartum states [51].

Patients with bipolar disorder have an average of four episodes during the first 10 years of their illness. In general, poorer functioning and poorer psychosocial adjustment before the onset of illness predict worse outcome [52, 53]. After that, the average length of time between episodes is between 1 and

2 years. In both Bipolar I and II disorder, 60–70% of manic episodes occur immediately before or after a major depressive episode, and the interval between episodes tends to decrease as the individual ages. Differentiation of mood congruence of psychotic features in mania evidently has prognostic validity. Mood-incongruent psychotic features during the index manic episode predicted a shorter time in remission at 4 years [54]. Higher occupational status, initial mixed presentation, and any co-morbidity predicts depressive rather than manic onset [14]. Higher number of hospitalizations and less rapid cycling is associated with Bipolar I disorder as compared to Bipolar II [55, 56].

Personality traits and temperament

Personality and temperament are thought to impact prognosis and the clinical manifestation of bipolar disorder. Studies have suggested that mixed episodes may result from a mixture of inverse temperamental factors to a manic syndrome [57]. Some studies question the current categorical split of mood disorders into bipolar and depressive disorders, suggesting that two highly unstable personality features, i.e., the cyclothymic temperament and borderline personality disorder, have more in common with Bipolar II disorder than major depressive disorder [58]. Several research findings that are in line with current familial-genetic models of this disorder suggest that the DSM-IV characterization of Bipolar disorder II must include a greater emphasis on temperamentally based mood and anxious reactivity [59]. Such phenotypic characterization may assist in genotyping; however its predictive value on outcome still requires more research [60].

Family history and genetics

The application of genomics to clinical practice is limited at present, but is expected to grow rapidly. Despite some recent successes, identifying genes for bipolar disorder through classic human genetic studies is not consistent; the main issue is the lack of replication of the findings in this field [61]. There are many possible reasons for this relatively slow discovery. Bipolar disorder is a complex polygenic disorder, with variable penetrance and phenotypic heterogeneity, and it overlaps and is interdependent with other neuropsychiatric disorders. In addition, the effects of environmental factors (epigenetic modifications, effects of stress, infections, drugs, medications) on the expression of the phenotype are not fully understood nor factored into human genetic linkage studies [62]. There is increasing evidence that genome-wide association studies represent a powerful approach to the identification of genes involved in common human diseases [63]. The first genome-wide association study of bipolar disorder showed that several genes, each of modest effect, reproducibly influence disease risk [64].

Bipolar II depression, subsyndromal depression, and mixed depression

Mixed depression is probably a key component of the continuum concept of mood disorders, and it might have a predictive role in the course of bipolar disorder. Recent findings suggest that the prevalence of mixed depression is high in patients with bipolar disorders. Mixed depression is defined by the combination of depression (major depressive episode) and non-euphoric, usually subsyndromal, manic or hypomanic symptoms [65]. The reemerging concept of mixed depression also influences how we see the boundaries between bipolar and depressive disorders.

Bipolar II disorder and mixed depression are relatively understudied, despite a prevalence of about 5% in the community and about 50% in depressed outpatients [65]. Prospective studies have shown that the longitudinal weekly symptomatic course of Bipolar I disorder is chronic, that the symptomatic structure is primarily depressive rather than manic, and that subsyndromal and minor affective symptoms predominate, although symptom severity levels fluctuate [66]. Depressive episodes and symptoms, which dominate the course of Bipolar I and II disorder, appear to be more disabling than corresponding levels of manic or hypomanic symptoms. Table 1 summarizes the predictive value of depressive symptoms on the course of bipolar disorder. Subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment; and subsyndromal hypomanic symptoms appear to enhance functioning in Bipolar II disorder [67]. Sub-syndromal symptoms in bipolar disorder impair functioning and diminish quality of life. Findings suggest that the presence of subsyndromal depressive symptoms during the first 2 months significantly increases the likelihood of depressive relapse [26]. Patients with psychotic features and those with a greater number of previous depressive episodes were more likely to experience subsyndromal depressive symptoms.

As noted previously, because a substantial number of patients with bipolar disorder present with an index depressive episode, it is likely that many are misdiagnosed with unipolar major depression. Whether or not antidepressants worsen the course of bipolar disorder is still being debated, because misdiagnosed patients are often treated with antidepressants, which, if used improperly, are known to induce mania and provoke rapid cycling [68]. Furthermore, it appears that a first depressive rather than manic episode in bipolar disorder might lead to a subsequent course with a greater burden of depressive symptoms [69]. Depressive-onset bipolar disorder is significantly associated with more lifetime depressive episodes and a greater proportion of time with depression and anxiety in the year prior to assessment. However, the quantity and severity of weeks in symptomatic affective states are possibly greater predictors of affective burden in Bipolar I patients than the quantity and direction of affective switches [70]. Analysis of assessments in clinical trials revealed that over 80% of the treatment effect is attributable to the indirect effects of improvements in the depressive factors of the Montgomery-Asberg

Table 1. Predictive value of depressive symptoms in the course of bipolar disorder*

Onset and index episode
• Index mixed episodes have been found to predict relapse into a depressive episode
• It is likely that many patients presenting with an index depressive episode are misdiagnosed with unipolar major depression
• One third of preadolescents with major depressive disorder experience a manic episode and manifest bipolar disorder within 5 years
• Lower initial depression ratings are associated with shorter time to syndromal recovery
• A depressive onset is predicted by higher occupational status, initial mixed presentation, and any co-morbidity
• Polarity of patients' first reported mood episode suggests a depression-prone subtype with a greater probability of past suicide attempt
• Depressive-onset bipolar disorder is significantly associated with more lifetime depressive episodes and a greater proportion of time with depression and anxiety
Course, number and length of episodes
• The symptomatic structure of bipolar II disorder is primarily depressive rather than manic
• Twice as many patients develop depressive episodes as manic, hypomanic, or mixed episodes
• Residual depressive or manic symptoms at recovery and proportion of days depressed are significantly associated with shorter time to depressive recurrence
• The longest duration of episodes was found for mixed episodes, while depressive episodes have an intermediate duration and manic episodes are the shortest
• 60–70% of manic episodes occur immediately before or after a major depressive episode, and manic episodes often precede or follow the major depressive episodes
• Shorter time to a depressive recurrence can be predicted if residual depressive or manic symptoms are still present at recovery
• Rapid cycling can be related to a higher number of prior depressive episodes
• Patients with psychotic features and those with a greater number of previous depressive episodes were more likely to experience subsyndromal depressive symptoms
• 80% of the treatment effect is attributable to the indirect effects of improvements in the depressive symptoms
Risk for long term-prognosis
• Breakthrough depression represents higher risks for long-term treatment than mania
• Every new episode of depression brings a new risk for mania
• The risk of depression developing into bipolar disorder remains constant lifelong
• Subsyndromal depressive symptoms during the first 2 months after recovery significantly increases the likelihood of depressive relapse
Functional Recovery – Outcome
• Depressed patients are more impaired than euthymic or hypomanic patients on tests of verbal recall and fine motor skills
• Residual depression predicts poorer residential and social/leisure outcomes independent of personality disorders or maladaptive traits
• Suicide attempters come mainly from mixed depressives with predominantly Bipolar II base
• Subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment

* All the statements in this table are referenced in the text

Depression Rating Scale like sadness, negative thoughts, detachment, and neurovegetative symptoms, and changes in factor scores are highly correlated with changes in clinical improvement [71].

Co-morbidity

Bipolar disorder has frequent co-morbidities that worsen prognosis, especially in association with substance use disorders [72, 73]. The relative age at onset of alcohol use and bipolar disorders is associated with differences in the course of both conditions. A first hospitalization for mania is associated with a period of recovery from co-morbid alcohol abuse [74, 75]. Those patients with alcohol-use problems prior to bipolar disorder are usually older, more likely to recover, and more likely to recover quickly than those whose alcohol problems occur after their diagnosis of bipolar disorder. In contrast, those who have bipolar disorder first spend more time with affective episodes and symptoms of an alcohol-use disorder during follow-up. Co-morbid alcoholism is also usually related to poorer psychosocial adjustment [55].

Slower recovery has been associated with co-morbid drug abuse [76, 77]. Attention deficit/hyperactivity disorder and anxiety disorders, including those present during relative euthymia, also predict a poorer bipolar course [78, 79]. Co-morbid panic disorder is associated with a higher likelihood of rapid cycling [56]. One recent study showed that anxiety co-morbidity impacts health-related quality of life in patients with Bipolar disorder I but not in Bipolar disorder II [80].

Little is known about the treatment of psychiatric co-morbidities in bipolar disorder, because their treatment is largely empirically based rather than based on controlled data [81]. Many studies have examined the prevalence and predictive validity of axis II personality disorders among unipolar depressed patients, but few have examined these issues among bipolar patients [82]. Findings suggest that clinicians should be more vigilant for co-morbid personality and bipolar disorder, and less reluctant to diagnose it [82, 83]. When structured assessment of personality disorder is performed during a clinical remission, less than one in three bipolar patients meets full syndromal criteria for an axis II disorder [84]. Borderline personality disorder and bipolar disorder can often co-occur, but their relationship is not consistent or specific. Existing data fail to support the conclusion that borderline personality disorder and bipolar disorders exist on a spectrum, but allows for the possibility of partially overlapping etiologies [85].

Bipolar patients with lifetime smoking are more likely to have earlier age at onset of mood disorder, greater severity of symptoms, poorer functioning, history of a suicide attempt, and a lifetime history of co-morbid anxiety and substance use disorders. Smoking may also be independently associated with suicidal behavior in bipolar disorder [86]. The effects of the sequence of onset of bipolar and cannabis use disorders are less pronounced than observed in co-

occurring alcohol and bipolar disorders [87]. Cannabis use is associated with more time in affective episodes and with rapid cycling. Most cannabis use disorders remit immediately after hospitalization, followed by rapid rates of recurrence.

Individuals with bipolar disorder are differentially affected by several stress-sensitive medical disorders such as circulatory disorders, obesity, and diabetes mellitus. Individuals with respiratory disorders, infectious diseases, epilepsy, multiple sclerosis, migraine, and circulatory disorders may also have a higher prevalence of bipolar disorder [88]. The increasing medical burden in bipolar disorder is not simply a result of psychiatric symptoms and the attendant dysfunction [89]. Psychiatric co-morbidity is often associated with earlier onset of bipolar symptoms, more severe course, poorer treatment compliance, and worse outcomes related to suicide and other complications. It is still uncertain whether the medical co-morbidities are subsequent to the bipolar diagnosis or subsequent to its treatment [90]. To ensure prompt, appropriate intervention while avoiding iatrogenic complications, the clinician must evaluate and monitor patients with bipolar disorder for the presence and the development of co-morbid psychiatric and medical conditions.

Life events

Stressful life events can unfavorably alter the course of the illness, and negatively influence the adherence to maintenance treatment. They have been associated with slower recovery and higher relapse rates. Stress is linked to changes in mood symptoms among bipolar adolescents, although correlations between life events and symptoms vary with age [91]. There is no significant interaction between stress and episode number in the prediction of bipolar recurrence, and the interaction of early adversity severity and stressful life events significantly predicts recurrence in a manner consistent with the sensitization hypothesis [92].

Few studies have examined the prognostic value of family factors in the course of bipolar disorder. Patients who were more distressed by their relatives' criticisms had more severe depressive and manic symptoms and proportionately fewer days well [93]. Besides associations between high emotionality and unipolar depression, studies that examine the relationship between temperament, recent, and remote life events, and psychopathology among the offspring of parents with bipolar disorder found that there is an association between psychopathology and the number of recent negative life events, but no association between psychopathology and the number of early losses [94]. In this population, any effect of undesirable life events would appear to be mediated through the association with emotionality. Childhood adversity may be a risk factor for vulnerability to early onset illness, and an array of stressors may be relevant not only to the onset, recurrence, and progression of affective episodes, but the highly prevalent substance abuse co-morbidities as well [95].

Neurocognition

Recent analyses have revealed modest impairment in executive functioning, memory, and attention in both hypomanic and depressed bipolar patients, with additional fine motor skills impairment in the latter [96]. Bipolar depressed and hypomanic patients differ with respect to the nature of their memory impairment. Depressed patients are more impaired compared to euthymic patients on tests of verbal recall and fine motor skills. Psychosocial functioning is impaired across all three patient groups, but only in depressed and hypomanic patients does this correlate significantly with neuropsychological performance. These cognitive difficulties, especially related to verbal memory, may help explain the impairment regarding daily functioning, even during remission [97], and these are in line with the findings that full symptomatic recovery (remission) does not guarantee functional recovery [6, 14, 24].

While considerable evidence suggests that neurocognition declines steadily over the early course of schizophrenia, but is more stable in bipolar disorder, very little known about the longitudinal trait stability of neurocognitive performance in bipolar disorder. One recent study found that patients with bipolar disorder showed stability over time in attentional measures but greater variability in other domains over a 5-year period [98]. Impaired insight and other neurocognitive dysfunctions are correlated among symptomatic as well as remitted bipolar patients [99]. Cognitive impairment seems to be related to a worse clinical course and poor functional outcome, however further studies are needed to clarify whether a severe course of illness is associated with more pronounced cognitive disorders and whether psychotic symptoms during the acute phase of the illness can predict cognitive deficits in patients with bipolar disorder later in the illness. Recent findings suggest that patients with bipolar disorder lose hippocampal, fusiform, and cerebellar gray matter at an accelerated rate compared with healthy control subjects. This tissue loss can be associated with deterioration in cognitive function and illness course [100].

Future trends and research

Despite considerable research efforts in this area, the psychiatric interview and an examination focusing on the longitudinal course specifiers remain the main source of prognostic information to guide physicians in their assessment of bipolar disorder. Although tailored therapy is the favorable future goal of an individual treatment plan, more research is needed to establish better and more reliable course predictors for individual patients. Besides pharmacogenomic evaluation of subject data from long-term naturalistic studies, more dimensional descriptions of the disorder are warranted to maximize subtype homogeneity. The predictive value and use of mood-congruent *versus* mood-incongruent psychotic symptoms, mixed episodes, cognitive symptoms, and predominant polarities is limited by current specifiers of bipolar disorder [101].

DSM-V needs to consider a change in the categorical descriptors to more reliable dimensional ones, thus stimulating and refining research in the field further [102]. Depressive symptoms, which dominate the longitudinal symptomatic course of bipolar disorder, should receive more attention in the clinical assessment of patients, and the predictive role and impact of these depressive aspects on treatment decisions should be clarified further in upcoming research.

References

1 Kessler RC, Akiskal HS, Angst J, Guyer M, Hirschfeld RM, Merikangas KR, Stang PE (2006) Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. *J Affect Disord* 96: 259–269

2 Wittchen HU, Mhlig S, Pezawas L (2003) Natural course and burden of bipolar disorders. *Int J Neuropsychopharmacol* 6: 145–154

3 Goldberg JF, Harrow M, Grossman LS (1995) Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am J Psychiatry* 152: 379–384

4 Hirschfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 64: 161–174

5 Franchini L, Zanardi R, Smeraldi E, Gasperini M (1999) Early onset of lithium prophylaxis as a predictor of good long-term outcome. *Eur Arch Psychiatry Clin Neurosci* 249: 227–230

6 Tohen M, Waternaux CM, Tsuang MT (1990) Outcome in Mania. A four year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry* 47: 1106–1111

7 Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD (1999) Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am J Psychiatry* 156: 1264–1266

8 Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL (2005) A 20-month, double-blind, maintenance trial of lithium *versus* divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 162: 2152–2161

9 Scott J, Colom F, Vieta E (2007) A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. *Int J Neuropsychopharmacol* 10: 123–129

10 Ketter TA, Houston JP, Adams DH, Risser RC, Meyers AL, Williamson DJ, Tohen M (2006) Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. *J Clin Psychiatry* 67: 95–101

11 Post RM, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Keck PE Jr, McElroy SL, Kupka R, Nolen WA, Grunze H et al (2003) An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). *Bipolar Disord* 5: 310–319

12 Tohen M, Waternaux CM, Tsuang MT, Hunt AT (1990) Four year follow-up of twenty-four first-episode manic patients. *J Affect Disord* 19: 79–86

13 Tohen M, Hennen J, Zarate C, Baldessarini R, Strakowski S, Stoll A, Faedda G, Suppes T, Gebre-Medhin P, Cohen B (2000) The McLean/Harvard First Episode Project: Two-year syndromal and functional recovery in 219 cases of major affective disorders with psychotic features. *Am J Psychiatry* 157: 220–228

14 Tohen M, Zarate CA, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ (2003) The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry* 160: 2099–2107

15 Salvatore P, Tohen M, Khalsa HM, Baethge C, Tondo L, Baldessarini RJ (2007) Longitudinal research on bipolar disorders. *Epidemiol Psichiatr Soc* 16: 109–117

16 Angst J, Sellaro R, Stassen HH, Gamma A (2005) Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* 84: 149–157

17 Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Lopez-Castroman J, Fernandez del Moral AL, Jimenez-Arriero MA, Gronzalez de Rivera JL, Saiz-Ruiz J, Leiva-Murillo JM, de Prado-Cumplido M et al (2007) Diagnostic stability and evolution of bipolar disorder in clinical practice: a prospective cohort study. *Acta Psychiatr Scand* 115: 473–480
18 Judd LL, Schettler PJ, Solomon DA, Maser JD, Coryell W, Endicott J, Akiskal HS (2008) Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *J Affect Disord* Nov 14 [Epub ahead of print]
19 Marneros A, Deister A, Rohde A (1991) [Phenomenologic constellations of persistent alterations in idiopathic psychoses. An empirical comparative study] (German) *Nervenarzt* 62: 676–681
20 Angst J, Gamma A, Sellaro R, Lavori PW, Zhang H (2003) Recurrence of bipolar disorders and major depression. A life-long perspective. *Eur Arch Psychiatry Clin Neurosci* 253: 236–240
21 Nolen WA, Luckenbaugh DA, Altshuler LL, Suppes T, McElroy SL, Frye MA, Kupka RW, Keck PE Jr, Leverich GS, Post RM (2004) Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. *Am J Psychiatry* 161: 1447–1454
22 Calabrese JR, Vieta E, El-Mallakh R, Findling RL, Youngstrom EA, Elhaj O, Gajwani P, Pies R (2004) Mood state at study entry as predictor of the polarity of relapse in bipolar disorder. *Biol Psychiatry* 56: 957–963
23 Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L (2006) Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. *J Clin Psychiatry* 67: 712–719
24 Tohen M, Zarate CA, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ (2003) The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry* 160: 2099–2107
25 Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW, Gyulai L et al (2006) Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 163: 217–224
26 Tohen M, Bowden CL, Calabrese JR, Lin D, Forrester TD, Sachs GS, Koukopoulos A, Yatham L, Grunze H (2006) Influence of sub-syndromal symptoms after remission from manic or mixed episodes. *Br J Psychiatry* 189: 515–519
27 DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM (2007) Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry* 164: 582–590
28 Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, Malhi GS, Gonzalez-Pinto A, Daban C, Alvarez-Grandi S et al (2007) Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord* 9: 103–113
29 Loftus ST, Jaeger J (2006) Psychosocial outcome in bipolar I patients with a personality disorder. *J Nerv Ment Dis* 194: 967–970
30 Jamison KR (2000) Suicide and bipolar disorder. *J Clin Psychiatry* 61(Suppl): 47–51
31 Chaudhury SR, Grunebaum MF, Galfalvy HC, Burke AK, Sher L, Parsey RV, Everett B, Mann JJ, Oquendo MA (2007) Does first episode polarity predict risk for suicide attempt in bipolar disorder? *J Affect Disord* 104: 245–250
32 Simon NM, Zalta AK, Otto MW, Ostacher MJ, Fischmann D, Chow CW, Thompson EH, Stevens JC, Demopulos CM, Nierenberg AA et al (2007) The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. *J Psychiatr Res* 41: 255–264
33 Balazs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS (2006) The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. *J Affect Disord* 91: 133–138
34 Simon GE, Bauer MS, Ludman EJ, Operskalski BH, Unützer J (2007) Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *J Clin Psychiatry* 68: 1237–1245
35 Berk M, Hallam KT, McGorry PD (2007) The potential utility of a staging model as a course specifier: A bipolar disorder perspective. *J Affect Disord* 100: 279–281
36 Thompson KN, Conus PO, Ward JL, Phillips LJ, Koutsogiannis J, Leicester S, McGorry PD (2003) The initial prodrome to bipolar affective disorder: prospective case studies. *J Affect Disord* 77: 79–85
37 Conus P, Berk M, McGorry PD (2006) Pharmacological treatment in the early phase of bipolar disorders: what stage are we at? *Aust N Z J Psychiatry* 40: 199–207

38 Conus P, McGorry PD (2002) First-episode mania: a neglected priority for early intervention. *Aust N Z J Psychiatry* 36: 158–172
39 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 26: 1711–1722
40 Zarate CA Jr, Tohen M (2004) Double-blind comparison of the continued use of antipsychotic treatment *versus* its discontinuation in remitted manic patients. *Am J Psychiatry* 161: 169–171
41 Frye MA, Yatham LN, Calabrese JR, Bowden CL, Ketter TA, Suppes T, Adams BE, Thompson TR (2006) Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *J Clin Psychiatry* 67: 1721–1728
42 Tohen M, Calabrese J, Vieta E, Bowden C, Gonzalez-Pinto A, Lin D, Xu W, Corya S (2007) Effect of comorbid anxiety on treatment response in bipolar depression. *J Affect Disord* 104: 137–146
43 Leverich GS, Post RM, Keck PE Jr, Altshuler LL, Frye MA, Kupka RW, Nolen WA, Suppes T, McElroy SL, Grunze H et al (2007) The poor prognosis of childhood-onset bipolar disorder. *J Pediatr* 150: 485–490
44 Birmaher B, Axelson D (2006) Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol* 18: 1023–1035
45 Geller B, Fox LW, Clark KA (1994) Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *J Am Acad Child Adolesc Psychiatry* 33: 461–468
46 Tohen M, Shulman KI, Satlin A (1994) First-episode mania in late life. *Am J Psychiatry* 151: 130–132
47 Marneros A (2006) Mood disorders: epidemiology and natural history. *Psychiatry* 4: 119–122
48 Kawa I, Carter JD, Joyce PR, Doughty CJ, Frampton CM, Wells JE, Walsh AE, Olds RJ (2005) Gender differences in bipolar disorder: age of onset, course, comorbidity, and symptom presentation. *Bipolar Disord* 7: 119–125
49 Benedetti A, Fagiolini A, Casamassima F, Mian MS, Adamovit A, Musetti L, Lattanzi L, Cassano GB (2007) Gender differences in bipolar disorder type 1: a 48-week prospective follow-up of 72 patients treated in an Italian tertiary care center. *J Nerv Ment Dis* 195: 93–96
50 Keller MB, Lavori PW, Coryell W, Andreasen NC, Endicott J, Clayton PJ, Klerman GL, Hirschfeld RM (1986) Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. *JAMA* 255: 3138–3142
51 American Psychiatric Association (2002) Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159: 1–50
52 Tsai SM, Chen C, Kuo C, Lee J, Lee H, Strakowski SM (2001) 15-year outcome of treated bipolar disorder. *J Affect Disord* 63: 215–220
53 Meeks S (1999) Bipolar disorder in the latter half of life: symptom presentation, global functioning and age of onset. *J Affect Disord* 52: 161–167
54 Tohen M, Tsuang MT, Goodwin DC (1992) Prediction of outcome in mania by mood-congruent or mood-incongruent psychotic features. *Am J Psychiatry* 149: 1580–1584
55 Coryell W, Keller M, Endicott J, Andreasen N, Clayton P, Hirschfeld R (1989) Bipolar II illness: course and outcome over a fiveyear period. *Psychol Med* 19: 129–141
56 Coryell W, Endicott J, Keller M (1992) Rapidly cycling affective disorder: demographics, diagnosis, family history, and course. *Arch Gen Psychiatry* 49: 126–131
57 Rottig D, Rottig S, Brieger P, Marneros A (2007) Temperament and personality in bipolar I patients with and without mixed episodes. *J Affect Disord* 104: 97–102
58 Benazzi F (2006) Does temperamental instability support a continuity between bipolar II disorder and major depressive disorder? *Eur Psychiatry* 21: 274–279
59 Akiskal HS, Kilzieh N, Maser JD, Clayton PJ, Schettler PJ, Traci Shea M, Endicott J, Scheftner W, Hirschfeld RM, Keller MB (2006) The distinct temperament profiles of bipolar I, bipolar II and unipolar patients. *J Affect Disord* 92: 19–33
60 Akiskal HS, Akiskal KK, Perugi G, Toni C, Ruffolo G, Tusini G (2006) Bipolar II and anxious reactive "comorbidity": toward better phenotypic characterization suitable for genotyping. *J Affect Disord* 96: 239–247
61 Kato T (2007) Molecular genetics of bipolar disorder and depression. *Psychiatry Clin Neurosci* 61: 3–19
62 Le-Niculescu H, McFarland MJ, Mamidipalli S, Ogden CA, Kuczenski R, Kurian SM, Salomon DR, Tsuang MT, Nurnberger Jr, JI, Niculescu AB (2007) Convergent functional genomics of bipolar disorder: from animal model pharmacogenomics to human genetics and biomarkers. *Neurosci*

Biobehav Rev 31: 897–903
63 Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447: 661–678
64 Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nöthen MM et al (2008) A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry* 13: 197–207
65 Benazzi F. (2007) Bipolar disorder – focus on bipolar II disorder and mixed depression. *Lancet* 369: 935–945
66 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537
67 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB (2005) Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry* 62: 1322–1330
68 Goldberg JF (2003) When do antidepressants worsen the course of bipolar disorder*? J Psychiatr Pract* 9: 181–194
69 Perlis RH, Delbello MP, Miyahara S, Wisniewski SR, Sachs GS, Nierenberg AA (2005) STEP-BD investigators. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. *Biol Psychiatry* 58: 549–553
70 Mysels DJ, Endicott J, Nee J, Maser JD, Solomon D, Coryell W, Leon AC (2007) The association between course of illness and subsequent morbidity in bipolar I disorder. *J Psychiatr Res* 41: 80–89
71 Williamson D, Brown E, Perlis RH, Ahl J, Baker RW, Tohen M (2006) Clinical relevance of depressive symptom improvement in bipolar I depressed patients. *J Affect Disord* 92: 261–266
72 Tohen M (ed.) (1999) *Comorbidity in affective disorders*. Marcel Decker, NY
73 Tohen M, Greenfield SF, Weiss RD, Zarate CA, Vagge L (1998) The effect of comorbid substance use disorders on the course of bipolar disorder. *Harvard Rev Psych* 6: 133–141
74 Strakowski SM, Tohen M, Stoll AL, Faedda GL, Goodwin DC (1992) Comorbidity in mania at first hospitalization. *Am J Psychiatry* 149: 554–556
75 Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE Jr, Arnold LM, Amicone J (2005) Effects of co-occurring alcohol abuse on the course of bipolar disorder following a first hospitalization for mania. *Arch Gen Psychiatry* 62: 851–858
76 Strakowski SM, Keck PE Jr, McElroy SL, West SA, Sax KW, Hawkins JM, Kmetz GF, Upadhyaya VH, Tugrul KC, Bourne ML (1998) Twelve months outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiatry* 55: 49–55
77 Baethge C, Baldessarini RJ, Khalso H-M K, Hennen J, Salvatore P, Tohen M (2005) Substance abuse in first-episode Bipolar I disorder: indications for early intervention. *Am J Psychiatry* 162: 1008–1010
78 Otto MW, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, Frank E, Nierenberg AA, Marangell LB, Sagduyu K, STEP-BD Investigators (2006) Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. *Br J Psychiatry* 189: 20–25
79 Baldassano CF (2006) Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder. *J Clin Psychiatry* 11: 8–11
80 Albert U, Rosso G, Maina G, Bogetto F (2008) Impact of anxiety disorder comorbidity on quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. *J Affect Disord* 105: 297–303
81 Singh JB, Zarate CA Jr, (2006) Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials*. Bipolar Disord* 8: 696–709
82 George EL, Miklowitz DJ, Richards JA, Simoneau TL, Taylor DO (2003) The comorbidity of bipolar disorder and axis II personality disorders: prevalence and clinical correlates. *Bipolar Disord* 5: 115–122
83 Barbato N, Hafner RJ (1998) Comorbidity of bipolar and personality disorder. *Aust N Z J Psychiatry* 32: 276–280
84 Paris J, Gunderson J, Weinberg I (2007) The interface between borderline personality disorder and bipolar spectrum disorders. *Compr Psychiatry* 48: 145–154

85 Stromberg D, Ronningstam E, Gunderson J, Tohen M (1998) Pathological narcissism in bipolar disorder patients. *J Personal Disord* 12: 179–185
86 Ostacher MJ, Nierenberg AA, Perlis RH, Eidelman P, Borrelli DJ, Tran TB, Marzilli Ericson G, Weiss RD, Sachs GS (2006) The relationship between smoking and suicidal behavior, comorbidity, and course of illness in bipolar disorder. *J Clin Psychiatry* 67: 1907–1911
87 Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE, Arnold LM, Amicone J (2007) Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch Gen Psychiatry* 64: 57–64
88 McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, Konarski JZ, Kennedy SH (2007) Medical comorbidity in bipolar disorder: reprioritizing unmet needs. *Curr Opin Psychiatry* 20: 406–416
89 Kupfer DJ (2005) The increasing medical burden in bipolar disorder. *JAMA* 25: 2528–2530
90 Krishnan KR (2005) Psychiatric and medical comorbidities of bipolar disorder. *Psychosom Med* 67: 1–8
91 Kim EY, Miklowitz DJ, Biuckians A, Mullen K (2007) Life stress and the course of early-onset bipolar disorder. *J Affect Disord* 99: 37–44
92 Dienes KA, Hammen C, Henry RM, Cohen AN, Daley SE (2006) The stress sensitization hypothesis: understanding the course of bipolar disorder. *J Affect Disord* 95: 43–49
93 Miklowitz DJ, Wisniewski SR, Miyahara S, Otto MW, Sachs GS (2005) Perceived criticism from family members as a predictor of the one-year course of bipolar disorder. *Psychiatry Res* 136: 101–111
94 Duffy A, Alda M, Trinneer A, Demidenko N, Grof P, Goodyer IM (2007) Temperament, life events, and psychopathology among the offspring of bipolar parents. *Eur Child Adolesc Psychiatry* 16: 222–228
95 Post RM, Leverich GS (2006) The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol* 18: 1181–1211
96 Malhi GS, Ivanovski B, Hadzi-Pavlovic D, Mitchell PB, Vieta E, Sachdev P (2007) Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disord* 9: 114–125
97 Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M (2004) Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry* 161: 262–270
98 Burdick KE, Goldberg JF, Harrow M, Faull RN, Malhotra AK (2006) Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. *J Nerv Ment Dis* 194: 255–260
99 Varga M, Magnusson A, Flekkoy K, Ronneberg U, Opjordsmoen S (2006) Insight, symptoms and neurocognition in bipolar I patients. *J Affect Disord* 91: 1–9
100 Moorhead TW, McKirdy J, Sussmann JE, Hall J, Lawrie SM, Johnstone EC, McIntosh AM (2007) Progressive gray matter loss in patients with bipolar disorder. *Biol Psychiatry* 62: 894–900
101 Vieta E (2006) On Bipolar Disorder. In: *Deconstructing Psychosis. Future of Psychiatric Diagnosis: Refining the Research Agenda. Conference on DSM-V*, American Psychiatric Association, Arlington, Virginia, USA, 16–17
102 Kupfer, DJ, First MB, Regier DA (2007) *A Research Agenda for DSM-V*. American Psychiatric Publishing, Washington DC

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Suicide and bipolar disorder

Zoltán Rihmer

Department of Clinical and Theoretical Mental Health, and Department of Psychiatry and Psychotherapy, Semmelweis Medical University, Kútvölgyi Clinical Centre, Kútvölgyi út 4, 1125 Budapest, Hungary

Abstract

Bipolar disorders are common illnesses with markedly elevated premature mortality, but they remain frequently under-referred, under-diagnosed, and under-treated. Suicide is the cause of death in up to 15% of patients with bipolar disorders, and about half of them make at least one suicide attempt in their lifetime. The suicide rate of (untreated) bipolar patients is 25 times higher than the same rate in the general population. Suicidal behaviour in bipolar patients occurs almost exclusively during severe major depressive episodes, and less frequently in mixed affective episodes or in dysphoric mania. In contrast, suicidal behaviour occurs very rarely during euphoric mania, hypomania, or euthymia, suggesting that suicidal behaviour in bipolar patients is a state- and severity-dependent phenomenon. However, because the majority of bipolar patients never commit (and up to 50% of them never attempt) suicide, risk factors other than bipolar disorder itself also play a significant contributory role. This chapter summarises the clinically most relevant suicide risk and protective factors in bipolar disorders, and touches briefly on the most effective suicide prevention strategies.

Introduction

Bipolar disorders are associated with a substantial burden of illness-related health and economic problems. Given the 1.3–5.0% lifetime prevalence of Bipolar I and Bipolar II disorders [1] they are among the most frequent and also the potentially most life-threatening psychiatric illnesses [2–7]. This elevated risk of premature death is predominantly due to suicide, but increased incidence of accidents, cardiovascular morbidity, and complications due to comorbid substance-use disorders are also contributing causes [2, 4–7]. In spite of the great clinical and public health significance of bipolar disorders, they are still under-referred, under-diagnosed, and under-treated [1, 6]. Because successful acute and long-term treatment with mood stabilisers and other psychotropics markedly reduces the risk of attempted and completed suicide in Bipolar I and Bipolar II disorders [3, 4, 7–9], the early recognition and appropriate acute and long-term treatment of bipolar patients is a key element in suicide prevention for this population. Although suicidal behaviour is very rare in the absence of current major mental disorders [2, 3, 5], suicide is not the linear consequence of psychiatric disorders. It is a very complex and multicausal

human behaviour involving several psychosocial and cultural components. This chapter summarises the clinically most relevant suicide risk and protective factors in bipolar disorders, and also touches briefly on the most effective prevention strategies.

Suicidal behaviour in major mood disorders

In their meta-analysis of studies on suicide risk in all psychiatric disorders, Harris and Barraclough [10] analysed separately the risk of completed suicide in patients with an index diagnosis of unipolar major depression (23 reports, more than 8,000 patients) and in bipolar disorder (14 reports, more than 3,700 patients); some studies had followed these patients for many decades. They found that the risk of completed suicide (i.e., the standardised mortality ratio, SMR) was about 20-fold for patients with an index diagnosis of unipolar major depression, and 15-fold for bipolar disorders. However, this type of analysis cannot provide a precise estimate of separate suicide risk in unipolar and bipolar disorders (i.e., it overestimates the risk for unipolar depression and underestimates the same risk for bipolar disorders). The main source of this imprecision is that the index diagnosis frequently changes over the long-term course of illness from unipolar depression to Bipolar I or Bipolar II disorder [7, 11]; in the studies reviewed by Harris and Barraclough [10] the diagnostic category of Bipolar II depression (major depression with history of hypomania but not with mania), which is the most common form of bipolar disorders [1, 6], was not considered separately. Therefore it is very likely that most Bipolar II patients in these studies were included in the unipolar major depressive subgroup.

Moreover, recent findings showed that up to 50% of patients with unipolar depression were found to have bipolar depression when subthreshold hypomania as well as the bipolar spectrum disorders (i.e., 'unipolar' major depression with bipolar family history, treatment-associated hypomania/mania in major depression, and depressive mixed state/agitated depression) were also considered [1, 6, 12, 13]. Indeed, the most recent meta-analysis of 28 reports, published between 1945 and 2001 (including only patients with an index diagnosis of bipolar disorder without long-term lithium treatment) by Tondo and colleagues [3] found that during an average 10 years of follow-up the SMR for completed suicide in bipolar patients was as high as 22 (15 for males and 21 for females). These authors also calculated that suicide rates in bipolar disorder patients average 0.4%/year, which is more than 25 times higher than the same rate in the general population [3].

However, in a 40–44 years' prospective follow-up study of 406 formerly hospitalised (186 unipolar and 220 bipolar) major mood disorder patients, in which the unipolar–bipolar conversion was carefully considered during the follow-up, Angst and colleagues [7] found that 14.5% of unipolar and 8.2% of bipolar (I+II) patients committed suicide, and the SMR for suicide in unipolar

and bipolar patients were 26 and 12, respectively. In contrast, a very recent long-term prospective follow-up study (average 11 years) of 1983 unipolar major depressives and 843 bipolar (I+II) patients found a much higher rate of completed suicide in Bipolar I and II patients than in unipolar patients (0.25% of patients/year *versus* 0.05% of patients/year) [14].

Suicide risk factors in bipolar disorders

Suicidal behaviour (suicide, suicide attempt) and suicidal ideation in bipolar patients occur mostly during the severe major depressive episodes and less frequently in mixed affective episodes and dysphoric mania. They are very rare during euphoric mania, hypomania, and euthymia [2, 5, 15–17], indicating that suicidal behaviour in bipolar patients is a state- and severity-dependent phenomenon. However, because the majority of bipolar patients never commit (and up to 50% of them never attempt) suicide [2, 3, 4, 18–23], risk factors other than bipolar disorder itself also play a significant contributory role. These include special clinical characteristics as well as some personality, familial, and psychosocial risk and protective factors [2–4, 9, 12]. Most suicide risk factors in bipolar disorders are related to the acute (mostly depressive) major mood episodes but there are several historical and personality factors that can help clinicians identify highly suicidal bipolar patients.

Previous suicide attempt is the most powerful predictor of future completed suicide, particularly in patients with major mood disorders [2, 4, 5, 10, 15]. Considering only the 10 clinical studies (including more than 3,100 patients) in which unipolar and bipolar (I+II) patients were analysed separately, it has been found that the lifetime rate of prior suicide attempt(s) was much higher in bipolar (I+II) patients (mean: 28%, range: 10–61%) than in patients with unipolar depression (mean: 13%, range: 9–30%) [4]. A recent long-term prospective study also found that the rate of suicide attempts during follow-up was more than double in bipolar (I+II) than in unipolar patients [14]. Community-based epidemiological studies from the United States [18, 19] and Hungary [20] also showed that the lifetime rate of prior suicide attempts was 1.5 to 2.5 higher in bipolar (I+II) than in unipolar patients. Similarly, it has been reported that current suicidal ideation, the major precursor of suicidal behaviour [2, 15], was more frequent in Bipolar I and II (36–64%) than in unipolar (32–46%) depressed inpatients and outpatients [21–23].

The clinical conditions that are the most alarming for suicidal behaviour in bipolar disorder are the recent suicide attempt and the severe (mostly melancholic) major depressive episode, particularly when the latter is accompanied by hopelessness, guilt, agitation, insomnia [3, 13, 15, 24], few reasons for living, suicidal ideation [2, 3, 4, 9, 15, 16], and psychotic features [7, 15]. Recent results strongly suggest that mixed depressive episodes (major depression plus three or more co-occurring intra-depressive hypomanic symptoms) substantially increases the risk of both attempted and committed suicide [9, 12, 15,

22–25]. These episodes correspond to the category of 'agitated depression' that is present in up to 60% of bipolar depressives [12, 13, 22, 23].

Moreover, these results offer an explanation for the rarely occurring 'antidepressant-induced' suicidal behaviour; antidepressant monotherapy, unprotected by mood stabilisers or atypical antipsychotics, particularly in bipolar and bipolar spectrum disorder (including 'unipolar' depressive mixed state) can favour not only hypomanic/manic switches and rapid cycling, but also worsen the pre-existing mixed state or generate *de novo* mixed conditions. This makes the clinical picture more serious and ultimately leads to self-destructive behaviour [12, 22, 24, 26]. The role of mood instability in suicidal behaviour was also supported by a recent study showing that a history of rapid mood switching and panic attacks was associated with an increased likelihood of history of self-reported suicidal thoughts or actions in patients with bipolar disorders [27].

However, suicidal behaviour in bipolar patients is not exclusively restricted to depressive episodes. In contrast to classical (euphoric) mania, where suicidal tendencies are extremely rare, suicidal thoughts and attempts are relatively common in patients with mixed affective episode and dysphoric mania [2, 3, 14, 16], supporting the common clinical sense that suicidal behaviour in bipolar patients is linked to depressive symptomatology [7, 14–16].

Although bipolar disorders, in general, carry the highest risk of suicide [3, 4, 9, 14] several studies have shown that Bipolar II patients have an even higher risk than Bipolar I subjects [4, 9, 21, 23, 28–30]. However, other studies have found that suicide risk does not seem to vary according to bipolar subtype [2, 7, 14, 16, 31].

Bipolar disorders show a high frequency of psychiatric and medical co-morbidities [1, 31] and it is well documented that co-morbid anxiety/anxiety disorders [2, 4, 15, 18, 30–32], substance-use disorders [2, 4, 27, 30–32], personality disorders (especially borderline personality disorder) [4, 16, 31], and serious medical illnesses [2, 31], particularly in the case of multiple co-morbidities, also increase the risk of all forms of suicidal behaviour. Although successful acute and long-term treatment of bipolar disorder substantially reduces the risk of both completed and attempted suicide [3, 4, 7–9], lack of medical and family support as well as the first few days of the therapy when antidepressants usually do not work (or rarely can worsen the depression) [24], also should be considered as risk factors for suicide.

As noted previously, prior suicide attempt(s), particularly in the case of violent or more lethal methods, is the single most powerful predictor of future attempts and fatal suicide [2–4, 15, 16, 27]. Bipolar patients in general [33] and Bipolar II patients in particular [14, 34] use more violent and more lethal suicide methods than unipolar depressives and Bipolar I patients respectively, and this is characteristic first of all for males. Therefore, higher rates of suicidal behaviour (mainly completed suicide) in patients with bipolar disorder than in unipolar major depression may be due to a specific effect of bipolar disorder on males, resulting in more dangerous suicidal behaviours [33]. Other

historical variables that have been shown to increase the chance of both attempted and completed suicide include early onset, early stage of bipolar disorder [3, 5, 7, 14, 27, 32], rapid cycling course, predominant depressive polarity, and more prior hospitalisations for depression [2, 3, 7, 16, 31].

Personality characteristics also play a significant role in the development and particularly in the manifestation of suicidal behaviour. The voluminous literature on this subject consistently shows that aggressive/impulsive personality traits [16, 27, 33, 35–37], especially in combination with high level of current hopelessness and pessimism [35, 36], markedly increase the risk of suicidal behaviour in patients with bipolar and other psychiatric disorders. Recently it has been also reported that in Bipolar I and II depressed patients, the level of impulsivity and the rate of prior suicide attempts increased with increasing number of intra-depressive hypomanic symptoms [37], supporting the strong relationship between the bipolar nature of depression and impulsive behaviour [38]. Irritable mood (a core symptom of mania and hypomania) and anger attacks (inappropriate, sudden spells of anger associated with autonomic arousal symptoms and behavioural outbursts) are closely linked to each other, and anger attacks are much more common in bipolar depression than in unipolar depression [13, 38]. Moreover, if anger attacks occur during unipolar major depression, the bipolar nature of these 'unipolar' depressions are supported by their association with most key validating variables (early onset, atypical features of depression, depressive mixed state, bipolar family history) of bipolar disorder [38]. The interaction between personality features and illness characteristics in suicidal behaviour was best formulated by Mann and colleagues [35] in their 'stress-diathesis model', which suggests that suicidal behaviour in psychiatric patients is determined not only by the stressor (acute major psychiatric illness), but also by a diathesis (impulsive, aggressive, pessimistic personality traits).

Cyclothymia/cyclothymic temperament – the attenuated form of bipolar disorder – also seems to be a predisposing factor for suicidal behaviour. Cyclothymic personality appears to be significantly related to lifetime and current suicidal behaviour (ideation and attempts) both in adults and in a pediatric sample [39, 40].

Despite the fact that most suicide victims in the general population are males and the opposite is true for suicide attempters [5, 10, 15, 24], this difference is much smaller among suicidal patients with bipolar disorder [2, 3, 7, 27, 32]. This suggests that gender is not a significant predictor for committed and attempted suicide in this otherwise high-risk population. However, same-sex oriented and bisexual persons, mainly cross-gendered individuals, are at elevated risk for suicidal behaviour, particularly if other suicide risk factors are also present [41].

With regards to suicide risk factors related to personal history, early negative life-events (e.g., parental loss, isolation, or emotional, physical, and sexual abuse) [2, 4, 15, 31, 35], permanent adverse life situations (e.g., unemployment, isolation) [2, 4, 15], and acute psychosocial stressors (e.g., loss events,

financial disasters) [4, 15, 31, 42] are the most important and clinically useful indicators of possible suicidality, primarily if other risk factors are also present. However, acute psychosocial stressors commonly depend on the victim's own behaviour, particularly in the case of Bipolar I disorder [42]. For example, hypomanic and manic periods can easily lead to aggressive-impulsive behaviour, financial extravagance, or episodic promiscuity, thus generating several interpersonal conflicts, marital breakdown, and new negative life events, all of which have a negative impact on the further course of the illness.

Family history of suicidal behaviour and/or major mood disorders in first- and second- degree relatives is also a strong risk factor for both attempted and completed suicide in psychiatric patients in general, and in bipolar patients in particular [2, 4, 15, 27, 31, 35]. However, the familial component of suicidal behaviour seems to be independent of psychiatric disorders. Suicidal persons are over 10 times more likely than relatives of comparison subjects to attempt or complete suicide after controlling for psychopathology [43].

Table 1 Clinically detectable suicide risk factors in bipolar disorders

1. Risk factors related to acute mood episodes
   A. Severe major depressive episode
      - Current suicide attempt, plan, ideation
      - Hopelessness, guilt, few reasons for living
      - Agitation, depressive mixed state, insomnia
      - Psychotic features
      - Bipolar II diagnosis
      - Co-morbid Axis I, Axis II, and serious Axis III disorders
      - Lack of medical treatment and family/social support
      - First few days of the treatment (particularly if appropriate care and co-medication is lacking)
   B. Mixed affective episode (simultaneously occurring manic and major depressive episodes)
   C. Dysphoric mania (mania and three or more intra-manic depressive symptoms)
2. Risk factors related to prior course of the illness
   - Previous suicide attempt/ideation (particularly the violent/highly lethal methods)
   - Early onset/early stage of the illness
   - Rapid cycling course
3. Risk factors related to personality features
   - Aggressive/impulsive personality traits
   - Cyclothymic temperament
   - Same-sex orientation, bisexuality
4. Risk factors related to personal history
   - Early negative life events (separation, emotional, physical, and sexual abuse)
   - Permanent adverse life situations (unemployment, isolation)
   - Acute psychosocial stressors (loss events, financial catastrophe)
5. Risk factors related to family history
   - Family history of mood disorders (first and second degree relatives)
   - Family history of suicide and/or suicide attempt (first and second degree relatives)

The clinically explorable suicide risk factors in bipolar disorders are listed in Table 1. Because suicidal behaviour in bipolar patients is very rare in the absence of major mood episodes, suicide risk factors related to these conditions are the most powerful predictors of suicide, particularly if other risk factors (and high lethality suicide methods) are also present. The higher the number of risk factors, the higher the chance of suicidal behaviour.

Suicide protective factors in bipolar disorders

In contrast to what is known about risk factors for suicide, few circumstances are known to protect against suicidal behaviour. Good family and social support, pregnancy and postpartum period (but also see Chapter by Roy and Payne, this volume), having a great number of children, holding strong religious beliefs, and restricting lethal suicide methods whenever possible (e.g., reducing domestic and car exhaust gas toxicity, and introducing stricter laws on gun control), seem to have some protective effect [4, 5, 44–47]. However, the most extensively studied suicide protective factor in major mood disorders is acute and long-term pharmacological treatment, particularly with lithium (see below) [3, 4, 7–9, 15, 24].

Although suicide is a rare event in the community, it is very frequent among patients with bipolar disorder, and most of them come into contact with varying levels of healthcare some weeks or months before their death [3, 4, 8, 15, 29]. The high rate of bipolar disorders and recent medical contact before suicidal behaviour underlines the priority role of healthcare workers in suicide prevention. Unfortunately, less than one-third of bipolar suicide victims and suicide attempters were receiving appropriate pharmacotherapy at the time of their suicide event [29, 30, 48]. Because about two-thirds of suicide victims die in their first attempt [5, 15, 49], the risk of suicide in bipolar patients is very high even if a patient has never attempted suicide before. The careful estimation of all suicide risk factors (see Tab. 1) is helpful in assessing suicide risk as early as possible and intervening prior to the patient making the first suicidal act.

Prevention of suicidal behaviour in bipolar patients

Several open clinical studies and randomised controlled trials have consistently found that acute and long-term treatment with lithium and other mood stabilisers (sometimes in combination with antidepressants and antipsychotics) markedly reduces the risk of attempted and completed suicide in Bipolar I and Bipolar II patients [3, 4, 7, 24]. It has been also reported that the overall suicide rate of bipolar patients decreased progressively with increasing number of prescriptions for mood stabilisers [50]. Bipolar patients with long-term pharmacotherapy frequently need (and more frequently receive) antidepressants and/or antipsychotics in addition to their mood stabilisers for shorter or longer

period of time. However, there is a growing body of evidence suggesting that antidepressant monotherapy can worsen the course and outcome of bipolar disorder [6, 8, 9, 22, 24]. For instance, the most recent naturalistic, prospective chart review analysis of 405 Bipolar I and II patients also showed that mood stabiliser monotherapy markedly reduced the risk of suicidal behaviour; however, the frequency of suicidal behaviour was highest in patients with antidepressant and antipsychotic monotherapy, lowest in patients with mood stabiliser monotherapy, and the risk to patients with combination therapy (mood stabilisers + antidepressants or antipsychotics) was intermediate, suggesting that a combination of antidepressants or antipsychotics with mood stabilisers markedly reduces (but does not fully eliminate) this increased suicide risk [51–53]. However, it is possible that those patients receiving a combination of medications may have a more severe form of the illness, thus making it appear that that monotherapy is better.

These results support and extend prior findings [8, 9, 24] and suggest that not only antidepressants but also antipsychotics can worsen the cross-sectional and longitudinal course of bipolar disorders, and this worsening is most clearly reflected in the elevated rate of suicidality. Doctors should keep their bipolar patients on these supplementary medications as short a time as possible and the main component of the long-term treatment should be mood stabiliser pharmacotherapy. However, because the risk reduction for suicidal behaviour among bipolar patients treated with mood stabilisers, although clinically significant, is still incomplete, development of alternative or supplementary treatment strategies is also required.

Recently, several effective psychosocial interventions in the field of bipolar disorders were developed (psychoeducation, cognitive-behavioural therapy, interpersonal and social rhythm therapy, etc.), initially to help noncompliant, drug-intolerant, and drug-nonresponsive patients [4, 54, 55]. Because they are designed for relapse/recurrence prevention, they might be effective in suicide prevention as well, and a combination of these methods with long-term pharmacotherapy may substantially decrease suicide risk.

References

1 Rihmer Z, Angst J (2005) Epidemiology of bipolar disorder. In: S Kasper, RMA Hirschfeld (eds): *Handbook of bipolar disorder*. Taylor and Francis, New York, 21–35
2 Hawton K, Sutton L, Haw C, Sinclair J, Harris L (2005) Suicide and attempted suicide in bipolar disorder: A systematic review of risk factors. *J Clin Psychiatry* 66: 693–704
3 Tondo L, Isacsson G, Baldessarini RJ (2003) Suicidal behavior in bipolar disorder. *CNS Drugs* 17: 491–511
4 Rihmer Z (2005) Prediction and prevention of suicide in bipolar disorder. *Clin Neuropsychiatry* 2: 48–54
5 Goodwin FK, Jamison KR (2007) *Manic-Depressive Illness: Bipolar disorders and recurrent depression*. Oxford University Press, New York
6 Dunner DL (2003) Clinical consequences of under-recognized bipolar spectrum disorder. *Bipolar Disord* 5: 456–463

7 Angst J, Angst F, Gerber-Werder R, Gamma A (2005) Suicide in 406 mood-disorder patients with and without long-term medication: A 40 to 44 years' follow-up. *Arch Suic Res* 9: 279–300
8 Rihmer Z (2007) Pharmacological prevention of suicide in bipolar patients – A realizable target. (Editorial). *J Affect Disord* 103: 1–3
9 Akiskal HS (2007) Targeting suicide prevention to modifiable risk factors: Has bipolar II been overlooked? (Editorial). *Acta Psychiat Scand* 116: 395–402
10 Harris EC, Barraclough B (1997) Suicide as an outcome for mental disorders: A meta-analysis. *Br J Psychiatry* 170: 205–228
11 Goldberg JF, Harrow M, Whiteside JE (2001) Risk for bipolar illness in patients initially hospitalized for unipolar depression. *Am J Psychiatry* 158: 1265–1270
12 Akiskal HS, Benazzi F, Perugi G, Rihmer Z (2005) Agitated "unipolar" depression re-conceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. *J Affect Disord* 85: 245–258
13 Benazzi F (2006) Mood patterns and classification in bipolar disorder. *Curr Opin Psychiatry* 19: 1–8
14 Tondo L, Lepri B, Baldessarini R (2007) Suicidal risk among 2826 Sardinian major affective disorder patients. *Acta Psychiat Scand* 116: 419–428
15 Rihmer Z (2007) Suicide risk in mood disorders. *Curr Opin Psychiatry* 20: 17–22
16 Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa E (2005) Suicidal ideation and attempts in bipolar I and bipolar II disorders. *J Clin Psychiatry* 66: 1456–1462
17 Sokero P, Eerola M, Rytsala H, Melartin T, Leskela U, Lestela-Mielonen P, Isometsa E (2006) Decline in suicidal ideation among patients with MDD is preceded by decline in depression and hopelessness *J Affect Disord* 95: 95–102
18 Chen YW, Dilsaver SC (1996) Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biol Psychiatry* 39: 896–899
19 Kessler RC, Borges G, Walters EE (1999) Prevalence and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 56: 617–626
20 Szádóczky E, Vitrai J, Rihmer Z, Füredi J (2000) Suicide attempts in the Hungarian adult population. Their relation with DIS/DSM-III-R affective and anxiety disorders. *Eur Psychiatry* 15: 610–617
21 Hantouche EG, Akiskal HS, Lancreon S, Allilare J-F, Sechter D, Azorin J-M, Burgeois M, Fraud J-P, Chatenet-Duchénne L (1998) Systematic clinical methodology for validating bipolar II disorder: Data in mid-stream from a French national multi-site study. *J Affect Disord* 50: 163–173
22 Benazzi F (2005) Suicidal ideation and depressive mixed states. *Psychother Psychosom* 74: 107–108
23 Sato T, Bottlender R, Kleindienst N, Möller H-J (2005) Irritable psychomotor elation in depressed inpatients: A factor validation of mixed depression. *J Affect Disord* 84: 187–196
24 Rihmer Z, Akiskal HS (2006) Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *J Affect Disord* 94: 3–13
25 Balázs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS (2006) The close link between suicide attempts and mixed (bipolar) depression: Implications for suicide prevention. *J Affect Disord* 91: 133–138
26 Rihmer Z, Benazzi F, Gonda X (2007) Suicidal behavior in unipolar depression: Focus on mixed states. In: R Tatarelli, M Pompili, P Girardi (eds): *Suicide in psychiatric disorders*. Nova Science Publishers Inc, New York, 223–235
27 MacKinnon DF, Potash JB, McMahon FJ, Simpson SG, dePaulo Jr, JR, the National Institutes of Mental Health Bipolar Disorder Genetics Initiative, Zandi PP (2005) Rapid mood switching and suicidality in familial bipolar disorder. *Bipolar Disord* 7: 441–448
28 Bulik CM, Carpenter L, Kupfer DJ, Frank E (1990) Features associated with suicide attempts in recurrent depression. *J Affect Disord* 18: 29–37
29 Rihmer Z, Barsi J, Arató M, Demeter E (1990) Suicide in subtypes of primary major depression. *J Affect Disord* 18: 221–225
30 Balázs J, Lecrubier Y, Csiszér N, Koszták J, Bitter I (2003) Prevalence and comorbidity of affective disorders in persons making suicide attempts in Hungary: Importance of the first episode and of bipolar II diagnosis. *J Affect Disord* 76: 113–119
31 Leverich GS, Altshuler Frye MA, Suppes T, Keck PE, McElroy SL, Denicoff KD, Obrocea G, Nolen WA, Kupka R, Walden J et al (2003) Factors associated with suicide attempts in 684

patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry* 64: 506–515
32 Simon GE, Hunkeler E, Fireman B, Lee JY, Savarino J (2007) Risk of suicide attempt and suicide death in patients treated for bipolar disorder. *Bipolar Disord* 9: 526–530
33 Zalsman G, Braun M, Arendt M, Grunebaum MF, Sher L, Burke AK, Brent D, Chaudhury SR, Mann JJ, Oquendo MA (2006) A comparison of the medical lethality of suicide attempts in bipolar and major depressive disorder. *Bipolar Disord* 8: 558–565
34 Vieta E, Benabarre A, Colom F, Gastó C, Nieto C, Otero A (1997) Suicidal behavior in bipolar I and bipolar II disorder. *J Nerv Ment Dis* 185: 407–409
35 Mann JJ, Waternaux C, Haas GL, Malone KM (1999) Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 156: 181–189
36 Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ (2004) Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder and bipolar disorder. *Am J Psychiatry* 161: 1433–1441
37 Swann AC, Moeller FG, Steinberg JL, Schneider L, Barratt ES, Dougherty DM (2007) Manic symptoms and impulsivity during bipolar depressive episode. *Bipolar Disord* 9: 206–212
38 Benazzi F (2003) Major depressive disorder with anger: A bipolar spectrum disorder? *Psychother Psychosom* 72: 300–306
39 Akiskal HS, Hantouche EG, Allilare JF (2003) Bipolar II with and without cyclothymic temperament: dark and sunny expressions of soft bipolarity. *J Affect Disord* 73: 49–57
40 Kochman FJ, Hantouche EG, Ferrari P, Lancrenon S, Bayart D, Akiskal HS (2005) Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *J Affect Disord* 85: 181–189
41 Fritzpatrick KK, Euton SJ, Jones JN, Schmidt NB (2005) Gender role, sexual orientation and suicide risk. *J Affect Disord* 87: 35–42
42 Isometsa E, Heikkinen M, Henriksson M, Aro H, Lönnqvist J (1995) Recent life events and completed suicide in bipolar affective disorder: A comparison with major depressive disorder in Finland. *J Affect Disord* 33: 99–106
43 Kim CD, Seguin M, Therrien N, Riopel G, Chawkay N, Lesege AD, Turecki G (2005) Familial aggregation of suicidal behavior: A family study of male suicide completers from the general population. *Am J Psychiatry* 162: 1017–1019
44 Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Hartwell N, Iqbal MI (1997) Lower risk of suicide during pregnancy. *Am J Psychiatry* 154: 122–123
45 Dervic K, Oquendo MA, Grunebaum MF, Ellis S, Burke AK, Mann JJ (2004) Religious affiliation and suicide attempt. *Am J Psychiatry* 161: 2303–2308
46 Driver K, Abed R (2004) Does having offspring reduce the risk of suicide in women? *Int J Psychiat Clin Pract* 8: 25–29
47 Rihmer Z (2004) Suicide prevention strategies – A brief review. *Neuropsychopharmacol Hung* 6: 195–199
48 Isometsa ET, Henriksson MM, Aro HM, Lönnqvist JK (1994) Suicide in bipolar disorder in Finland. *Am J Psychiatry* 151: 1020–1024
49 Isometsa ET, Lönnqvist JK (1998) Suicide attempts preceding completed suicide. *Br J Psychiatry* 173: 531–533
50 Sondergard L, Lopez AG, Andersen PK, Kessing LV (2008) Mood stabilizing pharmacological treatment in bipolar disorders and the risk of suicide. *Bipolar Disord* 10: 87–94
51 Yerevanian BI, Koek RJ, Mintz J (2007) Bipolar pharmacotherapy and suicidal behavior. Part I: Lithium, divalproex and carbamazepine. *J Affect Disord* 103: 5–11
52 Yerevanian BI, Koek RJ, Mintz J, Akiskal HS (2007) Bipolar pharmacotherapy and suicidal behavior. Part 2: The impact of antidepressants. *J Affect Disord* 103: 13–21
53 Yerevanian BI, Koek RJ, Mintz J (2007) Bipolar pharmacotherapy and suicidal behavior. Part 3: Impact of antipsychotics. *J Affect Disord* 103: 23–28
54 Michalak EE, Yatham LN, Lam RW (2004) The role of psychoeducation in the treatment of bipolar disorder: A clinical perspective. *Clin Appr Bipol Disord* 3: 5–11
55 Rucci P, Frank E, Kostelnik B, Fagiolini A, Malinger AG, Swartz HA, Thase ME, Siegel L, Wilson D, Kupfer DJ (2002) Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. *Am J Psychiatry* 159: 1160–1164

Section B:
Bipolar depression: Neurobiology

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

The genetic basis of bipolar disorder

Thomas G. Schulze and Francis J. McMahon

Unit on the Genetic Basis of Mood and Anxiety Disorders, Mood & Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Department of Health & Human Services, Bethesda, MD 20892, USA

Abstract

Bipolar disorder has long been known to have a strong genetic component, with heritability estimates ranging between 80–90%. However, major breakthroughs on the molecular genetic level have remained elusive. Linkage and candidate gene association studies produced a host of reports, but failed to deliver consistently replicable results. This may in part be attributed to limited sample sizes and high degrees of phenotypic and genotypic heterogeneity. The advent of genome-wide association studies (GWAS) has spurred new hopes for the identification of true susceptibility genes. After close to a century of genetic studies, bipolar disorder is emerging as a complex (non-Mendelian) disorder with a polygenic etiology. The search for common genetic variants with small effects by GWAS will probably have to be complemented by approaches that can detect rare genetic variations with larger effects, such as copy number variants. Progress would be much enhanced by improved phenotype definitions that reduce genetic heterogeneity.

Introduction

In this chapter, we attempt to review some of the basic principles underlying advances in our understanding of the genetic basis of bipolar disorder. We take advantage of a large body of published work that has already thoroughly reviewed family, twin, and adoption studies as well as genetic linkage and candidate gene-association studies of bipolar disorder and related conditions [1–15]. Interested readers are referred to these reviews for many of the details that we will merely summarize here. Our main goal is to broadly describe the progress of this field, and how we can use the knowledge gained over the course of the past century of research as the field attempts to master novel molecular and analytical techniques in the quest to unravel the genetic basis of bipolar disorder.

Genetic epidemiology: The first 100 years

Bipolar disorder is a highly heritable illness. This means that the majority of the individual variation in risk can be explained by genes. This has been a very

consistent finding over more than a century of research, despite differences in study populations, case definitions, and analysis methods (for review see [16]).

Early 20th century research demonstrated through systematic studies that bipolar disorder (and other mental illnesses) aggregates in families (reviewed in [17, 18]). Whereas the lifetime prevalence in the general population is around 1–2% (or higher, depending on whether broad or narrow phenotype definitions are used), multiple studies have reported that the lifetime risk for bipolar disorder in first-degree relatives of a patient with the illness is increased 10 to 20-fold.

Twin studies, published between 1930 and 2003 [19–22] have consistently supported the high heritability of bipolar disorder. Heritability estimates for bipolar disorder range between 80–90%. Two systematic adoption studies in bipolar disorder [23, 24], while performed in comparatively small samples, further support the notion that genetic factors contribute substantially more to the etiology of bipolar disorder than environmental factors.

Family studies are also an excellent way to define the range of clinical manifestations of underlying risk genotypes. Classically, probands are ascertained and diagnosed without regard to family history, and then their first- and (if available) second-degree relatives are systematically assessed for the presence of traits of interest. The best-known such studies in bipolar disorder were published in the 1980s [25, 26]. These studies showed that bipolar disorder, as well as unipolar (major depressive) disorder, dysthymia, cyclothymia, schizoaffective bipolar disorder, alcoholism, and anxiety disorders, were all increased among the first-degree relatives of probands with bipolar disorder. On the other hand, schizophrenia and other non-affective psychotic illnesses were not found to be increased in most studies. These data are generally interpreted as supporting the existence of a spectrum of bipolar-related conditions that are distinct from schizophrenia; however, some have challenged this conclusion [27].

The clear findings from classical family studies have not been matched by similarly clear findings in studies of the patterns of disease transmission in families. While some segregation analyses have supported a single major locus (Mendelian) model, most studies have been unable to exclude polygenic or multifactorial models. This probably reflects inherent limitations of the methods of segregation analysis to handle heterogeneity and complex modes of inheritance. This is further complicated by evidence that families of probands with bipolar disorder are characterized by assortative mating [28], genetic anticipation [29], and parent of origin effects that may reflect genomic imprinting [30], mitochondrial inheritance [31], or other factors.

Gene mapping

Genetic epidemiology provided compelling evidence that genetic factors play the major role in the etiology of bipolar disorder, and laid the foundation for

future studies. However, the methods of genetic epidemiology cannot identify the genes involved or pinpoint the genetic variation that explains the high heritability of bipolar disorder. This task requires a method of genetic mapping, and the advent of genetic linkage studies in humans seemed to fit the bill.

The phenomenon of genetic linkage was first described by Thomas Hunt Morgan in his studies of fruit flies. He found that certain traits, such as eye color and wing shape, did not assort independently, in apparent violation of Mendel's Second Law. Instead, they tended to be inherited together from generation to generation in a probabilistic fashion. Morgan's insight was that this apparent linkage between traits actually reflected a physical proximity of the responsible genes on the same chromosome. The further apart that two genes lie on a chromosome, the more likely they are to be separated by recombination during meiosis. In fact, despite conformational forces that make two recombination events on the same chromosome arm very unlikely, the relative position of two genes on a chromosome can be reliably inferred by the frequency with which traits encoded by those genes run together across the generations. To this day, the Morgan (and its 100th part, the centimorgan) remains the standard unit of genetic distance, in honor of Morgan's seminal work.

At first, the application of Morgan's principles to humans proved challenging. Outward traits can be difficult to measure, and the limited observational space of human pedigrees made linkage difficult to establish, except in unusual situations such as chromosome X-linked traits. Not long after the Nobel prize-winning discovery of restriction enzymes by Arber, Nathans and Smith in 1978, it was discovered that these DNA-slicing proteins sometimes failed to make the cut, reflecting single base-pair differences in the DNA sequence, and resulting in DNA restriction fragments that varied in size between individuals. The era of the restriction fragment-length polymorphism (RFLP) was thus born. In 1980, Botstein and colleagues proposed that RFLPs could be used to map genes by linkage even in the human genome [32]. Their prediction was soon proven true, with the mapping of markers linked to cystic fibrosis [33, 34], Huntington's Disease [35], and bipolar disorder [36].

The former two genetic linkages were quickly confirmed, and disease-causing mutations identified. But the latter was not, and was soon retracted [37]. This false start foretold much of what would follow in the ensuing decade of genetic linkage studies of bipolar disorder. It also embodied many of the difficulties – genetic heterogeneity, small effect sizes, and non-Mendelian inheritance patterns – that would by the 1990s come to be seen as the key characteristics of all complex genetic conditions like bipolar disorder, type II diabetes, and cardiovascular disease.

In the early days of this molecular era of bipolar genetic research, researchers' moods would very often switch between exuberance and disappointment as linkage findings were reported – sometimes with great fanfare – only to fail to find support in subsequent studies [38]. The problems that these early linkage studies had to confront were manifold: small sample sizes, par-

tially informative sets of genetic markers, and statistical methods that were originally designed for Mendelian disorders with monogenic inheritance, where the mode of inheritance, penetrance, and the clinically unaffected status of probands' relatives can be specified reliably. With the advent of larger, multi-center studies, the availability of denser sets of more informative markers, and the use of non-parametric linkage algorithms (e.g., affected sib pair design), many of these problems could be alleviated.

Yet, robust linkage findings remained elusive. Half a decade ago, we argued that large-scale linkage studies would in the end succeed in gene identification, or at least serve as the starting point for systematic molecular genetic research in bipolar disorder [39]. Since then, many genetic linkage signals have been detected, several of which – one on essentially every chromosome but Y – have been identified by more than one study. Yet definitive findings have remained elusive. Three meta-analyses of linkage studies of bipolar disorder have been published [40–42]. While providing support for loci on chromosomes 6q, 8q, 13q, 18q, and 22q, each study tended to highlight non-overlapping sets of loci. In 2003, during a meeting celebrating the 50th anniversary of the discovery of the double helix, Eric Lander lamented that linkage studies had become "mumbo jumbo". We were thus stating the obvious when we wrote in early 2007 that "the passing of the linkage era would not be widely mourned" [43].

Linkage analysis is now no longer seen as a powerful tool to pinpoint susceptibility genes for complex traits and diseases. While many of the reported linkage regions may ultimately be found to harbor risk alleles, the genetic (or locus) heterogeneity of bipolar disorder may be so high that it defeats the ability of linkage analysis to separate true findings from a large number of false positives, even with very large sample sizes. Nevertheless, incorporating the information gained from linkage studies into future analyses and continuing to collect and phenotypically characterize multiply-affected families might still prove very valuable [44, 45].

Positional cloning efforts by means of candidate-gene association mapping have made some headway, but with little consensus around the main findings. Several studies, in particular systematic linkage disequilibrium mapping (LD) in linkage regions and large-scale candidate gene studies, have identified potential susceptibility genes for bipolar disorder [3, 6, 7, 15], but results remain inconsistent across studies. While corroboration at the gene level has been reached for some of these genes (Tab. 1), replications at the allelic level, i.e., association with the identical allele of a particular single nucleotide polymorphism (SNP) across studies, are rare [46].

Moving into the next 100 years

As with genetic research in other complex disorders, the genetics of bipolar disorder entered the 21st century against the backdrop of important developments in human genetics. These included the publication of the sequence of

Table 1 Promising candidate genes for bipolar disorder

Gene	Symbol	Key polymorphisms	Individual association studies or meta-analyses (MA)	Evidence
Serotonin transporter	*SLC6A3*	LPR	Anguelova et al 2003 (MA) [101]	+++
D-amino acid oxidase activator (G72)	*DAOA*	Various	Detera-Wadleigh and McMahon 2006 (MA) [46]	+++
Disrupted-in-schizophrenia-1	*DISC1*	Various	Hodgkinson et al. 2004; Thomson et al. 2005; WTCCC 2007; Perlis et al. 2008 [53, 104–106]	++
Tryptophan hydroxilase 2	*TPH2*	Various	Harvey et al. 2004; Van den Bogaert et al. 2006; Lopez et al. 2007; Harvey et al. 2007; Cichon et al. 2007 [107–111]	++
Brain-derived neurotrophic factor	*BDNF*	Val/Met	Kanazawa et al 2007 (MA); Fan and Sklar 2008 (MA) [102, 103]	+
Aryl hydrocarbon receptor nuclear translocator-like	*ARNTL (heterodimer with CLOCK)*	Various	Mansour et al. 2006; Nievergelt et al. 2006 [112, 113]	+
Cadherin gene (homolog of the Drosophila tumor suppressor gene *fat*)	*FAT*	Various	Blair et al. 2006; Abou Jamra et al. 2008 [114, 115]	+

+ supported by 2 studies or evidence quite mixed
++ supported by several studies
+++ supported by meta-analysis of three or more samples

the human genome [47, 48], the completion of the HapMap project (www.hapmap.org; [49]), and the advent of DNA microchip technology. These landmark developments have virtually eradicated one major impediment in complex genetic research: technical feasibility. Now, financial resources allowing, several thousand samples can be genotyped with several hundred thousand genetic markers or sequenced over hundreds of megbases in a small fraction of the time that such an endeavor would have taken just a few years ago. Genome-wide association studies (GWAS), large-scale surveys of copy number variation, and large-scale resequencing studies are all early products of these technological developments. Although it is impossible to predict the future, it is already clear that GWAS have opened new windows into the genetic architecture of common complex disorders such as age-related macular degeneration, type II diabetes, and cardiovascular disease.

Genome-wide association studies

There are probably about 10,000,000 SNPs in the human genome. Previous case-control association studies could assay only a fraction of this important source of genetic variation. In a GWAS, several hundred thousand SNPs are rapidly scanned across the complete genome of a large number of case and control individuals (or, less commonly, case-parent trios). SNPs are selected on the basis of informativeness, without a specific prior hypothesis of etiological involvement in disease; thus GWAS are commonly referred to as 'hypothesis-free' studies.

GWAS have now been performed for several complex phenotypes, such as type I and type II diabetes [50–53], obesity [54], coronary heart disease [53, 55, 56], hypertension [53], rheumatoid arthritis [53], age-related macular degeneration [57, 58], Crohn's disease [53, 59, 60], prostate cancer [61, 62], and bipolar disorder [53, 63, 64]. At the time of this writing, within the Genetic Association Information Network (GAIN), further large-scale studies on kidney disease in type I diabetes, psoriasis, attention deficit/hyperactivity disorder, schizophrenia, and bipolar disorder are underway (http://www.fnih.org/GAIN2/home_new.shtml).

Although these GWAS cover a wide range of disease phenotypes, some overall conclusions can be drawn (for a review, see [65]). First, and most importantly, GWAS methods can re-energize gene-mapping efforts even in diseases that have suffered long stretches of stalled progress. This may best be illustrated by the case for Type II diabetes, where several novel and some previously implicated genes could be detected and unambiguously replicated at the allele level across several samples [66]. Second, the implicated genes often challenge our limited etio-pathological reasoning by implicating novel pathways to disease. For example, the identification of *ATG16L1* (a gene involved in the autophagosome pathway processing intracellular bacteria) as a susceptibility gene for Crohn's disease, offers intriguing fresh insights into the pathophysiological mechanisms of this disorder. Third, GWAS may point to variation lying in 'gene deserts' that would never have been considered by candidate gene studies, but that evidently play an important regulatory role. This is illustrated by chromosome 9p's association with cardiovascular disease. Fourth, GWAS have revealed that many complex disorders, while highly heritable, are actually the product of many genes with small individual effects that, together, increase risk of disease, similar to the classical polygenic threshold model [67].

At the time of this writing, three GWAS of bipolar disorder have been published. Although robust, unambiguously replicated findings have yet to emerge at this early stage, it seems clear that at least a part of the common genetic architecture of bipolar disorder will ultimately be revealed by GWAS methods. Some of the key bipolar disorder GWAS findings to date are summarized in Table 2.

However, in the same way that many psychiatric disorders have been more difficult to explore via linkage and candidate gene association studies than

Table 2 Published genome-wide association studies of bipolar disorder

Study	Cases : controls	Internal replication	Platform	Key findings	Gene overlaps	References
Baum et al. 2007	1233 : 1439	Yes	Illumina HumanHap550	DGKH ($p < 10–7$), among 88 replicated associations in 80 distinct genes	DFNB31 (WTCCC & Sklar); GRM7, JAM3, SLC39A3 (WTCCC); ANK3 (Sklar)	[63, 116]
WTCCC 2007	1838 : 2938	No	Affymetrix 500K	16p12, KCNC2, DFNB31, GABRB1, GRM7, among 14 hits at the $p < 10–5$ level	DFNB31 (Baum & Sklar); GRM7, JAM3, SLC39A3 (Baum); CACNA1A (Sklar)	[53]
Sklar et al. 2008	1000 : 1000	No	Affymetrix 500K	CACNA1A, TMEM, among 6 hits at the $p < 10–5$ level	DFNB31 (Baum, WTCCC); ANK3 (Baum); CACNA1A (WTCCC)	[64]

somatic disorders, bipolar disorder may hold some unique challenges for the GWAS approach. GWAS methods are not well-powered to detect uncommon alleles, and rare alleles may be missed entirely, unless they confer a very large risk of disease. Furthermore, some common disorders are related to many hundreds of alleles, each of small effect. GWAS methods alone cannot tell the whole story of truly polygenic disorders, because effect sizes much below 5% of the variance cannot be detected one locus at a time, even if the alleles are common.

Reconciling the polygenic nature of bipolar disorder and family recurrence risks: filling the risk gap

While it can be difficult to *dis*prove, the polygenic threshold model still offers the best overall fit to the existing family, linkage, and association findings for bipolar disorder. Polygenic disorders cluster in families and may be highly heritable, but in contrast to monogenic disorders do not show simple inheritance patterns. Classically, risk for disease is spread over many dozens – or hundreds – of distinct genes, each of which confers only a small part of the total risk for disease. Each person's disease risk is influenced by the total burden of risk alleles they carry, with fewer alleles conferring lower, and more alleles conferring greater, risk. Disease occurs when the allele burden crosses some threshold, although the exact disease threshold for a given person may be influenced by non-genetic factors.

The common disease/common variant (CDCV) hypothesis is a more modern theory than the polygenic threshold model, but the models have many similarities. Under the CDCV, human genetic variation is assumed to be relatively simple and finite, with only a few common haplotypes at each locus maintained in the population at one time. Risk for common diseases is postulated to result from common alleles and haplotypes at one or more loci.

While compelling and supported by findings in some common diseases, the CDCV hypothesis has repeatedly been challenged by an alternative theory whereby a large set of individually rare, high-risk alleles – each present in one or a few individuals – are thought to play the major role in risk for disease [68–71]. Individually rare, these alleles are proposed to occur in so many different genes that they can, together, account even for a common disease. Early results from studies of autism [45, 72] and schizophrenia [73, 74] suggest that the rare allele model may indeed have some explanatory power in the genetic basis of mental illness, but compelling rare-allele findings have not yet appeared for bipolar disorder.

Existing findings in bipolar disorder seem to point toward many alleles of small effect. But if this were the whole story, it is not clear how the relatively high recurrence rates in first-degree relatives (on the order of 10–15% [25]) could be explained. The true genetic architecture of common diseases like bipolar disorder probably encompasses both common alleles that alone confer

small risk (odds ratios 1.1–1.5), and uncommon or rare alleles (including copy number variants) that confer larger risks in a few people or families. From this perspective, it also seems likely that alleles will be found that shape the clinical picture and response to treatment. This idea will be developed further in the next section.

Alleles that shape the clinical picture: the bipolar phenome

Bipolar disorder as currently defined in the standard diagnostic manuals (DSM-IV and ICD 10) is a highly reliable but clinically variable entity. Most of the genetic work in bipolar disorder has focused on genes that contribute to the broader phenotype, but is not clear that such genes, if found, will be able to explain the clinical variability in terms of age at onset, symptoms, chronicity, co-morbidity, and treatment response that is a hallmark of the bipolar diagnosis. Without an operational diagnosis, large collaborative linkage and association studies of bipolar disorder would not have been possible, since case definitions would have varied too much from center to center. Diagnostic entities in psychiatry are still mainly constructs, without a well-defined shared biology. Correspondences between genotype and phenotype, when they finally emerge in psychiatry, are unlikely to show a close resemblance to our current diagnostic systems.

For example, several recent findings suggest a genetic overlap between schizophrenia and bipolar disorder [75, 76]. If true, these findings would challenge the assumption that the century-old Kraepelinian dichotomy between schizophrenia and mood disorders has a solid genetic basis. Indeed, some have called for abandoning this dichotomy in favor of an approach based on severity and course of illness, which accounts for developmental aspects that may better correspond to the underlying biology [77]. On the other hand, there are many examples of diseases with distinct symptoms, course, and treatment that share genetic risk factors. The B27 haplotype of the human leukocyte antigen (HLA) locus is a very strong risk factor for ankylosing spondylitis, anterior uveitis, and Reiter Syndrome, but each of these autoimmune diseases affects a different organ system, produces specific signs and symptoms, and responds best to specific treatments (reviewed in [78]). It is possible that alleles exist that increase risk for psychopathology in a fairly general way, with other alleles or non-genetic factors influencing precise clinical presentation.

Some studies have indeed found evidence of specific loci influencing symptomatology [75, 79–81], age at onset [82, 83], and clinical course [84] in bipolar disorder. If verified, such loci may help explain the variable clinical picture of bipolar disorder. More importantly, they may reveal aspects of pathophysiology that are good targets for novel treatments or preventive therapies.

If alleles exist that influence the clinical picture of bipolar disorder, how can we find them? Genetic linkage and candidate gene studies are two approaches, but still have the same limitations discussed above. GWAS data may be a

particularly good source of candidate alleles, but the problems of sample size, multiple testing, heterogeneity, and ascertainment bias inherent to all GWAS are that much more acute when the focus is on individual elements of the clinical picture. One approach is to use genetic markers to define phenotypic groupings that are distinguished by higher rates of allele-sharing (linkage data) or more deviant allele frequencies (association data) than are seen in traditional diagnostic categories (Fig. 1). We have called this approach 'reverse phenotyping' [14]. While replication testing is vital, reverse phenotyping has already shown promise as an approach to elucidating the genetics of bipolar disorder [75, 80, 85] and other complex phenotypes [86].

In addition to replication, a key issue in reverse phenotyping is the careful selection of traits to be studied. Many researchers favor traits that have shown a high degree of heritability or familiality. In bipolar disorder, this list includes several variables. Among these, psychosis, history of suicide attempts, alcoholism, substance abuse, OCD, level of social functioning, missing work due to mood disorder, number of manic episodes, episode frequency, and polarity of onset have all been the subjects of recent interest [79, 84, 87, 88].

Effective reverse phenotyping also requires access to large, well-characterized samples. While these are far from abundant, the field now has more suitable samples available than ever before. For example, the *Bipolar Phenome Database* [87] contains 197 clinical variables on 5,721 subjects in 1,177 families; DNA is available for 5,373 subjects. The Wellcome Trust Case Control

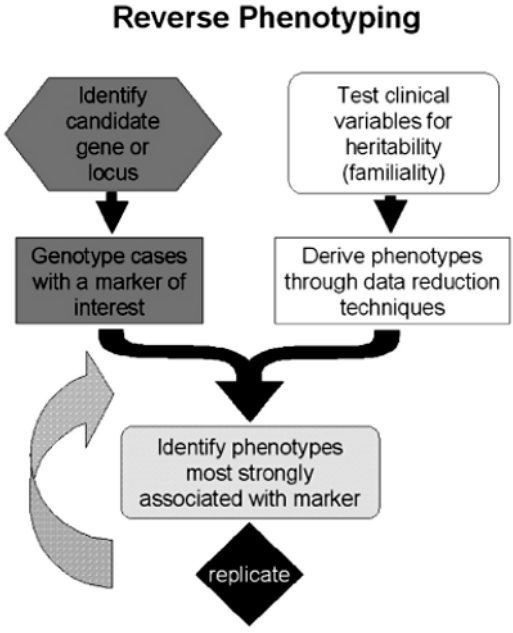


Figure 1. Reverse phenotyping.

Consortium (WTCCC) [53] and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) collaboration each have over 1,000 well-characterized cases with DNA, most of which is available to the public upon approval of a simple application form.

One fundamental question concerns the subphenotype structure (Fig. 2) we expect to find. Does bipolar disorder actually consist of subphenotypes that neatly present as clusters with only marginal overlap between them and other disorders? Or does the polygenic nature of bipolar disorder create an ill-defined multidimensional distribution of phenotypes – a 'phene space' – that cannot be easily cut into clusters but rather presents with poles enriched for specific phenotypic features? The statistical tools we want to use for pheno-

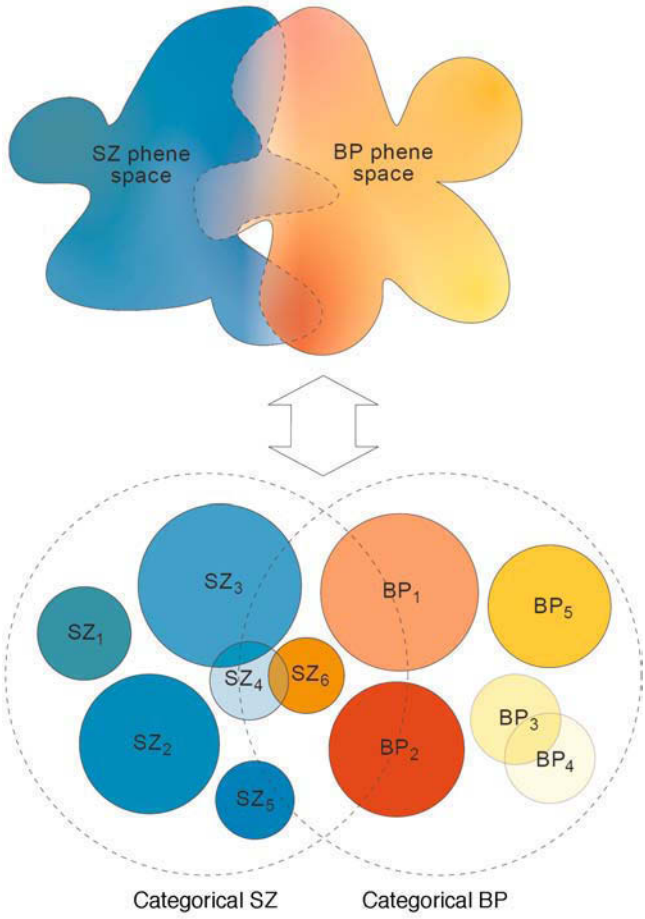


Figure 2. The subphenotype concept of psychiatric disorders. Schizophrenia (SZ) and bipolar disorder (BP) may comprise neatly clustering subphenotypes (indicated by circles and subscripts), or represent different points on an ill-defined multidimenisonal distribution of phenotypes, enriched for specific clinical features (indicated by smooth transitions of colors).

type refinement in bipolar disorder will need to be able to accommodate these different scenarios and modifications.

The field of pharmacogenetics has evolved within the past 40 years from a niche discipline to a major driving force in clinical pharmacology, and it is currently one of the most actively pursued disciplines in applied biomedical research in general, as Brockmöller and Tzvetkov put it [89]. Whereas genetic information may already be useful in identifying individual cases of poor or fast metabolism, the use of pharmacogenetic knowledge to predict actual outcome and truly individualize treatment is only just becoming feasible [90]. Recently, genetic studies from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) cohort on major depression have highlighted several markers associated with outcome and adverse events with citalopram treatment [91–94]. If replicated, findings such as these may ultimately prove to have considerable clinical utility.

In future phenotype refinement strategies, measures of treatment response and adverse events should be included alongside other variables. In bipolar disorder for instance, lithium response may be considered a prime phenotype [95, 96]. Sample size, however, will be the crucial issue. So far, pharmacogenetic studies of lithium response are characterized by small samples with a corresponding lack of statistical power [97–100]. International consortia and standardized phenotype characterization across centers are clearly needed for pharmacogenetic studies of lithium response or other measures of outcome in bipolar disorder.

Future frontiers

As we begin to accumulate data that may clarify genetic risk factors for bipolar disorder, questions have begun to accumulate. How much of a role will epigenetic factors play? How does SNP or CNV variation affect gene function? How do we best translate from a genetic association finding to a deeper understanding of disease biology and treatment? These questions are top priorities for the field of research into the genetic underpinnings of bipolar disorder, and will undoubtedly be addressed in the coming years.

References

1 Baron M (2002) Manic-depression genes and the new millennium: poised for discovery. *Mol Psychiatry* 7: 342–358
2 Berrettini WH (2001) Molecular linkage studies of bipolar disorders. *Bipolar Disord* 3: 276–283
3 Craddock N, Forty L (2006) Genetics of affective (mood) disorders. *Eur J Hum Genet* 14: 660–668
4 Craddock N, Jones I (2001) Molecular genetics of bipolar disorder. *Br J Psychiatry Suppl* 41: s128–s133
5 Detera-Wadleigh SD, McMahon FJ (2004) Genetic association studies in mood disorders: issues and promise. *Int Rev Psychiatry* 16: 301–310

6 Farmer A, Elkin A, McGuffin P (2007) The genetics of bipolar affective disorder. *Curr Opin Psychiatry* 20: 8–12
7 Kato T (2007) Molecular genetics of bipolar disorder and depression. *Psychiatry Clin Neurosci* 61: 3–19
8 Prathikanti S, McMahon FJ (2001) Genome scans for susceptibility genes in bipolar affective disorder. *Ann Med* 33: 257–262
9 Schumacher J, Cichon S, Rietschel M, Nothen MM, Propping P (2002) [Genetics of bipolar affective disorders. Current status of research for identification of susceptibility genes]. *Nervenarzt* 73: 581–592
10 Shih RA, Belmonte PL, Zandi PP (2004) A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *Int Rev Psychiatry* 16: 260–283
11 Sklar P (2002) Linkage analysis in psychiatric disorders: the emerging picture. *Annu Rev Genomics Hum Genet* 3: 371–413
12 Taylor L, Faraone SV, Tsuang MT (2002) Family, twin, and adoption studies of bipolar disease. *Curr Psychiatry Rep* 4: 130–133
13 Tsuang MT, Faraone SV (1990) *The Genetics of Mood Disorders*. Johns Hopkins University Press, Baltimore, MD
14 Schulze TG, McMahon FJ (2004) Defining the phenotype in human genetic studies: forward genetics and reverse phenotyping. *Hum Hered* 58: 131–138
15 Hayden EP, Nurnberger JI Jr, (2006) Molecular genetics of bipolar disorder. *Genes Brain Behav* 5: 85–95
16 Smoller JW, Finn CT (2003) Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet* 123C: 48–58
17 Propping P (2005) The biography of psychiatric genetics: from early achievements to historical burden, from an anxious society to critical geneticists. *Am J Med Genet B Neuropsychiatr Genet* 136B: 2–7
18 Schulze TG, Fangerau H, Propping P (2004) From degeneration to genetic susceptibility, from eugenics to genethics, from Bezugsziffer to LOD score: the history of psychiatric genetics. *Int Rev Psychiatry* 16: 246–259
19 Bertelsen A, Harvald B, Hauge M (1977) A Danish twin study of manic-depressive disorders. *Br J Psychiatry* 130: 331–351
20 Luxenburger H (1930) Psychiatrisch-neurologische Zwillingspathologie. *Zbl Ges Neurol Psychiat* 56: 145–180
21 McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A (2003) The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry* 60: 497–502
22 Rosanoff AJ, Handy LM, Plessett IR (1934) The etiology of manic-depressive syndromes with special reference to their occurrence in twins. *Am J Psychiatry* 91: 247–286
23 Mendlewicz J, Rainer JD (1977) Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 268: 327–329
24 Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I (1986) Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch Gen Psychiatry* 43: 923–929
25 Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, Targum SD, Nurnberger JI Jr, Goldin LR, Bunney WE Jr (1982) A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry* 39: 1157–1167
26 Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Thompson WD, Pauls DL, Guroff JJ (1984) Psychiatric disorders in the relatives of probands with affective disorders. The Yale University – National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry* 41: 13–21
27 Berrettini WH (2000) Are schizophrenic and bipolar disorders related? A review of family and molecular studies. *Biol Psychiatry* 48: 531–538
28 Dunner DL, Fleiss JL, Fieve RR (1976) The course of development of mania in patients with recurrent depression. *Am J Psychiatry* 133: 905–908
29 McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR Jr (1993) Anticipation in bipolar affective disorder. *Am J Hum Genet* 53: 385–390
30 Stine OC, Xu J, Koskela R, McMahon FJ, Gschwend M, Friddle C, Clark CD, McInnis MG, Simpson SG, Breschel TS et al (1995) Evidence for linkage of bipolar disorder to chromosome 18

with a parent-of-origin effect. *Am J Hum Genet* 57: 1384–1394
31 McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR Jr (1995) Patterns of maternal transmission in bipolar affective disorder. *Am J Hum Genet* 56: 1277–1286
32 Botstein D, White RL, Skolnick M, Davis RW (1980) Construction of a genetic linkage map in man using restriction fragment length polymorphisms. *Am J Hum Genet* 32: 314–331
33 Knowlton RG, Cohen-Haguenauer O, Van Cong N, Frezal J, Brown VA, Barker D, Braman JC, Schumm JW, Tsui LC, Buchwald M (1985) A polymorphic DNA marker linked to cystic fibrosis is located on chromosome 7. *Nature* 318: 380–382
34 Wainwright BJ, Scambler PJ, Schmidtke J, Watson EA, Law HY, Farrall M, Cooke HJ, Eiberg H, Williamson R (1985) Localization of cystic fibrosis locus to human chromosome 7cen-q22. *Nature* 318: 384–385
35 Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY (1983) A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 306: 234–238
36 Egeland JA, Gerhard DS, Pauls DL, Sussex JN, Kidd KK, Allen CR, Hostetter AM, Housman DE (1987) Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature* 325: 783–787
37 Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, Bale SJ, Pauls DL, Long RT, Kidd KK, Conte G (1989) Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. *Nature* 342: 238–243
38 Risch N, Botstein D (1996) A manic depressive history. *Nat Genet* 12: 351–353
39 Schulze TG, McMahon FJ (2003) Genetic linkage and association studies in bipolar affective disorder: a time for optimism. *Am J Med Genet C Semin Med Genet* 123C: 36–47
40 Badner JA, Gershon ES (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry* 7: 405–411
41 McQueen MB, Devlin B, Faraone SV, Nimgaonkar VL, Sklar P, Smoller JW, Abou Jamra R, Albus M, Bacanu SA, Baron M et al (2005) Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. *Am J Hum Genet* 77: 582–595
42 Seguardo R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI Jr, Craddock N, DePaulo JR Jr, Baron M, Gershon ES et al (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *Am J Hum Genet* 73: 49–62
43 McMahon FJ (2007) A success at the end of an era, and a glimpse of things to come. *Am J Psychiatry* 164: 999–1001
44 Clerget-Darpoux F, Elston RC (2007) Are linkage analysis and the collection of family data dead? Prospects for family studies in the age of genome-wide association. *Hum Hered* 64: 91–96
45 Morrow EM, Yoo SY, Flavell SW, Kim TK, Lin Y, Hill RS, Mukaddes NM, Balkhy S, Gascon G, Hashmi A et al (2008) Identifying autism loci and genes by tracing recent shared ancestry. *Science* 321: 218–223
46 Detera-Wadleigh SD, McMahon FJ (2006) G72/G30 in schizophrenia and bipolar disorder: review and meta-analysis. *Biol Psychiatry* 60: 106–114
47 The Celera Genomics Sequencing Team (2001) The sequence of the human genome. *Science* 291: 1304–1351
48 The International Human Genome Mapping Consortium (2001) A physical map of the human genome. *Nature* 409: 934–941
49 The International HapMap Consortium (2004) The International HapMap Consortium. The International HapMap Project. *Nature* 426: 789–796
50 Diabetes Genetics Initiative (2007) Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 316: 1331–1336
51 Scott LJ, Mohlke KL, Bonnycaste LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU et al (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 316: 1341–1345
52 Sladek R, Rochelau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S et al (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445: 881–885
53 The Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447: 661–678
54 Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott

KS, Lango H, Rayner NW et al (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316: 889–894
55 Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A et al (2007) A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 316: 1491–1493
56 McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennachio LA, Tybjaerg-Hansen A, Folsom AR et al (2007) A common allele on chromosome 9 associated with coronary heart disease. *Science* 316: 1488–1491
57 Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST et al (2005) Complement factor H polymorphism in age-related macular degeneration. *Science* 308: 385–389
58 Maller J, George S, Purcell S, Fagerness J, Altshuler D, Daly MJ, Seddon JM (2006) Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nat Genet* 38: 1055–1059
59 Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J et al (2007) A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet* 39: 207–211
60 Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW et al (2007) Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* 39: 596–604
61 Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A et al (2007) Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 39: 631–637
62 Yeager M, Orr N, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z et al (2007) Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet* 39: 645–649
63 Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nothen MM et al (2008) A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry* 13: 197–207
64 Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, Nimgaonkar VL, McQueen MB, Faraone SV, Kirby A et al (2008) Whole-genome association study of bipolar disorder. *Mol Psychiatry* 13: 558–569
65 Lango H, Weedon MN (2008) What will whole genome searches for susceptibility genes for common complex disease offer to clinical practice. *J Intern Med* 263: 16–27
66 Manolio TA, Brooks LD, Collins FS (2008) A HapMap harvest of insights into the genetics of common disease. *J Clin Invest* 118: 1590–1605
67 Falconer DS (1981) *Introduction to quantitative genetics*. Longman, London
68 Keller MC, Miller G (2006) Resolving the paradox of common, harmful, heritable mental disorders: which evolutionary genetic models work best? *Behav Brain Sci* 29: 385–404
69 Pritchard JK (2001) Are rare variants responsible for susceptibility to complex diseases? *Am J Hum Genet* 69: 124–137
70 Pritchard JK, Cox NJ (2002) The allelic architecture of human disease genes: common disease-common variant…or not? *Hum Mol Genet* 11: 2417–2423
71 Terwilliger JD, Haghighi F, Hiekkalinna TS, Goring HH (2002) A biased assessment of the use of SNPs in human complex traits. *Curr Opin Genet Dev* 12: 726–734
72 Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J et al (2007) Strong association of *de novo* copy number mutations with autism. *Science* 316: 445–449
73 Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda RL, Malhotra D, Bhandari A et al (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320: 539–543
74 Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M (2008) Strong association of *de novo* copy number mutations with sporadic schizophrenia. *Nat Genet* 40: 880–885
75 Schulze TG, Ohlraun S, Czerski PM, Schumacher J, Kassem L, Deschner M, Gross M, Tullius M, Heidmann V, Kovalenko S et al (2005) Genotype-phenotype studies in bipolar disorder showing association between the DAOA/G30 locus and persecutory delusions: a first step toward a molecular genetic classification of psychiatric phenotypes. *Am J Psychiatry* 162: 2101–2108

76 Williams NM, Green EK, Macgregor S, Dwyer S, Norton N, Williams H, Raybould R, Grozeva D, Hamshere M, Zammit S et al (2006) Variation at the DAOA/G30 locus influences susceptibility to major mood episodes but not psychosis in schizophrenia and bipolar disorder. *Arch Gen Psychiatry* 63: 366–373
77 Craddock N, Owen MJ (2007) Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry* 6: 84–91
78 Braun J, Sieper J (2006) Early diagnosis of spondyloarthritis. *Nat Clin Pract Rheumatol* 2: 536–545
79 Fisfalen ME, Schulze TG, DePaulo JR Jr, DeGroot LJ, Badner JA, McMahon FJ (2005) Familial variation in episode frequency in bipolar affective disorder. *Am J Psychiatry* 162: 1266–1272
80 McMahon FJ, Simpson SG, McInnis MG, Badner JA, MacKinnon DF, DePaulo JR Jr (2001) Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. *Arch Gen Psychiatry* 58: 1025–1031
81 Potash JB, Zandi PP, Willour VL, Lan TH, Huo Y, Avramopoulos D, Shugart YY, MacKinnon DF, Simpson SG, McMahon FJ et al (2003) Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. *Am J Psychiatry* 160: 680–686
82 Faraone SV, Glatt SJ, Su J, Tsuang MT (2004) Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. *Am J Psychiatry* 161: 625–630
83 Lin PI, McInnis MG, Potash JB, Willour VL, MacKinnon DF, DePaulo JR Jr, Zandi PP (2005) Assessment of the effect of age at onset on linkage to bipolar disorder: evidence on chromosomes 18p and 21q. *Am J Hum Genet* 77: 545–555
84 Kassem L, Lopez V, Hedeker D, Steele J, Zandi PP, Bipolar Disorder Consortium NIMH Genetics Initiative, McMahon FJ (2006) Familiality of polarity at illness onset in bipolar affective disorder. *Am J Psychiatry* 163: 1754–1759
85 Craddock N, Jones L, Jones I, Kirov G, Green EK, Grozeva D, Moskvina V, Nikolov I, Hamshere M, Vukcevic D et al (2008) Strong genetic evidence for a selective influence of GABAA receptors on a component of the bipolar disorder phenotype. *Mol Psychiatry* July 1, Epub ahead of print
86 Iannuzzi MC, Baughman RP (2007) Reverse phenotyping in sarcoidosis. *Am J Respir Crit Care Med* 175: 4–5
87 Potash JB, Toolan J, Steele J, Miller EB, Pearl J, Zandi PP, Schulze TG, Kassem L, Simpson SG, Lopez V et al (2007) The bipolar disorder phenome database: a resource for genetic studies. *Am J Psychiatry* 164: 1229–1237
88 Schulze TG, Hedeker D, Zandi PP, Rietschel M, McMahon FJ (2006) What is familial about familial bipolar disorder? Resemblance among relatives across a broad spectrum of phenotypic characteristics. *Arch Gen Psychiatry* 63: 1368–1376
89 Brockmoller J, Tzvetkov MV (2008) Pharmacogenetics: data, concepts and tools to improve drug discovery and drug treatment. *Eur J Clin Pharmacol* 64: 133–157
90 Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmoller J (2004) Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry* 9: 442–473
91 Laje G, Paddock S, Manji HK, Rush AJ, Wilson AF, Charney D, McMahon FJ (2007) Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *Am J Psychiatry* 164: 1530–1538
92 Lekman M, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, Lipsky R, Wisniewski SR, Manji HK, McMahon FJ et al (2008) The FKBP5-gene in depression and treatment response – an association study in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Cohort. *Biol Psychiatry* 63: 1103–1110
93 McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, Sorant AJ, Papanicolaou GJ, Laje G, Fava M et al (2006) Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet* 78: 804–814
94 Paddock S, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, Lipsky R, Wisniewski SR, Manji HK, McMahon FJ (2007) Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. *Am J Psychiatry* 164: 1181–1188
95 Alda M (2003) Pharmacogenetic aspects of bipolar disorder. *Pharmacogenomics* 4: 35–40
96 Winokur G (1975) The Iowa 500: heterogeneity and course in manic-depressive illness (bipolar). *Compr Psychiatry* 16: 125–131
97 Bremer T, Diamond C, McKinney R, Shehktman T, Barrett TB, Herold C, Kelsoe JR (2007) The

pharmacogenetics of lithium response depends upon clinical co-morbidity. *Mol Diagn Ther* 11: 161–170
98 Dmitrzak-Weglarz M, Rybakowski JK, Suwalska A, Slopien A, Czerski PM, Leszczynska-Rodziewicz A, Hauser J (2005) Association studies of 5-HT2A and 5-HT2C serotonin receptor gene polymorphisms with prophylactic lithium response in bipolar patients. *Pharmacol Rep* 57: 761–765
99 Rybakowski JK, Suwalska A, Czerski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J (2005) Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. *Pharmacol Rep* 57: 124–127
100 Rybakowski JK, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A, Czerski PM, Hauser J (2005) Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. *Pharmacopsychiatry* 38: 166–170
101 Anguelova M, Benkelfat C, Turecki G (2003) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. *Mol Psychiatry* 8: 574–591
102 Fan J, Sklar P (2008) Genetics of bipolar disorder: focus on BDNF Val66Met polymorphism. *Novartis Found Symp* 289: 60–72
103 Kanazawa T, Glatt SJ, Kia-Keating B, Yoneda H, Tsuang MT (2007) Meta-analysis reveals no association of the Val66Met polymorphism of brain-derived neurotrophic factor with either schizophrenia or bipolar disorder. *Psychiatr Genet* 17: 165–170
104 Hodgkinson CA, Goldman D, Jaeger J, Persaud S, Kane JM, Lipsky R, Malhotra D (2004) Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. *Am J Hum Genet* 75: 862–872
105 Perlis RH, Purcell S, Fagerness J, Kirby A, Petryshen TL, Fan J, Sklar P (2008) Family-based association study of lithium-related and other candidate genes in bipolar disorder. *Arch Gen Psychiatry* 65: 53–61
106 Thomson PA, Wray NR, Millar JK, Evans KL, Hellard SL, Condie A, Muir WJ, Blackwood D, Porteous DJ (2005) Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. *Mol Psychiatry* 10: 657–658
107 Cichon S, WInge I, Mattheisen M, Georgi A, Karpushova A, Freudenberg-Hua Y, Babadjanova G, van den Bogaert A, Abramova LI, Kapiletti S et al (2008) Brain-specific tryptophan hydroxylase 2 (TPH2): a functional Pro206Ser substitution and variation in the 5'-region are associated with bipolar affective disorder. *Hum Mol Genet* 17: 87–97
108 Harvey M, Gagne B, Labbe M, Barden N (2007) Polymorphisms in the neuronal isoform of tryptophan hydroxylase 2 are associated with bipolar disorder in French Canadian pedigrees. *Psychiatr Genet* 17: 17–22
109 Harvey M, Shink E, Tremblay M, Gagne B, Raymond C, Labbe M, Walther DJ, Bader M, Barden N (2004) Support for the involvement of TPH2 gene in affective disorders. *Mol Psychiatry* 9: 980–981
110 Lopez V, Detera-Wadleigh SD, Cardona I, NIMH Genetics Initiative Bipolar Disorder Consortium, Kassem L, McMahon FJ (2007) Nested association between genetic variation in tryptophan hydroxylase II, bipolar affective disorder, and suicide attempts. *Biol Psychiatry* 61: 181–186
111 van den Bogaert A, Sleegers K, De Zutter S, Heyrman L, Norrback KF, Adolfsson R, Van Broeckhoven C, Del-Favero J (2006) Association of brain-specific tryptophan hydroxylase, TPH2, with unipolar and bipolar disorder in a Northern Swedish, isolated population. *Arch Gen Psychiatry* 63: 1103–1110
112 Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, Monk TH, Devlin B, Nimgaonkar VL (2006) Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes Brain Behav* 5: 150–157
113 Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, McElroy SL, Keck PE Jr, Schork NJ, Kelsoe JR (2006) Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 141B: 234–241
114 Abou Jamra R, Becker T, Georgi A, Feulner T, Schumacher J, Stromaier J, Schirmbeck F, Schulze TG, Propping P, Rietschel M et al (2008) Genetic variation of the FAT gene at 4q35 is associated with bipolar affective disorder. *Mol Psychiatry* 13: 277–284
115 Blair IP, Chetcuti AF, Badenhop RF, Scimone A, Moses MJ, Adams LJ, Craddock N, Green EK,

Kirov G, Owen MJ et al (2006) Positional cloning, association analysis and expression studies provide convergent evidence that the cadherin gene FAT contains a bipolar disorder susceptibility allele. *Mol Psychiatry* 11: 372–383

116 Baum AE, Hamshere M, Green EK, Cichon S, Rietschel M, Noethen MM, Craddock N, McMahon FJ (2008) Meta-analysis of two genome-wide association studies of bipolar disorder reveals important points of agreement. *Mol Psychiatry* 13: 466–467

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Understanding the neurobiology of bipolar depression

Jun-Feng Wang and L. Trevor Young

Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, Canada

Abstract

Many studies have shown decreased brain volume and cell number in prefrontal and limbic regions of bipolar disorder subjects, suggesting presence of disturbed neuronal circuitry and impaired neuroplasticity in these regions. The serotonin system plays an important role in depression and is a target of antidepressants. Studies have shown that the major serotonin metabolite 5-HIAA and serotonin transporter activity are decreased in cerebrospinal fluid, brain or platelets of subjects with bipolar depression, indicating that an abnormal serotonin system also contributes significantly to this disease. Mitochondria regulate synthesis, release and uptake of neurotransmitters via energy production. Evidence has shown that glucose metabolic rate and cerebral blood flow are decreased in bipolar depression. Studies also suggest defects in mitochondrial electron transport chain and oxidative damage in bipolar disorder. These studies together indicate that bipolar depression may be associated with an abnormal serotonin system resulting from mitochondrial dysfunction-induced impaired neuroplasticity in neuronal circuitry related to mood regulation.

Introduction

The depressed phase of bipolar disorder remains an enormous challenge for patients, their families and to clinicians. Depression is far more common in bipolar disorder than is mania, and is associated with high rates of suicide or suicide attempts and marked impairment in function [1–5]. There has long been debate about whether bipolar depression is similar to or different from unipolar depression, with recognition of different treatment responses and clinical courses suggesting a different neurobiology.

Mood stabilizing drugs are useful for treatment of different phases of the illness including treatment of mania and depression acutely and prophylaxis against relapse into either state. There is a general consensus that treating either acute depression or preventing relapses into depression is more challenging than treating mania and that the drugs we use to treat the disorder are less effective for these symptoms [6]. Therefore, a better understanding of the molecular mechanism of bipolar disorder, and particularly of bipolar depression, is critical to improving treatment for the disease.

Many studies using brain imaging and postmortem brain tissue have revealed reduced brain volume and cell density in prefrontal cortex and limbic regions from subjects with bipolar disorder. These findings suggest that critical neuronal circuits made up of regions that modulate emotion and mood are disturbed, which subsequently affects synthesis, release, reuptake and other functions of neurotransmitters and results in impairment of neuroplasticity. Serotoninergic neurotransmitter system has been extensively studied in the pathology of major depressive disorder, and is targeted by antidepressants. Studies also implicate the serotoninergic system in bipolar depression and as a target for many mood stabilizing drugs, suggesting that the system may also have a critical role in the pathology of bipolar disorder. It remains to be determined what causes or promotes the loss in neuroplasticity and cell loss in bipolar disorder. Among several plausible hypotheses, the possibility that altered energy metabolism and oxidative stress occurs in the illness lead to cellular damage is becoming increasing accepted. Mitochondria are enriched in both dendrites and synaptic terminals, produce energy for many neuronal functions including synthesis, release and reuptake of neurotransmitters, and are important in regulation of neuronal plasticity and surviving. Increasing evidence suggest impaired energy metabolism and mitochondrial dysfunction in brain of bipolar disorder patients.

In the following chapter, we review findings on the neurobiology of depression. Most studies in bipolar disorder have not focused only on the depressed phase of illness but have looked at patients in all phases of illness. There is a long debate about whether these may be a specific neurobiology of depression in bipolar disorder and how it relates to unipolar depression. We have focused on the three areas described above as they are related to approaches that have been successful in the study of major depression. We suggest in this review that cell loss and decreased neuroplasticity occurred in key limbic and cortical regions lead to monoaminergic dysfunction including the serotonin system, which could contribute to depressive symptoms. Finally we suggest that altered energy metabolism occurs in bipolar disorder which ultimately results in cell damage and altered neurotransmission.

Structural abnormality in frontal and limbic brain regions of subjects with bipolar disorder

Mood regulation appears to be related to activity in the prefrontal cortex and anterior cingulate cortex, and in the hippocampal and amygdalar limbic brain regions, all of which together regulate behaviors such as emotion, attention, motivation and cognition. Prefrontal cortex plays a critical role in thought processes that control mood, cognition and motor behavior functions. Anterior cingulate cortex is important to attentional, emotional and cognitive mental functions, and in the initiation of motivated behavior. Hippocampal and amygdalar limbic regions are involved in production of emotion, in motivation, and

in emotional association with memory [7–10]. In patients with bipolar disorder, compelling evidence for structural abnormalities, cell loss and reduced cell density in these key brain regions associated with mood regulation has been provided by neuroimaging and postmortem brain studies.

Using magnetic resonance imaging, a number of these studies have found a decrease in grey matter volume in prefrontal cortex from bipolar and unipolar depression patients (Fig. 1) [11–14]. However, the findings for changes in hippocampal and amygdalar volume in adult bipolar subjects are equivocal compared to those for prefrontal cortex [15–21]. The reasons for the discrepant data for structural hippocampal and amygdalar changes may reflect the varied histories of illness diagnosis and treatment that are characteristic of adult bipolar disorder populations. On the other hand, recent studies in children and adolescents with bipolar disorder have consistently reported decreased amygdalar volume [22–25]. Altshuler et al. [26] found that amygdalar volume in bipolar disorder subjects with a history of psychoses was positively correlated with the number of manic episodes, indicating that course of illness may play a role in exacerbating volumetric changes.

Postmortem brain studies have provided direct evidence suggesting that reduced cell number and cell density may contribute to structural changes in the brain that have been observed in bipolar disorder subjects. Rajkowska et al.

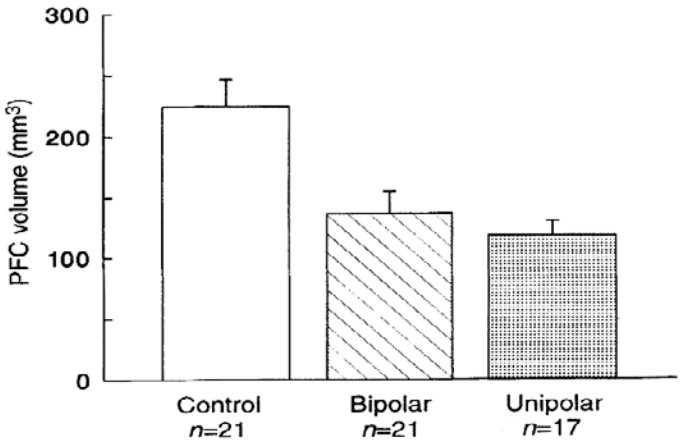


Figure 1. MRI-based volumes of the left subgenual prefrontal cortex (PFC) grey matter differed between the bipolar disordered, unipolar depressed and control groups (ANOVA, $F = 9.8$; $P < 0.0002$, co-varying for gender, age and whole brain volume). *Post hoc* tests (Tukey-Kramer) showed significant volumetric decreases in the bipolar and unipolar groups relative to the control group. Whole-brain MRI volume and skull X-ray measures (product of anterior-posterior distance between the inner tables of the skull at the estimated bicommissural segment and perpendicular distance from the midpoint of the bicommissural segment to the vertex) were slightly smaller in the unipolar group compared with the bipolar and control groups, and did not differ between the bipolar and control groups. The left subgenual PFC/whole brain volume ratio was also reduced in the bipolar and unipolar groups, being $1.8 \times 10^{-4} \pm 0.74 \times 10^{-4}$, $1.1 \times 10^{-4} \pm 0.64 \times 10^{-4}$, and $1.1 \times 10^{-4} \pm 0.51 \times 10^{-4}$ in the control, bipolar, and unipolar groups, respectively ($F = 8.4$; $P < 0.001$) [11].

[27] found, in the prefrontal area, that pyramidal cell density in layers III and V were decreased in bipolar disorder subjects. Non-pyramidal neurons were also reported to be decreased in layer II of anterior cingulate cortex and in the CA2 region of hippocampus [28, 29]. Recent data have also indicated decreased neuronal size and number in the lateral nucleus of the amygdala in subjects with bipolar disorder [30, 31]. Aberrant mossy fiber sprouting has been observed in the hippocampus of bipolar disorder subjects [32], which is suggestive of altered neuroplasticity. Levels of the neuronal viability marker N-acetyl-aspartate was shown to be decreased in *post mortem* prefrontal cortex of bipolar disorder subjects [33, 34]. Glial number and density were also reduced in the same region [27, 35]. The glial fibrillary acidic protein isoforms were found to be decreased in the prefrontal cortex of both bipolar disorder and unipolar depression subjects, suggesting decreased astrocytes [36]. It has also been reported that dystrophic alterations and reduced density occur in oligodendroglial cells in layer VI of BA 9/10 in bipolar disorder subjects [37–39]. These results suggest that both astrocytes and oligodendroglial cells are involved in the changes observed in glial cells.

Changes of volume and cell density in prefrontal and limbic brain regions suggest a possible disruption of neuronal circuits which regulate mood and emotion. Brain derived neurotrophic factor (BDNF) is abundantly and widely distributed in brain. It regulates synapse formation, differentiation and neuronal survival, and plays an important role in regulation of neuroplasticity and behaviors. Recent studies have shown that altered expression of BDNF occurs in brain in bipolar disorder, suggesting that it is an important factor in causing or promoting changes in neuronal structure or density in these brain regions. For example, it has been reported that levels of BDNF protein were lower in postmortem hippocampus of subjects with bipolar disorder than controls [40]. The val66met BDNF polymorphism has also shown to be associated with bipolar disorder [41–44]. Recently, a number of studies also found abnormal expression of BDNF in peripheral blood from bipolar patients. Cunha et al. [45] investigated serum BDNF levels in manic, depressive and euthymic states of BD patients and found that serum BDNF levels in manic and depressive states, but not in euthymic state, were decreased when compared with healthy controls. Decreased serum BDNF levels have also been found in euthymic patients with bipolar disorder, and depressed and euthymic patients with unipolar depression [46]. Our laboratory also found that BDNF levels were significantly lower in lymphoblasts from bipolar disorder subjects when compared with matched healthy controls [47] (Fig. 2). These findings together implicate BDNF may be one of the critical factors which ultimately contribute to a loss of neuroplasticity and cell loss in bipolar disorder.

There are many consequences to disruption of these neurons and impairment of neuroplasticity, one of which is the possibility that these changes may lead to a predisposition for depressive and manic affective responses. The serotoninergic system has long been identified as important in mood and in particular depression. Indeed, as reviewed below both older and very recent data

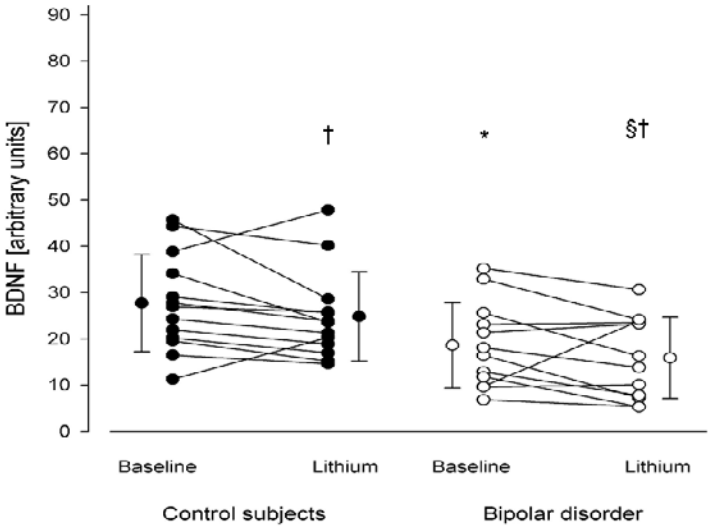


Figure 2. BDNF protein levels in transformed lymphoblasts from non-psychiatric controls and lithium-responsive bipolar subjects, with and without 1 mM lithium treatment for 7 days, and unaffected relatives. BDNF protein levels were 36% lower in subjects with bipolar disorder compared to non-psychiatric controls (*, $p = 0.02$), and this decrease remained (33%, §, $p = 0.02$) after lithium treatment. Lithium treatment decreased BDNF levels in both bipolar and control populations (†, $p = 0.05$). All measures are expressed as mean ± standard deviation [47].

suggest the importance of this same neurotransmitter in bipolar depression. We speculate that this may be one of the consequences of the cellular changes in brain of patients with bipolar disorder which is critical to the development of depressive symptoms and episodes.

Serotonin neurotransmitter system in subjects with bipolar depression

The serotonergic neurons project to many cortical brain regions and regulate many brain functions such as emotion, cognition, motor function, pain sensitivity and many others. Based upon evidence from neuroimaging, postmortem brain, peripheral blood cell, pharmacological and genetic studies, an abnormal serotoninergic system is well acknowledged to play an important role in the pathophysiology of unipolar depression. Although whether molecular and cellular mechanisms are distinct in unipolar depression and bipolar depression remains unclear, a number of studies have also suggested that the serotoninergic system, particularly serotonin level and serotonin transporter reuptake activity, is altered in bipolar depression.

Studies have shown that the turnover of serotonin is altered in bipolar depression. 5-hydroxyindoleacetic acid (5-HIAA) is the main metabolite of serotonin. Decreased concentrations of this serotonin metabolite have been

consistently reported in cerebrospinal fluid of bipolar depressed patients. It has been reported that the concentration of 5-HIAA in cerebrospinal fluid of depressed subjects, including both bipolar and unipolar subjects, was significantly lower than that of healthy controls [48]. The concentration of 5-HIAA in cerebrospinal fluid has also been found to be decreased in bipolar depression subjects with suicide attempts when compared with controls [49]. It is interesting that 5-HIAA levels of cerebrospinal fluid were significantly increased in female manic patients when compared with gender matched controls [50]. Decreased 5-HIAA levels in depression, and increased 5-HIAA levels in mania, suggest an important relevance of 5-HIAA in manic and depressive symptoms of bipolar disorder. In order to determine if monoamine metabolites are critical to lethality of suicide attempts in bipolar patients, Sher et al. [51] recently using high-performance liquid chromatography to analyze the relationship between 5-HIAA, dopamine metabolite homovanillic acid (HVA) and norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in cerebrospinal fluid, and maximum lethality of suicide attempts during a 2-year follow up in 27 bipolar depressed patients. They found that 5-HIAA, HVA, and MHPG levels were negatively correlated with the maximum lethality of suicide attempts during this follow-up period. Decreased levels of monoamine metabolites have also been found in postmortem brain tissue in subjects with bipolar depression. Young et al. [52] found that in bipolar disorder subjects who died while depressed, 5-HIAA levels were decreased in postmortem frontal and parietal cortex, and 5-HIAA/serotonin ratio was decreased in postmortem temporal cortex, while HVA levels were decreased in postmortem parietal cortex and HVA/dopamine ratios were decreased in postmortem occipital cortex when compared with controls. These studies suggest that decreased production or increased removal of 5-HIAA in cerebrospinal fluid and brain play an important role in bipolar depression, and also suggest that levels of monoamine metabolites may be used as predictors of lethality of suicide attempts in subjects with bipolar disorder.

Serotonin transporter in presynaptic terminals reuptakes the neurotransmitter serotonin from synaptic cleft into presynaptic neurons, and is a key molecule for control of synaptic serotonin levels. Serotonin transporter is also primary target for many antidepressants [53, 54]. A number of studies indicate abnormal serotonin transporter activity in subjects with bipolar depression. Among these studies, most reported that the serotonin transporter activity is decreased in this disorder, but some also reported that the serotonin transporter activity is not changed or increased.

Serotonin transporter activity has been measured by analyzing the binding of selective serotonin reuptake inhibitor with the transporter uptake site. Leake et al. [55] studied 15 subjects with depression, 9 with major depressive disorder and 6 with bipolar disorder, and found that the concentration of ^{3}H-citalopram binding to serotonin transporter was lower in postmortem frontal cortex from depressed subjects when compared with controls. They also found that serotonin uptake sites were attenuated in a trend in subjects with bipolar

depression. Human platelets are able to uptake serotonin and resemble presynaptic serotoninergic neurons [56], which provide a convenient model to investigate involvement of the serotonin system in the pathophysiology of mood disorders. Stahl et al. [57] found that serotonin uptake was significantly reduced in subjects with bipolar depression, but not in subjects with schizophrenia when compared to controls. It has also been found that the maximum rate for serotonin reuptake into platelets was reduced in subjects with bipolar depression and unipolar depression [58–60]. However, serotonin transporter activity in platelets has also been reported to be no change between subjects with controls and bipolar depression [61]. Although no difference of serotonin transporter activity between subjects with depression and healthy controls has also been found, serotonin transporter activity has been found to be significantly lower in subjects with bipolar depression than unipolar depression [62]. A difference in this transporter activity between subjects with bipolar depression and unipolar depression may be useful to classify clinically defined subtypes of depression in affective disorders.

Decreased serotonin transporter activity in bipolar depression was also confirmed by a study using positron emission tomography. Oquendo et al. [63] recently studied brain serotonin transporter binding using positron emission tomography and radiolabeled *trans*-1,2,3,5,6,10-β-hexahydro-6-[4-(methylthio) phenyl] pyrrolo-[2,1-a]-isoquinoline (^{11}C(+)-McN5652) in 18 medication-free patients with bipolar depression compared with 41 controls. They found that serotonin transporter binding activity was reduced by 16% to 26% in the midbrain, amygdala, hippocampus, thalamus, putamen, and anterior cingulate cortex of patients with bipolar depression (Fig. 3). Using the same technology, serotonin transporter binding activity has also been found to be decreased in subjects with unipolar depression [64–66]. Low serotonin transporter binding activity may represent serotonin transporter internalization that is facilitated by decreased serotonin levels in synaptic cleft in subjects with bipolar depression. Because serotonin transporter binding has been used as is a marker for serotoninergic neurons, low serotonin transporter binding activity may also indicate fewer serotoninergic neurons in subjects with bipolar depression [63, 67, 68]. [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C] DASB), a recently developed diphenyl sulfide radioligands, is able to higher selectively bind serotonin transporter *in vivo* than previously available radioligands. Cannon et al. [69, 70] analyzed the serotonin transporter binding potential in 18 unmedicated subjects with bipolar depression and 37 healthy controls using positron emission tomography and [^{11}C] DASB. They found that the serotonin binding activity was decreased in pontine raphe-nuclei of the brainstem, but increased in the thalamus, dorsal cingulate cortex, medial prefrontal cortex and insula when compared with controls. They also found that serotonin transporter binding was lower in the midbrain and higher in anterior cingulate cortex of bipolar subjects with a history of suicide attempts when compared to controls or bipolar subjects without suicide attempts. It is interesting that subjects with bipolar depression have shown lower serotonin transporter binding poten-

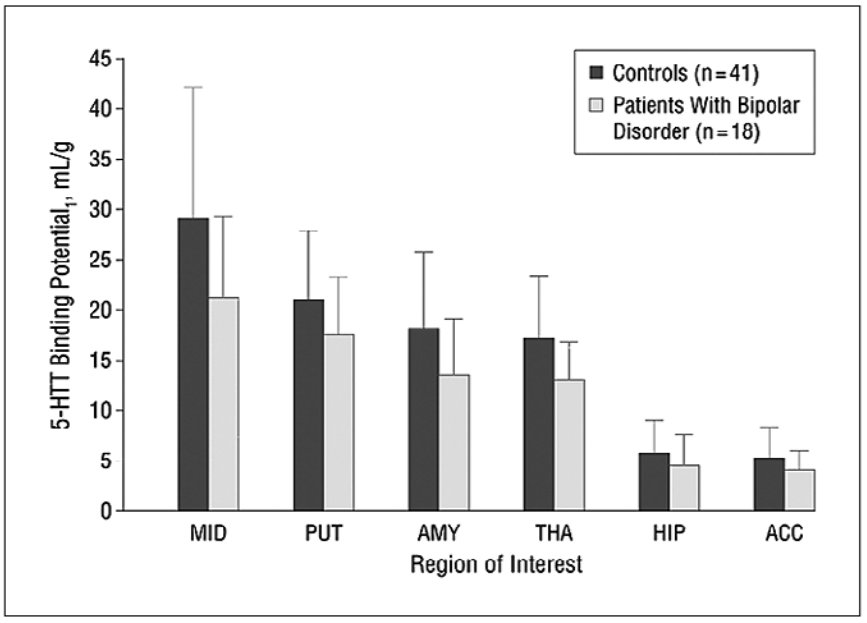


Figure 3. Lower radiolabeled trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{11}C](+)-McNeil 5652) binding potential (BP1) to the serotonin transporter (5-HTT) in nonmedicated patients with bipolar disorder in six regions of interest compared with controls ($F1,58 = 5.41$; $P = .02$). ACC indicates anterior cingulate cortex; AMY, amygdala; HIP, hippocampus; MID, midbrain; PUT, putamen; and THA, thalamus. Vertical bars represent the mean likelihood approach to the graphical method modeled BP1 (VT[region] – VT[cerebellum]) for each region; error bars, ±1 SD [63].

tial in pontine raphe-nuclei region than subjects with unipolar depression and controls, while subjects with unipolar depression have shown higher serotonin binding potential in periaqueductal gray of middle brain than subjects with bipolar and controls. This difference of serotonin binding potential in brainstem between unipolar depression and bipolar depression may be relevant to patterns of illness symptoms and pharmacological sensitivity for these disorders.

In summary, the levels of the major metabolite of serotonin 5-HIAA may be decreased in cerebrospinal fluid and brain of subjects with bipolar depression, suggesting that intra-synaptic serotonin levels are low in this disorder. The findings of serotonin transporter binding activity in bipolar depression however are inconsistent. Most studies have suggested that serotonin transporter binding activity is decreased in bipolar depression, while others have reported that serotonin transporter binding activity is increased. The inconsistency may result from small sample sizes, differing ligands, confounding medications, and differing reference tissues, among other reasons.

Serotonin reuptake appears to be dysregulated in bipolar depression quite similar to which is seen in unipolar depression [71]. Many studies suggest that

BDNF regulates the development and function of serotoninergic neurons [72–75]. Recent studies have also shown that administration of selective serotonin reuptake inhibitor antidepressants increase gene expression of BDNF [76–80]. As described above, decreased BDNF levels have also been shown in bipolar disorder. Since both serotoninergic system and BDNF play an important role in brain development via regulation of neurite outgrowth, synaptogenesis, and cell survival, dysregulation in serotoninergic system and BDNF imply impaired neuroplasticity in bipolar depression, resulting in the cell loss and damage found in brain imaging and *post mortem* brain studies.

Abnormal energy metabolism and dysfunctional mitochondria

While the factors that cause or promote cell loss and change in brain of patients with bipolar disorder, ultimately leading to altered neurotransmission, remain to be fully established, altered energy metabolism resulting in oxidative stress may be one important contributing factor. Mitochondria are enriched in both dendrites and synaptic terminals, and play important roles in neuroplasticity and cell viability via energy production. Therefore, abnormal regulation of serotonin system in bipolar depression may result from impaired neuroplasticity induced by abnormal energy metabolism and dysfunctional mitochondria.

Metabolic pathways for energy production in humans include glycolysis, the citric acid cycle and the electron transport chain. The primary source for energy production in the brain is glucose. During the glycolysis process, one molecule of glucose is converted into two molecules of pyruvate that are then used for making more molecules of ATP in the citric acid cycle and in the electron transport chain in mitochondria [81, 82]. A number of studies have indicated presence of impaired energy metabolism in bipolar depression. Baxter et al. [83] using positron emission tomography and fluorodeoxyglucose F18 in a small group of subjects (11 with unipolar depression, 5 with bipolar depression, 5 with mania, 3 with bipolar mixed states and 9 normal controls) found that subjects with bipolar depression have significant lower cerebral metabolic rates for glucose when compared with other groups. The ranking for glucose metabolic rates in the whole brain from low to high are bipolar depression, unipolar depression or a mixed state, manic state respectively. Later this research group [84] also analyzed cerebral glucose metabolism in a larger group of subjects with depression that included bipolar depression, unipolar depression and obsessive-compulsive disorder with secondary depression. They found that the glucose metabolic rate was significantly lower in subjects with bipolar depression and unipolar depression than in controls in the left dorsal anterolateral prefrontal cortex. The depressive subjects with medication showed increased glucose metabolic rates in this brain region, and the percentage of change was correlated with the Hamilton Rating Scale for Depression score. The rate of glucose metabolism was also found to be

decreased in the prefrontal cortex of subjects with familial bipolar depression and familial unipolar depression, but increased in subjects with mania [11]. However, it has been also reported that the rate of glucose metabolism was higher in subjects with either unipolar depression or bipolar depression than in healthy controls in the left amygdale [85]. These studies suggested that change of glucose metabolism represents changes in mood state, has brain regional difference and contributes a significant role in mood disorders. Glucose metabolic process in brain may also be targeted by pharmacological treatment.

Efficient cerebral blood flow is required to meet the brain's metabolic demands. Studies have shown lower cerebral blood flow in subjects with bipolar depression. Ito et al. [86] using ^{99m}Tc-hexamethylpropyleneamineoxime as a cerebral blood flow tracer for single photon emission computed tomography scan in 11 patients with unipolar depression, 6 patients with bipolar depression and 9 age-matched normal control subjects. They found that cerebral blood flow was significantly decreased in the prefrontal cortices, limbic systems and paralimbic areas of subjects with unipolar depression and bipolar depression, and there was no difference observed between these two types of depression. Using positron emission tomographic images, Drevets et al. [11] also found that cerebral blood flow was decreased in the prefrontal cortex of subjects with unipolar depression and bipolar depression. Rubin et al. [87] analyzed young adults in episodes of either acute mania or major depression. They found that cerebral blood flow was significantly lower in subjects with mania and depression than in controls in anterior cortical areas. In contrast to these studies, Tutus et al. [88] found that cerebral blood flow was decreased only in the left frontal lobe of subjects with unipolar depression but not bipolar depression when compared to subjects with and controls. Recently, Krüger et al. [89] found that cerebral blood flow was decreased in the orbitofrontal and inferior temporal cortices but increased in the dorsal/rostral anterior cingulate and anterior insula after induction of transient sadness in euthymic lithium responder bipolar patients and their healthy siblings. These findings suggest that energy metabolism is decreased in depressive mood states, but clear understanding of cerebral blood flow in bipolar depression requires further investigation.

Phosphorus-31 magnetic resonance spectroscopy allows detecting high-energy phosphates and the intracellular pH [90, 91]. Using this technology, Kato et al. [92, 93] found that subjects with bipolar disorder have shown increased phosphomonoester and intracellular pH in brain in the depressive mood state when compared with the euthymic state, while those values in the euthymic state were significantly lower as compared to age-matched normal controls. Increased phosphomonoester has also been found in the frontal lobe of subjects with unipolar depression when compared to age-matched controls. Phosphomonoester levels are correlated negatively with the degree of depression [94]. These studies suggest that disturbed phospholipid and intracellular high-energy phosphate metabolism may be common between bipolar depression and unipolar depression. Phosphocreatine is a high-energy compound

made from creatine and ATP. It has been found that phosphocreatine in brain was significantly decreased in subjects with Bipolar II in all hypomanic, euthymic and depressive states when compared to controls. Phosphocreatine was significantly lower in subjects with severe depression than subjects with mild depression [92, 95]. Further, the phosphocreatine levels were significantly lower in the left frontal lobe of subjects with bipolar depression than the normal controls, while phosphocreatine levels were lower in the right frontal lobe of the subjects in the manic and the euthymic states than controls. Phosphocreatine levels in subjects with bipolar depression were negatively correlated with the Hamilton Rating Scale for Depression score [96]. Decreased ATP values have also been found in the frontal lobe of subjects with unipolar depression [94]. It is interesting that creatine levels were significantly lower in the right frontal lobe of the female subjects with bipolar disorder than male subjects [97]. These results suggest that bipolar depression and unipolar depression are associated with abnormal metabolisms of high energy phosphate. Abnormal energy metabolism in brain may be closely related to mood state of mood disorders and is also gender dependent. Frye et al. [98] used proton magnetic resonance spectroscopy to scan the anterior cingulate/medial prefrontal cortex and found that levels of glutamate + glutamine, glutamate and creatine + phosphocreatine were significantly higher in subjects with bipolar depression than healthy controls. Dager et al. [99], using two-dimensional proton echo-planar spectroscopic imaging, analyzed 32 medication-free outpatients with bipolar disorder predominantly in a depressed or mixed-mood state, and found that subjects with bipolar disorder have shown increased lactate levels and increased levels of total glutamate, glutamine and gamma-aminobutyric acid in gray matter (Tab. 1). Abnormal metabolism of high-energy phosphates and increased gray matter lactate suggest that bipolar disorder may be associated with mitochondrial dysfunction that induces an energy production shift from more efficient oxidative phosphorylation in mitochondrial electron transport chain to less efficient anaerobic glycolysis.

Mitochondrial energy production is produced via the process of oxidative phosphorylation coupled to the electron transport chain complex I–V (complex I, NADH coenxyme Q reductase; complex II, succinate dehydrogenase; complex III, coenzyme Q cytochrome c reductase; complex IV, cytochrome *c* oxidase; and complex V, ATP synthase). Studies indicate increased deletion and mutation in genes coding for complex I subunits in subjects with bipolar [100–102]. Recent DNA microarray analysis in *post mortem* frontal cortex and hippocampus revealed that expression of many mRNAs, coding for subunits of complex I–V, is decreased in subjects with bipolar disorder [103, 104]. Recent genotyping studies also suggest that polymorphisms of complex I subunit NDUFV2 are associated with bipolar disorder [105, 106]. Complex I is one of the main sites where electrons are leaked to oxygen, resulting in ROS production [107]. Abnormal function of ETC complex I in BD suggests ROS overproduction that may induce oxidative stress in this disease. We recently found that oxidative damage to lipids is increased in *post mortem* cingulate cortex of

Table 1 Brain chemical concentrations by tissue type* [99]

	Cho	Cre	NAA	mI	Glx	Lactate
Gray matter chemical concentration, mM						
Bipolar	2.52 (0.66)	9.41 (0.74)	10.60 (1.26)	4.59 (0.98)	17.80 (2.51)†	0.97 (0.24)†
Control	2.30 (0.26)	9.11 (0.73)	10.18 (0.43)	4.36 (0.50)	16.18 (1.85)	0.81 (0.16)
White matter chemical concentration, mM						
Bipolar	2.59 (0.35)	7.98 (0.84)	9.76 (0.89)	4.50 (0.62)	15.69 (2.60)	0.97 (0.25)
Control	2.49 (0.28)	7.58 (0.63)	9.77 (0.44)	4.25 (0.75)	14.51 (1.99)	0.91 (0.23)
White-gray matter chemical regression slope						
Bipolar	–0.10 (1.67)	2.26 (1.07)	1.31 (2.53)	–0.08 (1.45)	2.89 (2.79)	–0.21 (0.60)
Control	–0.39 (0.52)	2.13 (1.13)	0.35 (0.87)	–0.14 (1.03)	2.24 (2.46)	–0.35 (0.52)

Abbreviations: Cho, choline-containing compounds; Cre, creatine and phosphocreatine; Glx, glutamate, glutamine, and γ-aminobutyric acid; mI, *myo*-inositol; NAA, *N*-acetyl aspartate
* Values are given as mean (SD)
† $P < .01$ vs control

BD subjects [108]. Increased oxidative damage to lipids has also been found in blood samples of BD patients [109, 110]. Additionally, Benes et al. [111] reported that expression of antioxidant enzyme GST A4 and M3 subtypes are reduced in *post mortem* hippocampus from BD subjects. These findings suggest that impairment of energy production and mitochondrial dysfunction in bipolar disorder may induce oxidative stress.

Summary

Converging lines of study suggest cell loss and damage in key brain regions which may lead to decreased volume of prefrontal and limbic brain regions of subjects with bipolar disorder. Persistent changes in these brain regions may cause disturbance in the function of neuronal circuitry involved in mood regulation, subsequently resulting in impairment of neuroplasticity. These changes may have consequences for monoaminergic neurotransmitters including serotonin, a key intermediary in major depression and a target of antidepressant drugs. Many studies of bipolar depression have shown a decrease in the main metabolite of serotonin 5-HIAA in cerebrospinal fluid and a decrease in serotonin transporter binding activity in brain and platelets.

Mitochondria are enriched in the neuronal terminals and dendrites that form synaptic connections, and its major role is generation of ATP. Mitochondria are important in regulating synthesis, release, uptake and other functions of neurotransmitters, including serotonin, via energy production. Recent evidence has shown decrease of glucose, cerebral blood flow and energy metabolism in bipolar depression, indicating deficiency of energy production in this disease.

Studies also suggest defects of mitochondrial electron transport chain complexes and oxidative damage in bipolar disorder. Mitochondrial electron transport chain is not only a highly efficient way to store energy, but it is also the major resource for generating reactive oxygen species. Therefore mitochondrial dysfunction in bipolar disorder not only reduces energy production, but also causes overproduction of the reactive oxygen species that induce oxidative damage, resulting in impairment of neuroplasticity in specific brain regions related to mood regulation.

The neurobiology of bipolar disorder continues to be unraveled which will help us further understand the multidimensional nature of the illness and the predisposition to both manic and depressive symptoms. It is hard to draw conclusions about the neurobiology of bipolar depression, but in this chapter we have outlined several potential processes which may be relevant to understanding the basis of this phase and illness. Given the limited success of treatment for all phases of bipolar disorder, it seems very likely that further elucidation of the neurobiological mechanisms underlying bipolar depression holds great promise for the development of safe and more effective treatment for this disease.

References

1 Isometsa ET, Henriksson MM, Aro HM, Lonnqvist JK (1994) Suicide in bipolar disorder in Finland. *Am J Psychiatry* 151: 1020–1024
2 Ferrier IN (1999) Treatment of major depression: is improvement enough? *J Clin Psychiatry* 60 (Suppl 6): 10–14
3 López P, Mosquera F, de León J, Gutiérrez M, Ezcurra J, Ramírez F, González-Pinto A (2001) Suicide attempts in bipolar patients. *J Clin Psychiatry* 62: 963–966
4 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537
5 Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA et al (2003) Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry* 64: 680–690
6 Mitchell PB, Malhi GS (2004) Bipolar depression: phenomenological overview and clinical characteristics. *Bipolar Disord* 6: 530–539
7 Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P (2001) The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Ann N Y Acad Sci* 935: 107–117
8 Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 26: 321–352
9 Iidaka T, Terashima S, Yamashita K, Okada T, Sadato N, Yonekura Y (2003) Dissociable neural responses in the hippocampus to the retrieval of facial identity and emotion: an event-related fMRI study. *Hippocampus* 13: 429–436
10 Phelps EA (2006) Emotion and cognition: insights from studies of the human amygdala. *Annu Rev Psychol* 57: 27–53
11 Drevets WC, Price JL, Simpson Jr, JR, Todd RD, Reich T, Vannier M, Raichle ME (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386: 824–827
12 Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, Yurgelun-Todd D, Zarate C, Kikinis R, Jolesz FA et al (1999) Subgenual cingulate cortex volume in firstepisode psychosis. *Am J Psychiatry* 156: 1091–1093
13 Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM (2002) Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biol Psychiatry* 52: 93–100

14 Frangou S, Hadjulis M, Chitnis X, Baxter D, Donaldson S, Raymont V (2002) The Maudsley Bipolar Disorder Project: brain structural changes in bipolar 1 disorder. *Bipolar Disord* 4: 123–124
15 Swayze VW 2nd, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC (1992) Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. *Biol Psychiatry* 31: 221–240
16 Altshuler LL, Bartzokis G, Grieder T, Curran J, Mintz J (1998) Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specificity. *Arch Gen Psychiatry* 55: 663–664
17 Ali SO, Denicoff KD, Altshuler LL, Hauser P, Li X, Conrad AJ, Smith-Jackson EE, Leverich GS, Post RM (2001) Relationship between prior course of illness and neuroanatomic structures in bipolar disorder: a preliminary study. *Neuropsychiatry Neuropsychol Behav Neurol* 14: 227–232
18 Strakowski SM, DelBello MP, Sax KW, Zimmerman ME, Shear PK, Hawkins JM, Larson ER (1999) Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch Gen Psychiatry* 56: 254–260
19 Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC (2005) Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. *Am J Psychiatry* 162: 1697–1705
20 Hauser P, Matochik J, Altshuler LL, Denicoff KD, Conrad A, Li X, Post RM (2000) MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. *J Affect Disord* 60: 25–32
21 Brambilla P, Harenski K, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2003) MRI investigation of temporal lobe structures in bipolar patients. *J Psychiatr Res* 37: 287–295
22 Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, Charney DS, Krystal JH, Peterson BS (2003) Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch Gen Psychiatry* 60: 1201–1208
23 DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM (2004) Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord* 6: 43–52
24 Chen BK, Sassi R, Axelson D, Hatch JP, Sanches M, Nicoletti M, Brambilla P, Keshavan MS, Ryan ND, Birmaher B et al (2004) Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. *Biol Psychiatry* 56: 399–405
25 Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A (2005) Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44: 565–573
26 Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, Wilkins J, Gerner R, Mintz J (2000) An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48: 147–162
27 Rajkowska G, Halaris A, Selemon LD (2001) Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry* 49: 741–752
28 Benes FM, Kwok EW, Vincent SL, Todtenkopf MS (1998) A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry* 44: 88–97
29 Benes FM, Vincent SL, Todtenkopf M (2001) The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol Psychiatry* 50: 395–406
30 Bezchlibnyk YB, Sun X, Wang JF, MacQueen GM, McEwen BS, Young LT (2007) Neuron somal size is decreased in the lateral amygdalar nucleus of subjects with bipolar disorder. *J Psychiatry Neurosci* 32: 203–210
31 Berretta S, Pantazopoulos H, Lange N (2007) Neuron numbers and volume of the amygdala in subjects diagnosed with bipolar disorder or schizophrenia. *Biol Psychiatry* 62: 884–893
32 Dowlatshahi D, MacQueen G, Wang JF, Chen B, Young LT (2000) Increased hippocampal supragranular Timm staining in subjects with bipolar disorder. *Neuroreport* 11: 3775–3778
33 Sassi RB, Stanley JA, Axelson D, Brambilla P, Nicoletti MA, Keshavan MS, Ramos RT, Ryan N, Birmaher B, Soares JC (2005) Reduced NAA levels in the dorsolateral prefrontal cortex of young bipolar patients. *Am J Psychiatry* 162: 2109–2115
34 Winsberg ME, Sachs N, Tate DL, Adalsteinsson E, Spielman D, Ketter TA (2005) Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. *Biol Psychiatry* 47: 475–481

35 Ongur D, Drevets WC, Price JL (1998) Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA* 95: 13290–13295
36 Johnston-Wilson NL, Sims CD, Hofmann JP, Anderson L, Shore AD, Torrey EF, Yolken RH (2000) Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. *Mol Psychiatry* 5: 142–149
37 Orlovskaya DD, Vikhreva OV, Zimina IS, Denisov DV, Uranova NA (1999) Ultrastructural dystrophic changes of oligodendroglial cells in autopsied prefrontal cortex and striatum in schizophrenia: a morphometric study. *Schizophr Res* 36: 82–83
38 Orlovskaya DD, Vostrikov VM, Rachmanova NA, Uranova NA (2000) Decreased numerical density of oligodendroglial cells in postmortem prefrontal cortex in schizophrenia, bipolar affective disorder and major depression. *Schizophr Res* 41: 105–106
39 Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V, Rachmanova V (2001) Electron microscopy of oligodendroglia in severe mental illness. *Brain Res Bull* 55: 597–610
40 Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF (2004) Stanley Neuropathology Consortium. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry* 9: 609–620
41 Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL (2002) The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am J Hum Genet* 71: 651–655
42 Sklar P, Gabriel SB, McInnis MG, Bennett P, Lim YM, Tsan G, Schaffner S, Kirov G, Jones I, Owen M et al (2002) Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Mol Psychiatry* 7: 579–593
43 Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr (2004) Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 161: 1698–1700
44 Lohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J, Berrettini WH (2005) Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder *Am J Med Genet B Neuropsychiatr Genet* 139: 51–53
45 Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Gonçalves CA, Santin A, Kapczinski F (2006) Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neurosci Lett* 398: 215–219
46 Monteleone P, Serritella C, Martiadis V, Maj M (2008) Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. *Bipolar Disord* 10: 95–100
47 Tseng M, Alda M, Xu L, Sun X, Wang JF, Grof P, Turecki G, Rouleau G, Young LT (2008) BDNF protein levels are decreased in transformed lymphoblasts from lithium-responsive bipolar disorder subjects. *J Psychiatry Neurosci* 33: 449–453
48 Asberg M, Bertillsson L, Martensson B, Scalia-Tomba GP, Thoren P, Traskman-Bendz L (1984) CSF monoamine metabolites in melancholia. *Acta Psychiatr Scand* 69: 201–219
49 Träskman L, Asberg M, Bertilsson L, Sjöstrand L (1981) Monoamine metabolites in CSF and suicidal behaviour. *Arch Gen Psychiatry* 38: 631–636
50 Swann AC, Secunda S, Davis JM, Robins E, Hanin I, Koslow SH, Maas JW (1983) CSF monoamine metabolites in mania. *Am J Psychiatry* 140: 396–400
51 Sher L, Carballo JJ, Grunebaum MF, Burke AK, Zalsman G, Huang YY, Mann JJ,
Oquendo MA (2006) A prospective study of the association of cerebrospinal fluid monoamine metabolite levels with lethality of suicide attempts in patients with bipolar disorder. *Bipolar Disord* 8: 543–550
52 Young LT, Warsh JJ, Kish SJ, Shannak K, Hornykeiwicz O (1994) Reduced brain 5-HT and elevated NE turnover and metabolites in bipolar affective disorder. *Biol Psychiatry* 35: 121–127
53 Rudnick G (2006) Serotonin transporters – structure and function. *J Membr Biol* 213: 101–110
54 White KJ, Walline CC, Barker EL (2005) Serotonin transporters: implications for antidepressant drug development. *AAPS J* 7: E421–433
55 Leake A, Fairbairn AF, McKeith IG, Ferrier IN (1991) Studies on the serotonin uptake binding site in major depressive disorder and control *post mortem* brain: neurochemical and clinical correlates. *Psychiatry Res* 39: 155–165

56 Sneddon JM (1973) Blood platelets as a model for monoamine containing neurons. *Prog Neurobiol* 1: 151–198
57 Stahl SM, Woo DJ, Mefford IN, Berger PA, Ciaranello RD (1983) Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders. *Am J Psychiatry* 140: 26–30
58 Scott M, Reading HW, Loudon JB (1979) Studies on human blood platelets in affective disorder. *Psychopharmacology (Berl)* 60: 131–135
59 Meltzer HY, Arora RC, Baber R, Tricou BJ (1981) Serotonin uptake in blood platelets of psychiatric patients. *Arch Gen Psychiatry* 38: 1322–1326
60 Marazziti D, Lenzi A, Cassano GB (1991) Serotonergic dysfunction in bipolar disorder. *Pharmacopsychiatry* 24: 164–166
61 Muscettola SA, Dilauro A, Giannini CP (1986) Platelet ^{3}H-imipramine binding in bipolar patients. *Psychiatry Res* 18: 343–353
62 Lewis DA, McChesney C (1985) Tritiated imipramine binding distinguishes among subtypes of depression. *Arch Gen Psychiatry* 42: 485–488
63 Oquendo MA, Hastings RS, Huang YY, Simpson N, Ogden RT, Hu XZ, Goldman D, Arango V, Van Heertum RL, Mann JJ et al (2007) Brain serotonin transporter binding in depressed patients with bipolar disorder using positron emission tomography. *Arch Gen Psychiatry* 64: 201–208
64 Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N et al (1998) Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry* 44: 1090–1098
65 Newberg AB, Plossl K, Mozley PD, Stubbs JB, Wintering N, Udeshi M, Alavi A, Kauppinen T, Kung HF (2004) Biodistribution and imaging with (123)I-ADAM: a serotonin transporter imaging agent. *J Nucl Med* 45: 834–841
66 Parsey RV, Hastings RS, Oquendo MA, Huang YY, Simpson N, Arcement J, Huang Y, Ogden RT, Van Heertum RL, Arango V et al (2006) Lower serotonin transporter binding potential in the human brain during major depressive episodes. *Am J Psychiatry* 163: 48–57
67 Ramamoorthy S, Blakely RD (1999) Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants. *Science* 285: 763–766
68 Soucy J-P, Lafaille F, Lemoine P, Mrini A, Descarries L (1994) Validation of the transporter ligand cyanoimipramine as a marker of serotonin innervation density in brain. *J Nucl Med* 35: 1822–1830
69 Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, Klaver JM, Charney DS, Manji HK, Drevets WC (2006) Serotonin transporter binding in bipolar disorder assessed using [^{11}C]DASB and positron emission tomography. *Biol Psychiatry* 60: 207–217
70 Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC (2007) Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [^{11}C]DASB; comparison with bipolar disorder. *Biol Psychiatry* 62: 870–877
71 Stockmeier CA (2003) Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *J Psychiatr Res* 37: 357–373
72 Madhav TR, Pei Q, Zetterstrom TS (2001) Serotonergic cells of the rat raphe nuclei express mRNA of tyrosine kinase B (trkB), the high-affinity receptor for brain derived neurotrophic factor (BDNF). *Brain Res* 93: 56–63
73 Djalali S, Höltje M, Grosse G, Rothe T, Stroh T, Grosse J, Deng DR, Hellweg R, Grantyn R, Hörtnagl H et al (2005) Effects of brain-derived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development. *J Neurochem* 92: 616–627
74 Rumajogee P, Madeira A, Verge D, Hamon M, Miquel MC (2002) Up-regulation of the neuronal serotoninergic phenotype *in vitro*: BDNF and cAMP share Trk B-dependent mechanisms. *J Neurochem* 83: 1525–1528
75 Hensler JG, Advani T, Monteggia LM (2007) Regulation of serotonin-1A receptor function in inducible brain-derived neurotrophic factor knockout mice after administration of corticosterone. *Biol Psychiatry* 62: 521–529
76 Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 15: 7539–7547
77 Nibuya M, Nestler EJ, Duman RS (1996) Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci* 16: 2365–2372

78 Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry* 50: 260–265
79 Dwivedi Y, Rao JS, Rizavi HS, Kotowski J, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003) Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 60: 273–282
80 Karege F, Vaudan G, Schwald M, Perroud N, La Harpe R (2005) Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Brain Res Mol Brain Res* 136: 29–37
81 Ferrari R, Pedersini P, Bongrazio M, Gaia G, Bernocchi P, Di Lisa F, Visioli O (1993) Mitochondrial energy production and cation control in myocardial ischaemia and reperfusion. *Basic Res Cardiol* 88: 495–512
82 Hertz L, Kala G (2007) Energy metabolism in brain cells: effects of elevated ammonia concentrations. *Metab Brain Dis* 22: 199–218
83 Baxter L, Phelps ME, Mazziotta JC, Schwartz JM, Gerner RH, Selin CE, Sumida RM (1985) Cerebral metabolic rates for glucose in mood disorders. Studies with positron emission tomography and fluorodeoxyglucose F 18. *Arch Gen Psychiatry* 42: 441–447
84 Baxter LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 46: 243–250
85 Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002) Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71: 431–447
86 Ito H, Kawashima R, Awata S, Ono S, Sato K, Goto R, Koyama M, Sato M, Fukuda H (1996) Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *J Nucl Med* 37: 410–414
87 Rubin E, Sackeim HA, Prohovnik I, Moeller JR, Schnur DB, Mukherjee S (1995) Regional cerebral blood flow in mood disorders: IV. Comparison of mania and depression. *Psychiatry Res* 61: 1–10
88 Tutus A, Simsek A, Sofuoglu S, Nardali M, Kugu N, Karaaslan F, Gönül AS (1998) Changes in regional cerebral blood flow demonstrated by single photon emission computed tomography in depressive disorders: comparison of unipolar *versus* bipolar subtypes. *Psychiatry Res* 83: 169–177
89 Krüger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg HS (2006) Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. *Am J Psychiatry* 163: 257–264
90 Moon R, Richards JH (1973) Determination of intracellular pH by 31P magnetic resonance. *J Biol Chem* 25: 7276–7278
91 Petroff OAC, Prichard JW, Behar KL, Alger JR, den Hollander JA, Shulman RG (1985) Cerebral intracellular pH by 31P nuclear magnetic resonance spectroscopy. *Neurology* 35: 781–788
92 Kato T, Takahashi S, Shioiri T, Inubushi T (1992) Brain phosphorous metabolism in depressive disorders detected by phosphorus-31 magnetic resonance spectroscopy. *J Affect Disord* 26: 223–230
93 Kato T, Shioiri T, Murashita J, Hamakawa H, Inubushi T, Takahashi S (1994a) Phosphorus-31 magnetic resonance spectroscopy and ventricular enlargement in bipolar disorder. *Psychiatry Res* 55: 41–50
94 Volz HP, Rzanny R, Riehemann S, May S, Hegewald H, Preussler B, Hübner G, Kaiser WA, Sauer H (1998) 31P magnetic resonance spectroscopy in the frontal lobe of major depressed patients. *Eur Arch Psychiatry Clin Neurosci* 248: 289–295
95 Kato T, Takahashi S, Shioiri T, Murashita J, Hamakawa H, Inubushi T (1994b) Reduction of brain phosphocreatine in bipolar II disorder detected by phosphorus-31 magnetic resonance spectroscopy. *J Affect Disord* 31: 125–133
96 Kato T, Shioiri T, Murashita J, Hamakawa H, Takahashi Y, Inubushi T, Takahashi S (1995) Lateralized abnormality of high energy phosphate metabolism in the frontal lobes of patients with bipolar disorder detected by phase-encoded 31P-MRS. *Psychol Med* 25: 557–566
97 Hamakawa H, Kato T, Shioiri T, Inubushi T, Kato N (1999) Quantitative proton magnetic resonance spectroscopy of the bilateral frontal lobes in patients with bipolar disorder. *Psychol Med* 29: 639–644

98 Frye MA, Watzl J, Banakar S, O'Neill J, Mintz J, Davanzo P, Fischer J, Chirichigno JW, Ventura J, Elman S et al (2007) Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression. *Neuropsychopharmacology* 32: 2490–2499
99 Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, Dunner DL, Renshaw PF (2004) Brain metabolic alterations in medication-free patients with bipolar disorder. *Arch Gen Psychiatry* 61: 450–458
100 Kato T, Kunugi H, Nanko S, Kato N (2001) Mitochondrial DNA polymorphisms in bipolar disorder. *J Affect Disord* 62: 151–164
101 Kato T, Kunugi H, Nanko S, Kato N (2000) Association of bipolar disorder with the 5178 polymorphism in mitochondrial DNA. *Am J Med Genet* 96: 182–186
102 Munakata K, Tanaka M, Mori K, Washizuka S, Yoneda M, Tajima O, Akiyama T, Nanko S, Kunugi H, Tadokoro K et al (2004) Mitochondrial DNA 3644 T–>C mutation associated with bipolar disorder. *Genomics* 84: 1041–1050
103 Sun X, Wang JF, Tseng M, Young LT (2006) Down regulation in components of mitochondrial electron transport chain in *post mortem* frontal cortex from subjects with bipolar disorder. *J Psychiatry Neurosci* 31: 189–196
104 Konradi C, Eaton M, MacDonald ML, Walsh J, Benes FM, Heckers S (2004) Molecular evidence for mitochondrial dysfunction in bipolar disorder. *Arch Gen Psychiatry* 61: 300–308
105 Washizuka S, Kakiuchi C, Mori K, Kunugi H, Tajima O, Akiyama T, Nanko S, Kato T (2003) Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 120: 72–78
106 Washizuka S, Iwamoto K, Kazuno AA, Kakiuchi C, Mori K, Kametani M, Yamada K, Kunugi H, Tajima O, Akiyama T et al (2004) Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with bipolar disorder in Japanese and the National Institute of Mental Health pedigrees. *Biol Psychiatry* 56: 483–489
107 Halliwell B (1992) Reactive oxygen species and the central nervous system. *J Neurochem* 59: 1609–1623
108 Wang JF, Shao L, Sun X, Young LT (2007) Increased lipid peroxidation in postmortem cingulate cortex from subjects with bipolar disorder and schizophrenia. *Soc Neurosci Abstr* 33, Program No. 707.11
109 Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N (2002) Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. *Cell Biochem Funct* 20: 171–175
110 Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP (2003) Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res* 121: 109–122
111 Benes FM, Matzilevich D, Burke RE, Walsh J (2006) The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. *Mol Psychiatry* 11: 241–251

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Non-pharmacological treatments and chronobiological aspects of bipolar disorder: implications for novel therapeutics

Wallace C. Duncan, Jr

Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, Maryland 20892, USA

Abstract

This chapter reviews prominent neurobiological effects of chronotherapies for the treatment of mood disorders and integrates previously described therapeutic mechanisms with current advances regarding molecular signaling pathways and neuroplasticity. Scientific discoveries associated with circadian rhythms, disrupted sleep-wake patterns, and mood cycling, have establish preliminary links between circadian clock genes and mood. Importantly, the recent description of lithium's effects on the molecular signaling pathways of the circadian system has advanced our understanding of the intracellular molecular bases of lithium's mood stabilizing properties. Specifically discussed are the convergent intracellular pathways of monoaminergic drug therapies and chronotherapies (sleep deprivation (SD), light treatment (LT), and sleep phase advance (SPA)), and the advantage of understanding their common pathways for developing novel therapeutic treatments.

Introduction

Bipolar disorder (BPD) is characterized by episodic mood cycles and disrupted circadian patterns of mood, sleep, and behavior. These mood cycles occupy time domains with well known (e.g., circadian, menstrual, seasonal cycles), and unknown (e.g., manic-depressive cycles) biological foundations. The fact that many of the patterns parallel biological cycles with known physiological and molecular underpinnings suggests that pathological elements of these cycles might be identified and targeted by novel treatments. Scientific breakthroughs associated with circadian rhythms, disrupted sleep-wake patterns, and mood cycling, have established preliminary links between circadian clock genes and mood. Gene linkage studies indicate that links between clock genes, gene products, and BPD are complex, but nevertheless provide clues of etiology and novel treatments. The recent description of lithium's effects on the molecular signaling pathways of the circadian system has helped to understand the molecular bases of lithium's mood stabilizing properties. With the continuing discovery of key genetic and molecular elements of the circadian clock,

our knowledge of the mechanisms of established non-pharmacological and drug-based therapies will certainly increase, as will the development of new treatments.

This chapter reviews the prominent neurobiological effects of mood disorder chronotherapies (CTs) and integrates previously described therapeutic mechanisms with current advances regarding molecular signaling pathways and neuroplasticity. The development and utility of non-pharmacological CTs in mood disorders/BPD are well-grounded in principles of circadian biology. There are several arguments for exploiting the findings of CT research to advance novel drug development:

1. Disordered sleep is a major symptom of depressive illness, and clock genes of risk associated with sleep-disorder related phenotypes are continually being identified. These clock genes and signaling pathways may contribute to the etiology of the illness and are potential targets of novel treatments.
2. The *convergent* pathways of effective a) mood stabilizing and monoamine drug treatments, and b) CTs on clock gene and intracellular signaling pathways are potential targets of novel treatments.
3. *Rapid onset* of remission is a beneficial feature of sleep deprivation (SD), sleep phase-advance (SPA), and light therapy (LT; Fig. 1). Because CTs involve the manipulation of sleep and the circadian system, the rapid onset mechanism(s) are likely to include clock gene signaling pathways, as well as other intracellular signaling pathways that are activated by neurotransmitters and hormones.

Mood, the sleep homeostat, and the clock

Over 30 years ago, a handful of CT interventions were introduced to both treat depression and explore the temporal relationships between mood changes, sleep, and the circadian clock. The treatment effects of these drug-free interventions (total SD, SPA, and LT) were based largely on functional properties of the circadian pacemaker [1] and the quantitative two process model of sleep regulation [2]. An exceptional feature of these interventions was their now well-known accelerated treatment response relative to traditional chronic drug-based treatments. Their clinical antidepressant effects *per se* were the major focus of CTs, and while some studies explored mechanisms linked to neurotransmitter effects or to light-suppression of melatonin, the central focus was on CT effects on formal properties of the sleep homeostat (SD, partial SD), the circadian clock (LT), or the interaction between the homeostat and the clock (SPA, LT).

The neurobiological effects of many CTs are now more fully described than when first applied, yet their antidepressant mechanism(s) are still unclear. A new focal point of research is the antidepressant and mood stabilizing roles of intracellular signaling pathways and clock gene signaling pathways for developing new treatments for mood disorders. Recent theoretical advances, such as

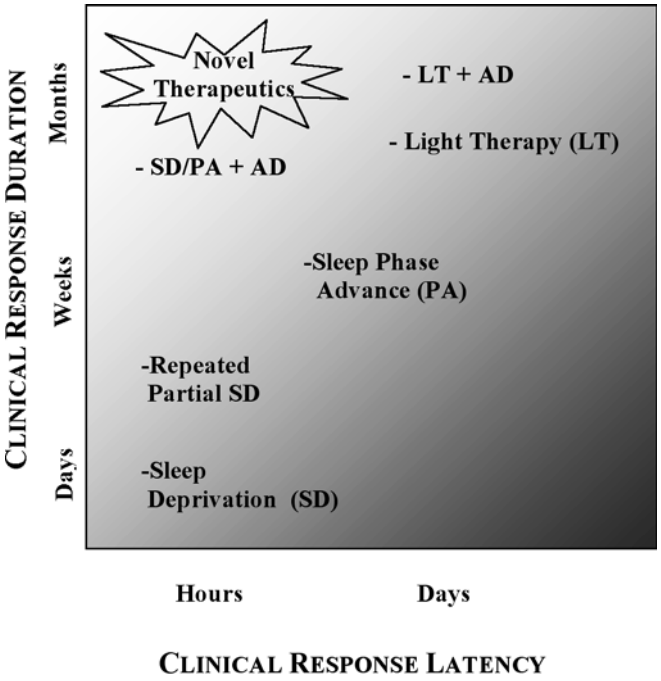


Figure 1 Chronotherapeutic methods used in the treatment of mood disorders are schematically depicted relative to their rate of therapeutic response latency, and to their duration of clinical response. Optimal treatments occupy the upper left quadrant; least desirable treatments occupy the lower right quadrant. A beneficial aspect of SD is the rapid onset of clinical response; the weakness is the brevity of the clinical response. The clinical response to SD may be lengthened by the use of partial SD or with maintenance AD or LT. Optimal treatment outcomes of novel therapeutics would be rapid onset and prolonged response duration. (Abbreviations: AD, antidepressants; SD, sleep deprivation; PA, phase-advance of the sleep-wake cycle; LT, light therapy).

the synaptic homeostasis hypothesis, are extending our understanding of SD's effect on mood to the molecular basis of neural plasticity. Similar to the advantage gained by considering the effects of antidepressant and mood stabilizing drugs downstream from their known extracellular effects, consideration of the neurobiological effects of CTs on clock gene signaling pathways and neural plasticity changes induced by SD may facilitate identification of novel treatments for mood disorders.

The sleep homeostat, synaptic potentiation, and downscaling

The synaptic homeostasis hypothesis [3], a conceptual and molecular advance of the quantitative two-process model of sleep regulation [2], proposes that synaptic potentiation and synaptic downscaling occur during wakefulness and sleep respectively, and suggests a molecular basis for the rapid antidepressant

effects of SD. Specifically, during the circadian cycle, synaptic potentiation during the waking phase is associated with an increase of norepinephrine as well as norepinephrine-dependent trophic factors [4] such as brain-derived neurotrophic factor (BDNF) and P-CREB. These substances are associated with increased synaptic strength, long-term potentiation (LTP), and slow wave homeostasis. The increase in synaptic potentiation during the waking phase contributes to elevated slow-wave activity (SWA) at the beginning of the sleep cycle, as predicted by the two-process model of sleep. The synaptic homeostasis hypothesis also suggests that local reductions in slow wave homeostasis during wakefulness reflect insufficient synaptic strength that may underlie the decreased SWA often observed in mood disorders.

In contrast to waking and synaptic potentiation, sleep is associated with synaptic downscaling. Sleep may be viewed as a behavioral cost associated with benefits of waking-associated synaptic plasticity; food intake and sensory input are decreased while cellular changes associated with prior wakefulness are tuned by downscaling. During SD experiments in animals (extended wakefulness), synaptic potentiation is extended (and downscaling is delayed). Prolonged wakefulness is associated with increased BDNF; recovery sleep has elevated SWA (for review see [3–5]). In humans, BDNF and SWA may be useful biomarkers of synaptic potentiation reflecting the capacity for brain plasticity. Similar to the association between increased SWA and a positive clinical response to SD, the neurotrophin BDNF might also be a useful biomarker of therapeutic response. Further, at a behavioral level, learning, a correlate of increased synaptic plasticity, is associated with increased SWA in EEG during subsequent sleep [6]. The synaptic homeostasis hypothesis considers at a molecular level the clinical effects of SD (see *SD, SWA, and Neuroplasticity*).

The molecular components of the circadian clock

The molecular circadian clock consists of genes and gene products whose transcription/translational feedback loops form the basis of circadian oscillations within and outside of the suprachiasmatic nucleus (SCN). At least three interacting loops have been identified, each with activating and repressor components (Fig. 2). In each of the three loops, the CLOCK/BMAL complex on the one hand, and PER and CRY proteins on the other hand, constitute activating and repressor components, respectively. E-box enhancers in the promoter regions of clock genes also function as important regulators of transcription of both clock genes and clock-controlled genes (CCGs, Fig. 2).

In the primary feedback loop (Fig. 2, top) CLOCK/BMAL1 initiates nuclear transcription of target clock genes (PER, CRY), and after phosphorylation by glycogen kinase 3β (GSK3β) in the cytoplasm, the translational products CRY and PER enter the nucleus and inhibit transcription by acting on the CLOCK/BMAL1 complex. This negative feedback limb is a recurrent feature in the two additional interconnected pathways.

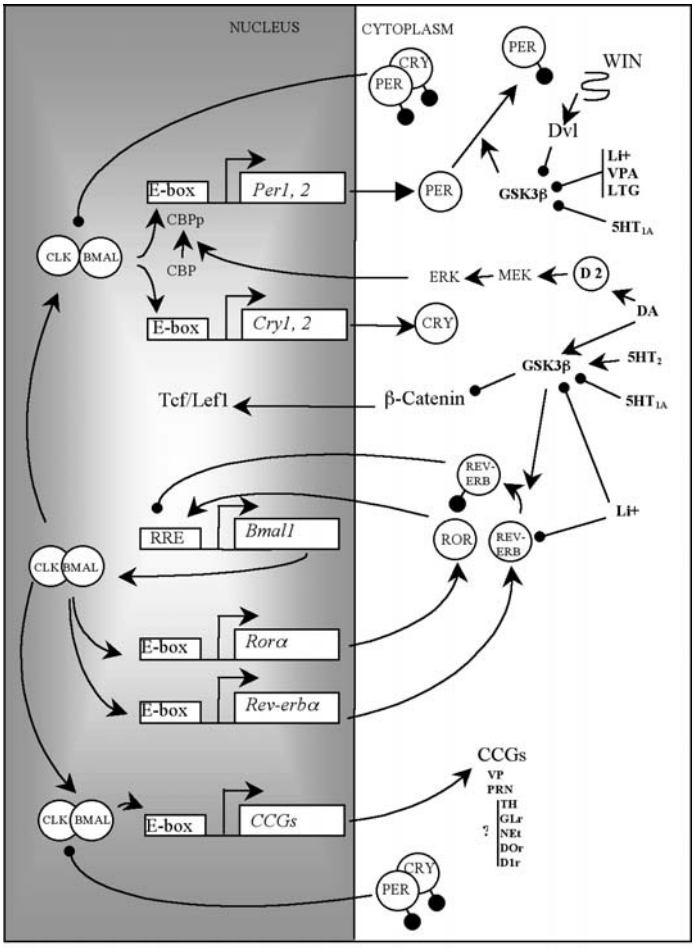


Figure 2 Transcription and translational feedback loops comprise the mammalian circadian clock. Three interacting regulatory loops are depicted, as well as a clock controlled gene output pathway, below. The main loop (top) consists of a CLOCK and BMAL1 heterodimer that initiates transcription of E-box sequences including *Period1-3* and *Cryptochrome 1-2*. Nuclear translocation of phosphorylated PER and CRY provide negative feedback (●–) that inhibits the CLOCK:BMAL1 heterodimer E-box enhanced transcription of *Per1/3* and *Cry1/2*, in each of the loops. A second regulatory loop (middle) is also initiated by the CLOCK:BMAL1 heterodimer that enhances the transcription of the retinoic acid-related orphan nuclear receptors *Rev-erbα* and *Rorα*. REV-ERB and ROR repress and activate, respectively, the transcription of *Bmal1* by competing to bind retinoic acid-related orphan receptor response elements (RRE) to the *Bmal1* promoter. Transcription of clock controlled genes *CCG* (bottom) is also initiated by CLOCK:BMAL1 heterodimer and inhibited by PER/CRY. Vasopressin (VP) and prolactin (PRN) are CCGs; TH, GLr, NEt, Dor, and D1r are putative CCGs (see abbreviations below). Lithium affects circadian clock gene and Wnt signaling pathways by inhibiting GSK3β thus decreasing PER phosporylation and delaying the circadian cycle. Lithium also acts to enhance degradation of REV-ERB, shrinking the pool of phosphorylated protein for nuclear entry and disinhibition of Bmal1. Lithium inhibition increases β-catenin and Tcf/Lcf1, thus stimulating axonogenesis and reducing apoptosis. Other mood stabilizers (lamotrigine and VPA) indirectly inhibit GSK3β (Abbreviations: TH, tyrosine hydroxylase; GLr, metabotropic glutamate receptor; NEt, norepinephrine transporter; DOr, delta opioid receptor; D1r, dopamine 1 receptor).

In the second feedback loop (Fig. 2, middle), characterized by the retinoic acid-related orphan nuclear receptors, *Rorα* and *Rev-erbα,* clock gene transcription is affected by positive and negative feedback of RORα and REV-ERBα, respectively, on orphan receptor response elements (RRE) in the Bmal1 promoter region. As shown (and discussed later), GSK3β (and lithium) act to control feedback of REV-ERBα on the Bmal1 promoter region. In a third regulated pathway (Fig. 2, bottom), clock genes (CLOCK, BMAL1) affect the transcription of clock-controlled genes (CCGs, e.g., vasopressin and prolactin). Some psychoactive and mood stabilizing drugs besides lithium (valproate (VPA), lamotrigine, selective serotonin reuptake inhibitors (SSRIs), antipsychotic drugs, etc.) as well as the neurobiological effects of non-pharmacological treatments (SD, LT), affect different clock control points (e.g., GSK3β, REV-ERBα, and E-box enhancer elements), and these treatments potentially affect clock gene transcription.

Circadian clock genes, bipolar depression, and sleep disorders

The presence of mood cycles in BPD, often with diurnal variation in mood, a clinical symptom associated with a positive clinical response to different antidepressant treatments, suggests linkage of treatment potential with circadian and infradian biological clocks. Numerous genetic linkage studies suggest an association between the circadian clock genes *Clock, Bmal1, Per3, Timeless,* and GSK3*β*, with various features of BPD (Tab. 1). Further, the clock genes *Npas2, Bmal1, Per2* and the gene for the circadian photoreceptor *OPN4,* are linked with Seasonal Affective Disorder (SAD); the circadian clock gene, *Clock*, is associated with Major Depressive Disorder (MDD), Delayed Sleep Phase Syndrome (DSPS), and morning/evening preference (Tab. 2). Regarding BPD, the fact that numerous interacting circadian clock genes of risk have been associated with the illness is consistent with its complex genetics, a pattern common to many psychiatric and sleep disorders. A notable exception is a form of Familial Advanced Sleep Phase Syndrome (FASPS) associated with a single clock gene *Per2,* and a CKIε/δ phosphorylation site; in other forms of FASPS multiple genes may be involved. Overall, numerous polymorphisms of many circadian clock genes are linked to both phenotypic features of BPD and to specific sleep disorders. An important relationship between clock and mood dysfunction is indicated by co-morbidity between FASPS and DSPS, and depression and anxiety [7–9] as well as the identification of insomnia as a risk factor for depression [10].

Another link between clock gene dysfunction and CT efficacy is indicated by the association of some clock gene and clock gene-related polymorphisms, with CTs and clinical symptoms (SD response: *GSK3*β; light treatment response: *OPN4* and *5HTTLPR*; diurnality: *Clock/Npas2* (Tabs 1 and 2)). Phenotypes, such as diurnal mood variation and mood variability *per se*, the SD response, and the level and pattern of SWA, are predictors of subsequent

Table 1 Circadian genes and mood disorders

Gene	Polymorphism	Genotype	Diagnosis	Effect	Reference
Npas2	targeted SNPs	471 Leu/Ser	SAD	Diurnal preference	[30, 86]
OPN4	SNP	P10L T/T	SAD	Increased association	[87]
Per2, Arntl, Npas2	SNP	interaction	SAD	Increased risk	[88]
Clock	SNP	3111 T/C	BPD	Recurrence rate	[14]
Clock	SNP	3111 T/C	BPD	Increased insomnia	[89, 90]
Clock	SNP	3111 T/C	BPD	Decreased sleep need	[89]
Clock	SNP	3117 G/T 3125 A/G	MDD	Cyclical insomnia (2 cases)	[91]
Clock	SNP	3111 T/C	MDD	Weak association	[92]
Bmal1 (Arntl)	targeted SNPs		BPD	Increased association	[93, 94]
Per3	targeted SNPs		BPD	Increased association	[94]
Timeless	SNP		BPD	Increased association	[93]
Gsk3β	SNP	–50 T/C	BPD	Later age of onset	[90, 95]
Gsk3β	SNP	–50 T/C	BPD	Increased SD and lithium responses	[18, 95]
Gsk3β	SNP	–50 T/C	BPII	Increased incidence in females	[96]
Per2	SNP	662 S/G CKIδ/ε binding site	BPD	No association	[97]
Cry1	SNP		BPD	No association	[98]

Table 2 Circadian genes and sleep disorders

Gene	Polymorphism/	Genotype	Effect	Ref
Per2	SNP	662 S/G CKIε binding site	FASPS	[99]
CKIδ	Missense mutation	T44A	FASPS	[9]
Clock	SNP	3111 T/C	DSPS	[89]
Per3	Structural polymorphisms		DSPS	[100, 101]
Clock	flanking	3111 T/T	Morning preference	[102, 103]
	polymorphism	3111 T/T	Evening preference	[102, 103]
Clock		3111C/C	Delayed sleep, increased daytime sleepiness	[103]
Clock	SNP	3111 T/C	no diurnal preference	[104]

clinical response to CTs as well as to antidepressant drugs. Polymorphisms of clock genes and related polymorphisms on clock gene signaling pathways that affect clock protein transport/degradation [11, 12] – such as serotonin signaling effects on clock timing by the serotonin transporter gene [13] and GSK3β (Tab. 1) – have also been linked to clinical response to SD [14]. Some clock gene mutations such as $Per2^{Brdm1}$ affect glutamate transmission by altering the glutamate transporter. Mice with this mutation show enhanced alcohol consumption that is blocked by acamprosate, a drug that reduces elevated glutamate levels [15]. The notion of a human *Per* mutation affecting a therapeutic clinical response to glutamatergic drugs is an intriguing possibility. Because different clock polymorphisms have been linked to different patient populations and treatment outcomes (Tabs 1 and 2), new treatment possibilities may be identified by examining these features in mood disorder patients. These clock-signaling related polymorphisms suggest that screening for clock gene mutations may optimize patient-specific treatments.

A brief overview of chronotherapy

Broadly defined, CT is a non-pharmacological manipulation of the biological timekeeping system that induces a clinical response. A common feature of CTs are their capacity to alter the temporal pattern of the internal circadian system. SD and partial SD produce a dramatic and rapid clinical antidepressant response [16, 17] by maintaining wakefulness at a circadian phase when sleep normally occurs. The molecular basis for the mood change may be associated with SD effects on neurotransmitters and trophic factors, such as the noradrenaline-mediated increase in synaptic potentiation and BDNF. *Phase-advance of sleep* (SPA) may correct a depressogenic, delayed sleep-wake cycle by advancing the hours of sleep by 6 h relative to body temperature, cortisol levels, and MHPG rhythms. *Light therapy and dark therapy* (LT, DT) employ a change in light intensity to either a) extend the duration/timing of biological day (bright LT) and improve mood, or b) to extend the duration/timing of biological night and bed-rest (DT) in order to reduce the frequency of mood swings. The neurobiological effects of SD, LT, and DT are described later (*Chronotherapeutics: extracellular monoamine and neurobiological effects*).

With regard to CT interventions themselves, rapid remission (often within hours), and the brief duration of treatment response (Fig. 1) are important features to explore. Among CTs, SD produces the most rapid antidepressant onset (hours) and the most rapid relapse (<24 h); SPA has a response onset of 2–3 days; LT has a later antidepressant onset (3–4 days). Regarding the rapid relapse after SD, the response is consistent with withdrawal of treatment, since remission can be maintained for a limited time using repeated partial SDs. The different temporal profiles of these responses point to different, possibly overlapping mechanisms. Because the CT clinical response can be extended with

antidepressant and mood stabilizing drugs, or with combined CTs (e.g., SD + LT), some CT and drug treatment mechanisms appear synergistic (for review see [13, 18, 19]). Clarifying the molecular signaling pathways underlying the positive mood response would greatly expand the range of putative drug targets drugs.

Bipolar, unipolar, schizoaffective, endogenous, and reactive depression [20] as well as secondary depression associated with postpartum [21], pregnancy, and Pervasive Developmental Disorder (PDD) [22] generally respond favorably to SD. In general however, BPD patients may have the most predictable response to SD. In a comparison of unipolar (UP) and BPD populations, 80% of BPD patients could be identified based on SD response [23]. Another predictor of positive treatment response is an abnormal response to the dexamethasone suppression test. The abnormal hypothalamic-pituitary-adrenal (HPA) axis response might be associated with hyperarousal and deficient SWA levels; corticotrophin releasing hormone antagonists reverse this effect [24] and also increase SWA.

While the functional importance of these associations has not clearly been established, there are promising leads (see sections on *Clock* and *Per2* and effects on dopamine and glutamate transmission). Pathological elements of circadian biology contribute to mood disorders, and these elements might be effectively modulated by novel interventions. Thus, the fact that some clock polymorphisms affect neurotransmitter levels, and these effects may in turn affect the sleep-wake process, underscores the complexity between clock gene signaling pathways and mood-altering processes such as synaptic potentiation and neural plasticity.

Chronotherapeutics: extracellular monoamine and neurobiological effects

Monoamines

The neural and monoaminergic treatment effects of SD and LT have been extensively detailed. Monoamine (norepinephrine, serotonin, and dopamine) function is clearly affected by CTs. CTs and antidepressant drug treatments have many common effects on neurotransmitters. However, despite many common effects, a notable distinction is the faster onset of clinical remission of CTs *versus* monoamine therapies, suggesting that their antidepressant mechanism(s) are quite different. This topic is discussed in detail later (see *Signaling pathways common to CTs and psychoactive drugs*). Serotonin and norepinephrine have been implicated in SD response and their circadian patterns might contribute to SD's antidepressant effect. Circadian rhythms of serotonin [25] and norepinephrine [26, 27] are high during waking, low during sleep, modulated by the light dark cycle, and linked with specific behaviors and sleep states. During SD, serotonin firing in dorsal raphe increases [28],

serotonin turnover increases [29], and the sensitivity of $5HT_{1A}$ inhibitory autoreceptors decreases [30]. The antidepressant response to SD is augmented by blockade of the $5HT_{1A}$ autoreceptor with pindolol [31]. SD also increases norepinephrine, tyrosine hydroxylase levels, and norepinephrine transporter mRNA in locus coeruleus [32, 33], and increases urinary catecholamine excretion in patients [34]. A positive response to SD is also linked to increased dopaminergic activity [35], decreased prolactin levels [36] (consistent with increased dopamine response), and in responders, increased dopamine release [37] and eyeblink response [38]. In addition to SD effects on monoamines, SD elevates levels of the neuromodulator adenosine in the forebrain, and is associated with cognitive deficits that are countered with adenosine antagonists such as caffeine. The effects of these substances on mood response are discussed in the next section (*Convergent pathways of antidepressant treatments and chronotherapeutics*).

In addition to CT effects on neurotransmitters, several brain regions are associated with CT response. The most extensive description of CT effects has been explored with SD. Brain localization of SD response using several imaging techniques [19, 39–42] (PET, HMPAO-SPECT, fMRI), implicates the anterior ventral anterior cingulate cortex with positive clinical response; baseline high metabolic rates are decreased by SD, a finding that is regionally consistent with brain regions implicated in emotion and cognition, with a positive drug treatment response [43], and with adenosine's biological effects on metabolism.

Similar to SD, LT alters serotonin signaling. LT increases serotonin levels in brain [44], normalizes serotonergic drug-challenge growth hormone responses to sumatriptan [45], as well as the cortisol and prolactin response to m-chlorophenylpiperazine [46]. Depletion of serotonin (or catecholamines) with amino-acid free diets decreases the antidepressant effects of LT [47]. The mood altering properties of LT may be associated with GSK3β since a) serotonin affects GSK3β, and b) GSK3β has both antidepressant and mood stabilizing properties (Fig. 2).

In addition to LT effects on serotonin, light *per se* (especially during dawn and dusk) initiates a glutamatergic-mediated hypothalamic signaling cascade that includes activation of a cAMP second messenger pathway and ends with CREB phosphorylation, *Per* transcription [48], and reset of the central clock and activity-rest cycle to the new light schedule. Such input to clock signaling pathways might be implicated in mood response (see *Chronotherapeutic inputs to clock gene signaling pathways*).

With regard to the effect of DT, extension of biological night is predicted to have opposite effects from those of LT described above. In brief, DT would decrease light-mediated serotonin, p-CREB, and *Per* transcription, as well as reset the prior light synchronized timing of the clock.

Serotonergic modulated light signaling

The relationship between serotonin, clock gene phosphorylation, light response and circadian entrainment is well described in *Drosophila*, where serotonin affects a molecular connection between serotonin signaling and the central clock component TIM, such that increased signaling by the serotonin receptor d5HT1B decreases SGG (a *Drosophila* GSK3β ortholog) activity (via phosphorylation). Phosphorylation of the SGG target protein TIM is reduced, and *Drosophila* photosensitivity is consequently reduced [12]. In mammals, considerable evidence indicates that serotonin [49], as well as antidepressants with serotonergic properties [12, 50, 51] also decrease light response albeit by a different serotonin mechanism.

Convergent pathways of antidepressant drug treatments and chronotherapeutics: gateways of drug discovery

Impaired cellular resilience and neural plasticity are important elements in the pathophysiology of mood disorders [52–56]. The impairments likely contribute to dysregulation of basic central neural circuits implicated in mood disorders, and are targets of therapeutic agents that normalize the deficits [57]. The major factors that contribute to impaired resilience and plasticity are a) stress and subsequent activation of the HPA axis [58], b) enhanced glutamate transmission and activation of NMDA and non-NMDA ionotropic receptors [59], particularly in hippocampal CA3 pyramidal neurons, and c) neurotrophins (NGF, BDNF, NT3, NT4/5, NT6) and several Trk receptors. The Trk receptor subtypes together offset the effects of severe stress [60] by modulating neurotransmission, synaptic plasticity, and cell survival, by activating mitogen-activated protein (MAP) and phophotidylinositol-3-kinase signaling pathways [61] and increasing levels of the antiapoptotic protein Bcl-2.

Signaling pathways common to chronotherapeutics and psychoactive drugs

While many antidepressant and mood stabilizing drugs were once thought to affect extracellular neurotransmitter systems, the fact that some effective agents (e.g., lithium, VPA) lack such extracellular effects prompted a new perspective on intracellular mechanisms. Current research suggests that relevant therapeutic mechanisms of antidepressant drugs and mood stabilizers include overlapping intracellular signaling cascades. Antidepressant drugs (SSRIs, monoamine oxidase inhibitors (MAOIs), etc.) increase extracellular levels of serotonin and norepinephrine, stimulate G-protein coupled receptors, and upregulate cAMP response element binding protein (CREB), thus increasing BDNF, Trk, and Bcl-2 [52, 62, 63], particularly in limbic regions. The mood stabilizer lithium acts via the Wnt signaling pathway to directly inhibit

GSK3β, thus allowing β-catenin to accumulate and reducing apoptosis by activation of the Tcf Lef1 promoter (Fig. 2). The mood stabilizers VPA and lamotrigine also act via GSK3β to prevent apoptosis but by different mechanisms. While mood stabilizers and antidepressant drugs have different therapeutic endpoints, they both seem to affect GSK3β, either by inhibition (mood stabilizers) or by inhibition and activation (antidepressants) [64].

Like traditional antidepressant drug therapies, CTs also have acute and chronic effects on central levels of monoamines. Similar to some drug treatments, their effects likely extend to intracellular molecular signaling pathways as well as to clock gene signaling. The mechanism of the faster onset of clinical remission of CTs compared with antidepressant drug treatment is unclear. One possibility is that the rapid onset may involve temporal differences in BDNF release *versus BDNF* gene expression (see [65] for review). A second possibility is that CT-associated rapid remission involves the activation of *multiple* neurotransmitter systems (norepinephrine, dopamine, and serotonin) and their intracellular molecular cascades. A third possibility, in addition to the effects of SD on increasing levels of BDNF and CREB [3, 5], is that both LT and SD may affect clock gene signaling by their signaling effects of extracellular serotonin and dopamine levels on intracellular GSK3β levels. The question of how CT-induced (particularly SD) extracellular effects of neurotransmitters might affect intracellular signaling, clinical remission, and relapse is unclear. These topics are discussed next.

SD, SWA and neuroplasticity

At a behavioral level, the sleep-wake cycle could be viewed as a behavioral expression of the alternating phases of cellular synaptic potentiation and downscaling. Synaptic potentiation increases during waking and is associated with SWA homeostasis, increased plasticity, LTP, and synaptic strength. The importance of norepinephrine to synaptic potentiation is shown by animal lesion studies that indicate SWA depends on norepinephrine, but not serotonin. In contrast, sleep-associated synaptic downscaling is a recovery process during which synaptic strength is reduced, and is mediated by alternating hyper- and depolarization cycles and SWA. The fact that SWA and cognitive processes are impaired in mood disorders is consistent with impaired synaptic homeostasis. Numerous factors, such as clock gene signaling (e.g., *Clock*, *GSK3*β; Tab. 1) and dopamine/noradrenaline linked polymorphisms [66] that potentially affect norepinephrine-dependent SWA homeostasis, as well as neuromodulator-related sleep factors (e.g., adenosine) [67, 68], or lifestyle-related sleep loss [69] may contribute to impaired sleep homeostasis in mood disorders. Several of these factors may also contribute to the rapid treatment effects of SD. Foremost are norepinephrine, BDNF, and GSK3β, each linked with SD either by affecting SWA homeostasis, or by association with clinical response to SD (Tab. 2).

SWA: a biomarker of neuroplasticity in novel drug evaluation

The synaptic homeostasis hypothesis indicates that wakefulness is accompanied by synaptic potentiation. Information storage that occurs through LTP is related to plasticity changes in selected cortical circuits. Elevated norepinephrine (but not serotonin) during wakefulness is critical for the induction of plasticity related genes (e.g., *P-CREB, Arc, and BDNF*). Theoretically, wake-dependent synaptic potentiation is linked to sleep-dependent SWA at the start of the next sleep episode. Accordingly, SWA might be a useful biomarker of neuroplasticity and synaptic potentiation induced by antidepressant drug treatment. This possibility is being tested with the anti-glutamatergic drug ketamine, an NMDA antagonist with efficacy in rapid remission of depression. Preliminary results are consistent with the synaptic homeostasis hypothesis, suggesting a link between ketamine-induced levels of SWA, clinical improvement, and neuroplasticity. Quantitative measurement of SWA waveform parameters may offer a promising biomarker to clinically evaluate new drug treatments that enhance neuroplasticity.

Norepinephrine

In rats, lesions of the noradrenergic system prevent waking associated increases of SWA as well as transcription of *BDNF, CREB* and *Arc*, i.e., genes that are normally induced by SD and therefore with the clinical response to SD. Further, norepinephrine mediates the expression of several neural plasticity-related molecules (Arc, BDNF, c-fos) regulated by the sleep wake cycle [5]. The fact that SD increases norepinephrine levels and locus coeruleus activity is consistent with a noradrenaline-mediated mechanism of rapid onset symptom remission in depression by SD. The fact that the clinical benefit from norepinephrine antidepressant drugs requires chronic treatment (acting thru G-protein coupled receptors, the cAMP second messenger system, and increases of BDNF, TrkB, etc.), but the SD-induced increase of norepinephrine activates a rapid-remission mechanism not activated by antidepressant drugs suggests that different mechanisms are at play. A circadian phase-dependent upregulation of norepinephrine signaling has been suggested [53] and the hypothesis is being tested by infusion of the A2 antagonist, yohimbine, during REM.

Serotonin and dopamine

As described earlier, both increased serotonin and dopamine signaling are linked to rapid CT antidepressant response. Acute administration of the $5HT_{1A}$ antagonist and beta-blocker pindolol, as well as the dopamine reuptake inhibitor, amineptine, enhance rapid clinical response to SD. Complex roles of

serotonin and dopamine are suggested by the diverse effects of non-acute monoamine interventions on treatment responses. As discussed later, GSK3β levels are plausibly affected by SD's effects on transmitters and receptor subtypes. First, serotonin depletion using a tryptophan-free diet, fails to prevent the rapid clinical response as predicted, but the depletion *prolongs* the treatment response. This suggests a link between serotonin and relapse whereas a dopaminergic mechanism might be linked with remission. Treatments that affect serotonin signaling (via $5HT_{1A}$ and $5HT_2$) regulate levels of GSK3β within 24 h [70], consistent with the time frame of rapid clinical response to SD. GSK3β inhibitors have antidepressant properties in rodents [71], and ECT, an effective treatment approach in drug-resistant depression, alters GSK3β levels [72]. While speculative, activation of $5HT_{1A}$ and $5HT_2$ receptors might inhibit and activate GSK3β respectively [70], separately accounting for rapid clinical remission and relapse after SD.

Second, *sub-chronic* treatment with amineptine prevents rapid clinical response, i.e., an effect opposite the acute response to amineptine. With regard to dopamine, *blockade* of the rapid SD response by *sub-chronic* amineptine may be mediated by Akt inhibition and GSK3β activation, as occurs after prolonged stimulation of D_2 striatal receptors [73]. However, since acute amineptine *enhances* rapid SD response, and would increase GSK3β levels, the interaction of dopamine and GSK3β in the rapid response is unclear. If dopamine is involved, it may activate a distinct clock gene signaling pathway that includes the D_2 receptor, and the MAP kinase signaling cascade that activates CLOCK/Bmal1 molecular clock (*Per*) transcription [74]. This signaling pathway is of interest because CLOCK/Bmal1 activated PER signaling is affected in mood-related circuitry (see *Clock gene signaling in reward related mood circuitry*).

Adenosine

The fact that SD and ECT increase both SWA and adenosine, upregulate A_1 receptors, and improve mood, supports a linkage between adenosine, neurotrophic factors, and the SD response [68]. Adenosine is predominantly an inhibitory neuromodulator in brain that regulates function of both neurons and glia. Activation of its two major receptors, A_1 and A_2, is related to decreased cerebral metabolic rate (CMR), and increased cerebral blood flow, respectively [75]. Adenosine might therefore mediate SD-induced reduction in CMR within the ventral anterior cingulate in depressed SD responders [41]. Particularly relevant is the presence of A_1 receptors in the hippocampus [76], where volume reductions are seen in patients with mood disorders [59]. The reduction of neuronal excitability by adenosine is mediated pre-synaptically by A_1 receptor inhibition of glutamate release [77], and post-synaptically by altering ion channel conductance and by affecting magnesium blockade of the NMDA receptor. Thus adenosine's antiglutamatergic and neuroprotective effects may contribute

to the rapid clinical benefits of SD, consistent with the rapid clinical effects of other antiglutamatergic treatments [78] such as ketamine.

Chronotherapeutic inputs to clock gene signaling pathways

Evidence suggests that the neurobiological effects of CT interventions are linked to intracellular clock signaling pathways via GSK3β and dopamine. First, preclinical studies show that serotonin [79] and dopamine receptor activation [74] alter synchronization by light and clock gene expression, respectively. Second, at control points other than GSK3β, such as the CLOCK/Bmal1 promoter region, the effects of CT on dopamine pathways appear to alter clock gene signaling. Third, because CT's effects on extracellular monoamines are likely to affect GSK3β activity, they are predicted to alter clock gene signaling of interconnected pathways. The fact that clock gene signaling pathways are altered in regional brain circuits also linked to mood disorders further implicates clock circuitry in their etiology.

Clock gene signaling in reward-related mood circuitry

At least two brain reward circuits are implicated in mood disorders: a) a limbic-thalamic-cortical (LTC) circuit linked via excitatory glutamatergic projections, consisting of the amygdala, the mediodorsal thalamus, and the orbital and medial prefrontal cortex, and b) an overlapping limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit. Clock gene mutations have been identified in the function LCSPT, which is a critical reward circuit that may be linked to hedonia and mania in BPD. Several lines of evidence indicate that clock genes, some interacting with hormonal (i.e., melatonin) input, function in this region to affect reward-related behavior. First, there is an association between hormonally regulated clock gene signaling and functional reward circuitry as indicated by a melatonin-dependent signal [80] of both a) a diurnal variation in cocaine sensitization (i.e., MT1 KOs exhibit equivalent day-night sensitization), and b) a circadian signal of striatal *Per1* mRNA and PER1 rhythms (pinealectomy abolishes clock gene diurnal rhythms). Interestingly, melatonin-linked gene polymorphisms of MEL1A [81] and AA-NAT, a gene associated with melatonin metabolism [82], are also associated with abnormal synchronization of the 24 h sleep wake cycle and possibly co-morbid mood disorders. Second, some clock gene mutant mice exhibit altered dopaminergic function and/or reward behavior. *Per1* KO mice do not exhibit cocaine-induced behavioral sensitization, whereas *Per2* KO mice exhibit enhanced sensitization [83]. *CLOCK* mutant mice exhibit many features of mania (hyperactivity, decreased sleep, cocaine preference) that are due to increased dopaminergic activity in the ventral tegmental area [84]. *Clock* KO mice have elevated levels of tyrosine hydroxylase as well as increased dopaminergic response to cocaine, and

lithium treatment; furthermore, grafts in the ventral tegmental area restore striatal dopamine input and reverse some manic-like behaviors. Although these mice do not exhibit behavioral cycling, which is a key feature of BPD, the animal model is useful for exploring the link between clock genes and BPD, and provides insight into novel treatments [84]. Overall, recent evidence suggests that clock gene-related signaling in the LTC or LCSPT may be linked to behavioral patterns relevant to mood disorders and BPD.

Gsk3β and REV-ERBα

While it is clear that further research is needed to determine whether CTs might affect mood cycling by altering circadian clock gene signaling, lithium provides clues that might guide further research. Lithium's two major clinical benefits are a) as a neuroprotective agent that promotes axonogenesis and reduces apoptosis (Fig. 2), and b) as a mood stabilizer. Its benefits may be mediated by the dual effects of lithium-mediated GSK3β and REV-ERBα inhibition. Lithium affects the phosphorylation of GSK3β and REV-ERB, two key elements of interacting clock gene feedback loops. In the primary loop, lithium inhibits GSK3β and delays the circadian clock in part by reducing PER phosphorylation. The delayed nuclear entry of PER and CRY protein following lithium treatment is associated with a delayed clock timing (Fig. 2). In a secondary loop, lithium-mediated inhibition of GSK3β, reduces phosphorylation of the clock protein REV-ERBα, a negative feedback component of a secondary clock loop, resulting in *disinhibition* of negative feedback on *Bmal1*. This disinhibition enhances *Bmal1* activity and shortens the cycle duration of this secondary loop. *In toto*, lithium may have opposing effects on these two interacting loops: lengthening the intrinsic cycle duration of the primary feedback loop and shortening the intrinsic cycle of the REV-ERBα regulatory loop. These opposing actions of lithium may strengthen the interaction between these feedback loops and contribute to its mood stabilizing effects. Through their Gsk3β inhibiting effects, the mood stabilizers VPA and lamotrigine are predicted to have similar effects; CTs and antidepressant drugs, because they often increase Gsk3β levels, are predicted to have mood destabilizing effects.

While lithium appears to stabilize mood cycles, the effects of CTs may be more complex and may alter mood as well as destabilize mood cycles. CT-induced changes in monoamines (see *Signaling pathways common to chronotherapeutics and psychoactive drugs*) may also affect intracellular signaling cascades via effects on GSK3β, one of several gateways for affecting clock gene signaling by monoamines. Monoamines inhibit (via $5HT_{1A}$) or activate (via D_2) GSK3β. Consistent with the view that monoamines alter clock signaling, antidepressant drugs alter cycle duration and light response of the circadian clock [12, 50, 51]. Two further consequences of neurotransmitter effects on clock gene signaling are of interest. First, the unintentional effects of sleep loss on monoamines (serotonin, dopamine) may also affect clock gene

signaling pathways and contribute to feed-forward effects of sleep loss on the induction of mania and rapid cycling. Second, it should be noted that because clock signaling comprises an interconnected and regulated feedback cycle with several input locations (e.g., GSK3β), the effects of clock gene polymorphisms *per se* on neurotransmitters (*Clock* on dopamine; *Per2* on glutamate, etc.) and *vice versa* (the effects of neurotransmitter polymorphisms (e.g., 5HTTLPR) on clock input), it is certainly plausible that some of the abnormal patterns in neurotransmitter signaling, or in circadian clock gene signaling, may be derived from complex interactions between neural and clock signaling.

Chronotherapeutic and drug effects on the CLOCK/Bmal1 promoter region

The effects of intracellular signaling on the CLOCK/Bmal1 promoter region may modulate clinical response latency or duration to relapse. For example, SD-induced effects on dopamine, and D2 receptor activation of the ERK pathway, may ultimately activate CLOCK/BMAL1-induced clock gene transcription of *Per2*. Clock gene control pathways, in which the products of clock gene transcription (CLOCK/BMAL1) alter the transcription of clock controlled genes (CCGs) by affecting activity in the E-box region of CCGs, have been hypothesized [85] to alter the transcription of numerous mood-related neuromodulator substances such as tyrosine hydroxylase, the norepinephrine transporter, and the glutamate receptor, each in close proximity to the Clock/Bmal1 promoter region. While support for drug effects on the E-box region is largely based on regional proximity of mood-related genes to the region, the potential to activate these mood-related modulator substances should highlight this promoter region as a potential target of novel drug development.

Conclusion

Identifying the specific and convergent molecular effects of chronotherapeutic treatments (CTs) with effective drug therapies such as lithium is important for novel drug development. For example, the mechanism of the rapid onset of remission that occurs after SD is unclear. Clarification of the molecular pathways that mediate rapid remission would clearly benefit traditional antidepressant therapies.

CTs such as SD and LT affect extracellular levels of norepinephrine, serotonin, and dopamine. The intracellular effects of these monoamines often affect clock gene signaling pathways implicated in the etiology of bipolar mood cycles and mood disorders. Preclinical studies suggest the effects of SD on rapid clinical remission may be mediated by a norepinephrine-mediated increase in BDNF and neuroplasticity. SD- and LT-mediated changes in dopamine and serotonin have complex effects on clock gene signaling, medi-

ated in part by GSK3β and REV-ERBα. A convergence of non-pharmacological and drug treatment effects is indicated by the mood stabilizer lithium, which reduces GSK3β and REV-ERBα activity.

The contribution of altered clock gene signaling to irregular circadian rhythms, sleep loss, and mood disturbance remains to be fully characterized. However, the fact that multiple and different therapeutic treatment modalities appear to alter common molecular elements suggests an important role for clock signaling pathways in both the etiology and treatment of mood disorders.

References

1 Pittendrigh CS, Daan S (1976) A functional analysis of circadian pacemakers in nocturnal rodents. V: Pacemaker structure. A clock for all seasons. *J Comp Physiol* 106: 333–355
2 Borbely A (1982) Two process model of sleep regulation. *Hum Neurobiology* 1: 195–204
3 Tononi G, Cirelli C (2006) Sleep function and homeostasis. *Sleep Med Rev* 10: 49–62
4 Cirelli C, Tononi G (2001) The search for the molecular correlates of sleep and wakefuless. *Sleep Med Rev* 5: 399–410
5 Cirelli C, Tononi G (2004) Locus Ceruleus control of state-dependent gene expression. *J Neurosci* 24: 5410–5419
6 Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. *Nature* 430: 78–81
7 Hamet P, Tremblay J (2006) Genetics of the sleep-wake cycle and its disorders. *Metabolism* 55: S7–S12
8 Shirayama M, Shirayama Y, Iida H, Kato M, Kajimura N, Watanabe T, Sekimoto M, Shirakawa S, Okawa M, Takahashi K (2003) The psychological aspects of patients with delayed sleep syndrome (DSPS). *Sleep Med* 4: 427–433
9 Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Ptacek LJ, Fu YH (2005) Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. *Nature* 434: 640–644
10 Riemann D, Voderholzer H (2003) Primary insomnia: a risk factor to develop depression. *J Affect Disorder* 76: 255–259
11 Uz T (2005) Effect of fluoxetine and cocaine on the expression of clock genes in the mouse hippocampus and striatum. *Neuroscience* 134: 1309–1316
12 Yuan Q, Lin F, Zheng X, Sehgal A (2005) Serontonin modulates circadian entrainment in Drosophila. *Neuron* 47: 115–127
13 Benedetti F, Colombo C, Serretti A, Lorenzi C, Pontggia A, Barbini B, Smeraldi E (2003) Antidepressant effect of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry* 54: 687–692
14 Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, Smeraldi E (2003) Influence of CLOCK polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet B Neuropsychiatr Genet* 123: 23–26
15 Spanagel R, Pendyala G, Abarca C, Zghoul T, Sanchis-Segura C, Manone M, Lascorz J, Depner M, Holzberg D, Soyka M et al (2005) The clock gene Per2 influences the glutamatergic system and modulates alcohol consumption. *Nat Med* 11: 35–42
16 Ostenfeld I (1986) Abstinence from night sleep as a treatment for endogenous depressions. The earliest observations in a Danish mental hospital (1954) and the analysis of the causal mechanism. *Dan Med Bull* 33: 45–49
17 Schulte W (1959) Sequelae of sleep deprivation. *Medizinische Klinik (Munich)* 54: 969–973
18 Benedetti F, Serretti A, Pontiggia A, Bernasconi A, Lorenzi C, Colombo C, Smeraldi E (2005) Long term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta-50 t/C SNP. *Neurosci Lett* 376: 51–55
19 Benedetti F, Bernasconi A, Blasi V, Cadioli M, Colombo C, Falini A, Lorenzi C, Radgelli D, Scotti

G, Smeraldi E (2007) Neural and genetic correlates of antidepressant response to sleep deprivation: a functional magnetic resonance imaging study of moral valence decision in bipolar depression. *Arch Gen Psychiatry* 64: 179–187
20 Liebenluft E, Wehr TA (1992) Is sleep deprivation useful in the treatment of depression? *Am J Psychiatry* 149: 159–168
21 Parry BL, Curran ML, Stuenkel CA, Yokimozo M, Tam L, Powell KA, Gillin JC (2000) Can critically timed sleep deprivation be used in pregnancy and postpartum depressions? *J Affect Disorder* 60: 201–212
22 Parry BL, Cover H, Mostofi N, LeVeau B, Sependa PA, Resnick A, Gillin JC (1995) Early *versus* late partial sleep deprivation in patients with premenstrual dysphoric disorder and normal comparison subjects. *Am J Psychiatry* 152: 404–412
23 Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smereldi E (1998) The unipolar-bipolar dichotomy and the resonse to sleep deprivation. *Psychiatr Research* 79: 43–50
24 Held K, Kunzel H, Ising M (2004) Treatment with the CRH1 receptor anatagonist R121919 improves sleep-EEG in patients with depression. *J Psychiatr Res* 38: 129–136
25 Ursin R (2002) Serotonin and sleep. *Sleep Med Review* 6: 57–69
26 Aston-Jones G, Chen S, Zhu Y, Oshinsky ML (2001) A neural circuit for circadian regulation of arousal. *Nat Neurosci* 4: 732–739
27 Gonzalez MM, Aston-Jones G (2006) Circadian regulation of arousal: role of the noradrenergic locus coeruleus system and light exposure. *Sleep* 29: 1327–1336
28 Gardner J, Fornal C, Jacobs B (1997) Effects of sleep deprivation on serotonergic activity in the dorsal raphe nucleus of the freely moving cat. *Neuropsychopharmacology* 17: 72–81
29 Asikainen M, DeBoer T, Porkka-Heiskanen T, Stenberg D, Tobler I (1995) Sleep deprivation increases brain serotonin turnover in the Djungarian hamster. *Neurosci Lett* 198: 21–24
30 Maudhuit C, Jolas T, Chastanet M, Hamon M, Adrien J (1996) Reduced inhibitory potency of serotonin reuptake blockers on central serotonergic neurons in rats selectively deprived of rapid eye movement sleep. *Biol Psychiatry* 40: 1000–1007
31 Smeraldi E, Benedetti F, Barbini B, Campari E, Colombo C (1999) Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. *Neuropsychopharmacology* 20: 380–385
32 Basheer R, Magner M, McCarley RW, Shiromani PJ (1998) REM sleep deprivation increases levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. *Mol Br Res* 57: 235–240
33 Hipolide DC, Moreira KM, Barlow KB, Wilson AA, Nobrega JN, Tufik S (2005) Distinct effects of sleep deprivation on binding to norepinephrine and serotonin transporters in rat brain. *Prog Neuropsychopharmacol Biol Psychiatry* 29: 297–303
34 Muller HU, Riemann D, Berger M, Muller WE (1993) The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. *Acta Psychiatr Scand* 88: 16–20
35 Zwicker AP, Calil HM (1986) The effects of REM sleep deprivation on striatal dopamine receptor sites. *Pharmacol Biochem Behav* 24: 809–812
36 Kasper S, Sack DA, Wehr TA, Kick H, Voll G, Viera A (1988) Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. *Biol Psychiatry* 24: 631–641
37 Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A (1994) Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation. Preliminary Results. *Biol Psychiatry* 35: 880–885
38 Ebert D, Albert R, Hammon G, Strasser B, May A, Merz A (1996) Eye-blink rate and depression. Is the antidepressant effect of sleep deprivation mediated by the dopamine system? *Neuropsychopharmacology* 15: 332–339
39 Clark C, Brown GG, Archibald SL (2002) Does amygdalar perfusion correlate with antidepressant response to sleep deprivation in major depression? *Psychiatry Res* 146: 43–51
40 Clark C, Brown GG, Frank L, Thomas L, Sutherland AN, Gillin JC (2006) Improved anatomic delineation of the antidepressant response to partial sleep deprivation in medial frontal cortex using perfusion weighted functional MRI. *Psychiatry Res* 146: 213–222
41 Gillin JC, Buchsbaum M, Wu J, Clark C, Bunney W (2001) Sleep deprivation as a model experimental antidepressant treatment: findings from functional brain imaging. *Depress Anxiety* 14: 37–49

42 Wu JC, Buchsbaum M, Bunney WE (2001) Clinical neurochemical implications of sleep deprivations effects on the anterior cingulate of depressed responders. *Neuropsychopharmacology* 25: S74–78
43 Mayberg HS (2003) Modulating dysfunctional limbic cortical circuits in depression: towards development of brain based algorithms for diagnosis and treatment. *Br Med Bull* 65: 193–207
44 Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD (2002) Effect of sunlight and season on serotonin turnover in the brain. *Lancet* 360: 1840–1842
45 Yatham LN, Lam RW, Zis AP (1997) Growth hormone response to sumatriptan (5HT1D agonist) challenge in seasona; affective disorder: effects of light therapy. *Biol Psychiatry* 42: 24–29
46 Garcia-Borreguero D, Jacobsen FM, Murphy DL, Joseph-Vanderpool JR, Chiara A, Rosenthal NE (1995) Hormonal responses to the administration of m-chlorophenylpiperazine in patients with seasonal affective disorder and controls. *Biol Psychiatry* 37: 740–749
47 Neumeister A, Turner EH, Matthews JR, Postolache TT, Barnett RL, Rauh M, Vetticad RG, Kasper S, Rosenthal NE (1998) Effects of tryptophan *versus* catecholamine depletion in patients with seasonal affective disorder in remission with light therapy. *Arch Gen Psychiatry* 55: 524–530
48 Gau D (2002) Phosphorylation of CREB Ser142 regulates light-induced phase-shifts of the circadian clock. *Neuron* 34: 245–253
49 Pickard GE, Rea MA (1997) Serotonergic innervation of the hypothalamic suprachiasmatic nucleus and photic regulation of circadian rhythms. *Biol Cell* 89: 513–523
50 Duncan WC (1996) Circadian rhythms and the pharmacology of affective illness. *Pharmacol Ther* 71: 253–312
51 Duncan WC, Johnson K, Wehr TA (1997) Decreased sensitivity and response to light of the photic entrainment pathway during chronic treatment with the MAOI clorgyline and lithium. *J Biol Rhythms* 13: 330–346
52 D'Sa C, Duman RS (2002) Antidepressants and neuroplasticity. *Bipolar Disord* 4: 183–194
53 Manji HK, Quiroz JA, Sporn J, Payne JL, Denikoff KD, Gray N, Zarate CA, Charney DS (2003) Enhancing neuronal plasticity and cellular resistance to develop novel improved therapeutics for difficult to treat depression. *Biol Psychiatry* 53: 707–742
54 Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002) Neurobiology of depression. *Neuron* 34: 13–25
55 Quiroz JA, Singh J, Gould TD, Denikoff KD, Zarate CA, Manji HK (2004) Emerging experimental therapeutics for bipolar disorder: clues from molecular pathphysiology. *Mol Psychiatry* 9: 756–776
56 Young L (2002) Neuroprotective effects of antidepressant and mood stabilizing drugs. *J Psychiatry Neurosci* 27: 8–9
57 Carlson PJ, Singh JB, Zarate CA, Drevets WC, Manji HK (2006) Neural circuitry and neuroplasticity in mood disorders: insights for novel therapeutic targets. *NeuroRx* 3: 22–41
58 McEwen B (1999) Stress and hippocampal plasticity. *Ann Rev Neurosci* 22: 105–122
59 Sapolsky R (2000) Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 57: 925–935
60 DeVries AC, Joh HD, Bernard O, Hattori K, Hurn PD, Traystman RJ, Alkayed NJ (2001) Social stress exacerbates stroke outcome by supressing Bcl-2 expression. *Proc Natl Acad Sci USA* 98: 11824–11828
61 Blum R, Konnerth A (2005) Neurotrophin-mediated rapid signaling in the central nervous system. *Physiology* 20: 70–78
62 Duman RS, Malberg J, Thome J (1999) Neural plasticity to stress and antidepressant treatment. *Biol Psychiatry* 46: 1181–1191
63 Thome J, Sakai N, Shin K, Steffen C, Zhang YJ, Impey S, Storm D, Duman RS (2000) cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J Neurosci* 20: 4030–4036
64 Beaulieu J-M (2007) Not only lithium: regulation of glycogen synthase kinase-3 by antipsychotics and serotonergic drugs. *Int J Neuropsychopharmacol* 10: 3–6
65 Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology* 33: 73–83
66 Serretti A, Macciardi F, Cusin C, Lattuada E, Souery D, Lipp O, Mahieu B, Van Broeckhoven C, Blackwood D, Muir W (2000) Linkage study of mood disorders with D2, D3, and TH genes: a multicenter study. *J Affect Disorder* 58: 51–61
67 Retey JV, Honneger E, Khatami R, Luhmann U, Jung H, Berger W, Landolt H-P (2005) A func-

tional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. *Proc Natl Acad Sci USA* 102: 15676–15681
68 van Calker D, Biber K (2005) The role of adenosine receptors in neural resilience and the neurobiology of mood disorders. *Neurochem Res* 30: 1205–1217
69 Kim Y, Laposky A, Bergmann BM, Turek FW (2007) Repeated sleep restriction in rats leads to homeostatic and allostatic responses during recovery sleep. *Proc Natl Acad Sci USA* 104: 10697–10702
70 Li X, Zhu W, Roh M, Friedman AB, Rosborough K, Jope RS (2004) *In vivo* regulation of gltcogen synthase kinase-3B (GSK3B) by serotonergic activity in mouse brain. *Neuropsychopharmacology* 29: 1426–1431
71 Gould TD, Einat H, Bhat B, Manji HK (2004) AR-A014418 a selective GSK-3 inhibitor pruduces antidepressant like effects in the forced swim test. *Int J Neuropsychopharmacol* 7: 387–390
72 Roh MS, Kang UG, Shin SY, Lee YH, Jung HY, Juhan YS, Kim YS (2003) Biphasic changes in the Ser-9 phosphorylation of glycogen kinase-3beta after electroconvulsive shock in the rat brain. *Prog Neuropsychopharmacol Biol Psychiatry* 7: 1–5
73 Beaulieu JM, Soynikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, Caron MG (2004) Lithium antagonizes dopamine-dependent behaviors mediated by an Akt/glucogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci USA* 101: 5099–5109
74 Yujnovsky I, Hirayama J, Doi M, Borelli E, Sassone-Corsi P (2006) Signaling mediated by the dopamine D2 receptor potentiates circadian regulation by CLOCK:BMAL1. *Proc Natl Acad Sci USA* 103: 6386–6391
75 Blood AB, Hunter CJ, Power GG (2003) Adenosine mediates decreased cerebral metabolic rate and increased cerebral blood flow during acute moderate hypoxia in the near-term fetal sheep. *J Physiol* 553: 935–945
76 Swanson TH, Drazba JA, Rivkees SA (1995) Adenosine A1 receptors are located predominantly on axons of the rat hippocampal formation. *J Comp Neurol* 363: 517–531
77 Eschke D, Brand A, Scheibler P, Hess S, Eger K, Allgaier C, Nieber K (2001) Effect of an adenosine A(1) receptor agonist and novel pyrimidoindole on membrane properties and neurotransmitter release in rat cortical and hippocampal neurons. *Neurochem Int* 38: 391–398
78 Zarate CA, Singh J, Manji HK (2006) Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 59: 1006–1020
79 Bradbury MJ, Dement WC, Edgar DM (1997) Serotonin containing fibers in the suprachiasmatic hypothalamus attenuate light-induced phase-delays in mice. *Brain Res* 768: 125–134
80 Uz T (2003) The pineal gland is critical for circadian Period1 expression in the striatum and for cocaine sensitization in mice. *Neuropsychopharmacology* 28: 2117–2133
81 Dauvilliers Y, Maret S, Tafti S (2005) Genetics of normal and pathological sleep in humans. *Sleep Rev Med* 9: 91–100
82 Hohjoh H, Takasu M, Shishikura K (2003) Significant association of the arylalkylamine N-acetransferase (AA-NAT) gene with delayed sleep phase syndrome. *Neurogenetics* 4: 151–153
83 Abarca C (2002) Cocaine sensitization and reward are under the influence of circadian genes and rhythm. *Proc Natl Acad Sci USA* 99: 9026–9030
84 Roybal K, Theobold D, Graham A, DiNieri J, Russo SJ, Krishnan V (2007) Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci USA* 104: 6406–6411
85 Manev H, Uz T (2006) Clock genes influencing and influenced by psychoactive drugs. *Trends in Pharmacological Science* 27: 186–189
86 Johansson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kieseppa T (2003) Circadian clock-related polymorphism in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 28: 734–739
87 Roecklein KA, Rohan KJ, Duncan WC, Rollag MD, Rosenthal NE, Lipsky RH, Provencio I (2008) A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. *J Affective Disorder* doi: 10.1016/j.jad.2008.08.005
88 Partonen T, Treutlein J, Alpman A, Frank J, Johansson C, Depner M, Aron L, Rietschel M, Wellek S, Soronen P (2007) Three circadian clock genes Per2, Arntl, Npas2 contribute to winter depression. *Annals Med* 39: 229–2328
89 Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, Smeraldi E (2003) Genetic dissection of psyschopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet B Neuropsychiatr Genet* 121: 35–38

90 Serretti A, Cusin C, Benedetti F, Mandelli L, Pirovano A, Zanardi R, Colombo C, Smeraldi E (2005) Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet* 137: 36–39
91 Pirovano A, Lorenzi C, Serretti A, Ploia C, Landoni S, Catalano M, Smeraldi E (2005) Two new rare variants in the circadian "clock" gene may influence sleep pattern. *Genet Med* 7: 455–457
92 Desan PH, Oren DA, Malison R, Price LH, Rosenbaum J, Smoller J, Charney DS, Gelernter J (2000) Genetic polymorphism at the CLOCK gene locus and major depression. *Am J Med Genet* 96: 418–421
93 Mansour HA, Wood J, Logue T, Chowdri KV, Dayal M, Kupfer DJ, Monk TH, Devlin B, Nimgaonker VL (2006) Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophenia. *Genes Brain Behavior* 5: 150–157
94 Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD (2006) Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 141: 234–241
95 Benedetti F, Serretti A, Columbo C, Lorenzi C, Tubazio V, Smeraldi E (2004) A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age of onset and response to total sleep deprivation in bipolar depression. *Neurosci Lett* 368: 123–126
96 Szczepankiewicz A, Skibinska M, Hauser J, Slopien A, Leszcynska-Rodziewicz A, Kapelski P, Dmitrzak-Weglarz M, Czerski PM, Rybakowski JK (2006) Association analysis of the GSK-3beta T-C gene polymorphism with schizophrenia and bipolar disorder. *Neuropsychobiology* 53: 51–56
97 Shiino Y, Nakajima S, Ozeki Y, Isono T, Yamada N (2003) Mutation screening of the human period 2 gene in bipolar disorder. *Neurosci Letter* 338: 82–84
98 Nievergelt CM, Kripke DF, Remick RA, Sadovnick AD, McElroy SL, Keck PE, Schork NJ, Kelsoe JR (2005) Examination of the clock gene Cryptochrome 1 in bipolar disorder: mutational analysis and absence of evidence of linkage or association. *Psychiatr Genet* 15: 45–52
99 Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptacek LJ, Fu YH (2001) An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 291: 1040–1043
100 Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, Von Schantz M (2003) A length polymorphism in the circadian gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 26: 413–415
101 Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M, Watanabe T, Sekimoto M, Shibui K, Kim K (2001) Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. *EMBO reports* 2: 342–346
102 Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi JS, Mignot E (1998) A CLOCK polymorphism associated with human diurnal preference. *Sleep* 21: 569–576
103 Mishima K, Tozawa T, Satoh K, Saitoh H, Mishima Y (2005) The 3111 T/C polymorphism of hClock is associated with evening preference and delayed sleep timing in a Japanese population sample. *Am J Med Genet B Neuropsychiatr Genet* 133: 101–104
104 Robilliard DL, Archer SN, Arendt J, Lockley SW, Hack LM, English J, Leger D, Smits MG, Williams A, Skene DJ et al (2002) The 3111 Clock gene polymorphism is not associated with sleep and circadian rhythmicity in phenotypically characterized human subjects. *J Sleep Res* 11: 305–312

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Neuroimaging studies of bipolar depression: therapeutic implications

Jonathan Savitz and Wayne C. Drevets

Section on Neuroimaging in Mood and Anxiety Disorders, Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, MD, USA

Abstract

Bipolar disorder (BPD) is characterized by pathophysiological changes to the visceromotor network, disrupting the regulation of endocrine and autonomic responses to stress, and hence emotion and behavior. Specifically, reductions in gray matter volume and a concomitant increase in glutamatergic neurotransmission, is observed in the pregenual (pgACC) and subgenual anterior cingulate cortex (sgACC), the orbitofrontal, frontal polar and ventrolateral prefrontal cortex (PFC), the posterior cingulate, ventral striatum, and hippocampus. While increased glutamatergic signaling is equally salient in the amygdala, the data are conflicting on the nature of volumetric changes in this region. Neuroreceptor imaging data provide preliminary evidence for serotonin, serotonin transporter (5-HTT), dopamine receptor, and cholinergic system dysfunction in BPD. Oft-reported abnormalities of the deep frontal and basal ganglia white matter, and enlargement of the third and lateral ventricles are likely associated with cerebrovascular disease. Mood stabilizers and antidepressant drugs may attenuate pathological limbic activity, and increase neurotrophic processes, restoring balance to the system.

Introduction

The World Health Organization ranks bipolar disorder (BPD) as the fifth leading cause of disability [1], yet almost nothing is known about this condition's pathogenesis. Because BPD is not associated with gross brain pathology or with clear animal models for spontaneous, recurrent mood episodes, the availability of tools allowing noninvasive assessment of the human brain proved critical to elucidating its neurobiology. The recent development of neuroimaging technologies that permit *in vivo* characterization of the anatomical, physiological, and neurochemical correlates of BPD thus has enabled significant advances toward illuminating the pathophysiology of this condition. Notably, the results of neuroimaging studies and the *post mortem* studies that have been guided by neuroimaging results have given rise to neurocircuitry-based models in which both functional and structural brain pathology play roles in the development of BPD.

To date, none of these abnormalities has shown sufficient sensitivity and specificity to prove useful as a diagnostic test. The variable presence and mag-

nitude of such abnormalities in mood disorders likely reflects the heterogeneity encompassed within the BPD syndrome with respect to pathophysiology and etiology. As long as psychiatric nosology depends on syndrome-based classifications, diagnosing BPD may continue to encompass patients with a range of conditions that appear clinically related but are neurobiologically distinct. This lack of precise and biologically verifiable definition of illness presumably contributes to the inconsistencies extant within the literature pertaining to neurobiological abnormalities associated with BPD, and to the variable responses of BPD patients to psychopharmacological treatment options. Ultimately the discovery of illness subtypes that are associated with specific genotypes is expected to improve the sensitivity and specificity of research findings as well as therapeutic approaches.

Neural circuits implicated in BPD

Evidence from neuroimaging, neuropathological, and lesion analysis studies implicates brain networks that normally regulate the evaluative, expressive, and experiential aspects of emotional behavior in the pathophysiology of BPD [3]. These circuits include the limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT) formed by the orbital and medial prefrontal cortex (OMPFC), amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal thalamic nucleus, and ventral pallidum [4]. The LCSPT circuits initially were related to *emotional behavior* on the basis of their anatomical connectivity with limbic structures that mediate emotional expression, such as the hypothalamus and periaqueductal grey (PAG) [5]. They were also initially implicated in the *pathophysiology of depression* by the observations that degenerative basal ganglia diseases and lesions of the striatum and orbitofrontal cortex (OFC) increased the risk of developing major depressive or manic syndromes [6].

In addition to involving LCSPT circuitry, the functional and structural brain abnormalities associated with mood disorders also affect an extended anatomical network formed by neural projections linking the LCSPT components to areas of the mid- and posterior cingulate cortex, superior and medial temporal gyrus, parahippocampal cortex, medial thalamic nuclei, and habenula [4]. This extended 'visceromotor' network functions to regulate autonomic, endocrine, neurotransmitter, and behavioral responses to aversive and rewarding stimuli and contexts by modulating neuronal activity within the limbic and brainstem structures that mediate and organize emotional expression (e.g., amygdala, bed nucleus of the stria terminalis (BNST), PAG, hypothalamus) [4]. Thus, impaired function within this network could disinhibit or alter emotional expression and experience, conceivably giving rise to the clinical manifestations of depression or mania. Compatible with this hypothesis, pharmacological, neurosurgical, and electrical stimulation treatments for mood disorders appear to inhibit pathological activity within visceromotor network structures such as the amygdala and subgenual anterior cingulate cortex (sgACC) [7–9].

Structural neuroimaging in BPD

Patients with BPD show abnormalities of morphology or morphometry in multiple structures that form the extended visceromotor network [7] (Tab. 1). The extent or prevalence of these abnormalities depends partly on clinical characteristics such as age at onset of illness, risk for developing psychosis as well as mania, and evidence for familial aggregation of illness. For example, elderly BPD or major depressive disorder (MDD) subjects with late-onset mood disorders show an increased prevalence of neuroimaging correlates of cerebrovascular disease, relative to both age-matched, healthy controls and to eld-

Table 1. Neuroimaging and histopathological abnormalities evident in the visceromotor network [4] in early-onset, recurrent MDD and/or BPD

Brain region	Grey matter volume	Cell counts, cell markers	Glucose metabolism, CBF	
	Dep *versus* Con	Dep *versus* Con	Dep *versus* Con	Dep *versus* Rem
Dorsal medial/anterolateral PFC (BA9)	Decreased	Decreased	Decreased	Increased
Frontal polar cortex (BA 10)		Decreased	Increased	Increased
Subgenual anterior cingulate cortex	Decreased	Decreased	Mixed findings[a]	Increased
Pregenual anterior cingulate cortex	Decreased	Decreased	Increased	Increased
Orbital C/Ventrolateral PFC	Decreased	Decreased	Increased	Increased
Posterior cingulate	Decreased		Increased	Increased
Parahippocampal cortex	Decreased	Decreased in BPD	Increased	Increased
Amygdala	Mixed findings[b]	Decreased in MDD	Increased	Increased
Ventromedial striatum	Decreased		Increased	Increased
Hippocampus	Decreased	Decreased in BPD	n.s.	n.s.
Superior temporal gyrus/ Temporopolar cortex	Decreased			Increased
Medial thalamus			Increased	Increased

[a] In the sgACC, the apparent reduction in CBF and metabolism in PET images of subjects with MDD is thought to be accounted for by the reduction in tissue volume in the corresponding cortex. After partial volume correction for the reduction in grey matter, the metabolism appears increased relative to controls.

[b] The literature disagrees with respect to amygdala volume in mood disorders (see text).

Abbreviations: Dep *versus* Con: Unmedicated individuals with MDD *versus* healthy controls; Dep *versus* Rem: Unmedicated individuals with MDD *versus* themselves in either the medicated or unmedicated remitted phases; n.s.: differences generally not significant; PFC – prefrontal cortex. Empty cells indicate insufficient data. Modified from [188].

erly individuals with MDD with an early age of onset [10]. Similarly, individuals with MDD and BPD who manifest either psychosis (delusions and/or hallucinations) or a late-life onset of illness show nonspecific signs of atrophy, such as lateral ventricle enlargement, that are absent in early-onset, non-psychotic MDD cases.

Volumetric MRI abnormalities identified in BPD

Early-onset, non-psychotic BPD cases also show volumetric abnormalities that are localized to some prefrontal cortex (PFC), cingulate, temporal lobe and striatal structures (Tab. 1). The most prominent volumetric abnormality reported to date has been a reduction in grey matter in the *left* anterior cingulate cortex (ACC) ventral to the corpus callosum *genu* (i.e., 'subgenual'), which is evident in MDD and BPD with evidence of familial clustering or with psychotic features [11–14]. This volumetric reduction exists early in the course of the illness and in young adults at high familial risk for BPD or MDD [11, 14]. In BPD this abnormality is evident for both BPD I and BPD II samples [15, 16]. Conventional antidepressant drug treatment and symptom remission do not appear to alter the reductions in grey matter volume in the sgACC [13], but chronic lithium treatment, which exerts robust neurotrophic effects in animal models, has been associated with increasing grey matter volume in treatment responders in the sgACC and other PFC areas [10, 17] (Fig. 1).

Grey matter volume also is reduced in the OFC (BA 11, 47) and ventrolateral PFC (VLPFC; BA 45, 47) in MDD [18] and BPD [16], in the frontal polar/dorsal anterolateral PFC (BA 9, 10) in MDD [10], and in the posterior cingulate cortex and superior temporal gyrus in BPD [19] (Fig. 2, see page 131). In BPD the peak difference in grey matter loss in the lateral OFC was found in the sulcal BA47 cortex [19], a region that appears to function as part of both the visceromotor and 'sensory' networks within the OMPFC [4]. Compatible with these data, the MRS study by Cecil and colleagues [20] found reduced NAA and choline concentrations in the orbitofrontal GM in BPD, suggesting decreased neuronal integrity.

Decreases in the volume of the dorsal PFC have also been reported in BPD and MDD [21]. For example, Frangou and colleagues [22] and Haznedar and colleagues [15] described GM volume reductions of the DLPFC (BA 8, 9, 45, 46) in medicated and remitted BPD I patients, and partially medicated, 'stable' bipolar-spectrum individuals, respectively. More circumscribed volume reductions of BA 9 also were reported in a medicated, euthymic pediatric BPD sample [23]. In a mixed BPD I and BPD II sample Lochhead and colleagues [24] reported reduced GM volume of the ACC immediately dorsal to the corpus callosum (CC).

In the hippocampus, at least half of the studies reported reductions in the volume of the whole hippocampus in MDD; in BPD, however, the volumetric reductions appear more specific to the anterior subiculum/ventral CA1 region

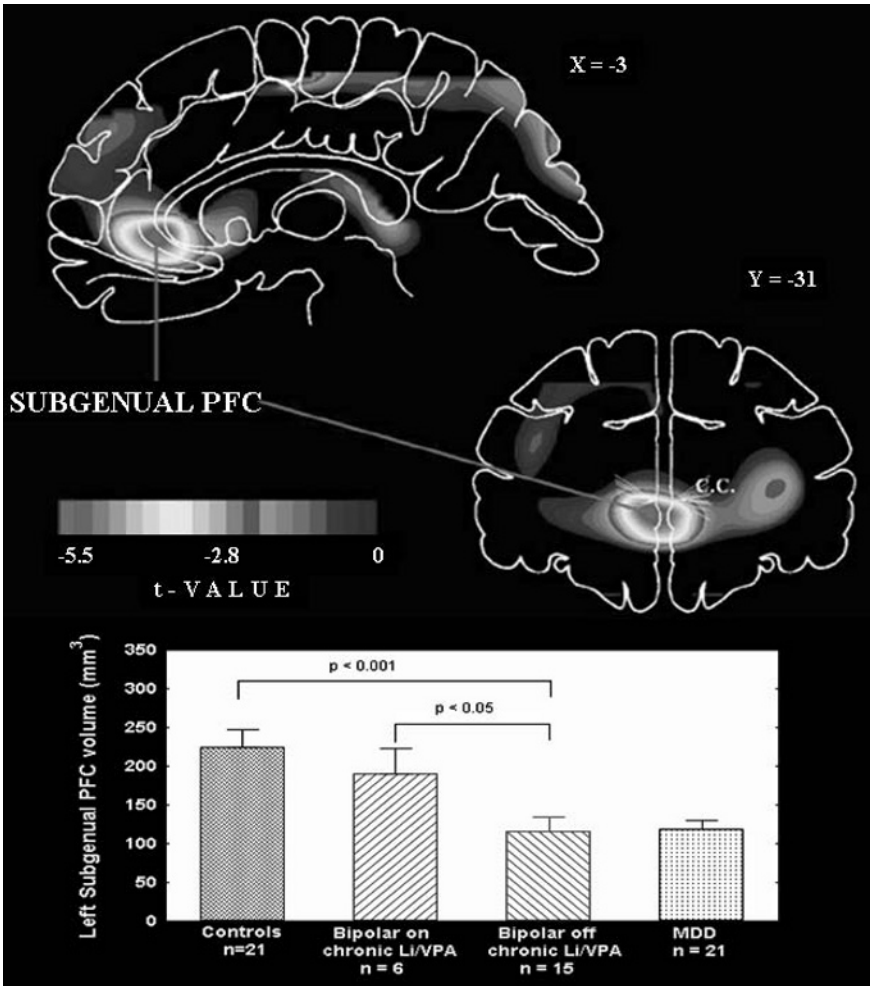


Figure 1. *Upper panel:* Coronal (31 mm anterior to the anterior commissure; y = 31) and sagittal (3 mm left of midline; x = –3) sections showing negative voxel t-values where glucose metabolism is decreased in depressives relative to controls. The reduction in activity in this prefrontal cortex (PFC) region located in the anterior cingulate gyrus ventral to the genu of the corpus callosum (i.e., subgenual) appeared to be accounted for by a corresponding reduction in cortex volume (Tab. 1; reproduced from [13]). Anterior or left is to left. *Lower Panel:* Although the PET data shown in the upper panel were obtained exclusively in unmedicated subjects, the volumetric MRI data from this study were obtained in a larger sample that included six cases who had been chronically receiving lithium or valproate prior to scanning. The bar histogram shows the mean subgenual ACC volumes in mm^3 for the healthy controls, individuals with MDD, unmedicated individuals with bipolar depression, and BPD subjects chronically medicated with lithium or valproate. Reproduced with permission from [17].

[10]. In contrast, the whole hippocampal volume was reported to be smaller in BPD subjects than controls in some studies, but not different from controls in most studies (reviewed in [21]). The reasons for this apparent difference in the

results between neuromorphometric studies of MDD *versus* BPD remain unclear. In MDD the reduction in hippocampal volume was limited to depressed women who suffered early-life trauma in some studies [25] and was correlated inversely with time spent depressed in other studies (e.g., [26]), but it remains unclear whether these relationships also extend to BPD.

One potential reason for the apparent discrepancies between MDD and BPD may be the neurotrophic/neuroprotective effects associated with mood stabilizing treatments. Animal studies demonstrate that lithium promotes hippocampal neurogenesis [27] and long-term potentiation (LTP) [28]. A sample of BPD patients treated for 4 weeks with lithium showed a 3% (24 cm^3) increase in whole brain gray matter volumes from baseline [29], an effect that appeared to result from the neurotrophic effect of the drug [30]. Four more recent studies [31–34] comparing lithium-treated and non-lithium treated groups demonstrated similar effects in large cortical areas, including the hippocampus. The phenomenon may not be restricted to lithium; comparable effects have been noted with other classes of mood stabilizers, especially valproate [35, 36]. In contrast, with the exception of the as yet rarely prescribed tianeptine [37–39], the neurotrophic properties of antidepressants are less persuasive (although see [40] and [41]).

Amygdala volume has been reported to be increased in some studies but decreased in others in individuals with MDD relative to controls [10]. In general these data suggest that the amygdala volume in patients with BPD shows an age-related dichotomy of findings. In adults, the predominant pattern is one of increased amygdala volume while in children and adolescents the reverse is true (reviewed in [21]). The findings in adults seem to hold even in samples with a long history of illness [22, 42, 43]. Parallels have been drawn with the temporal lobe epilepsy (TLE) literature, which suggests increased or preserved amygdala volume [44] despite the presence of hippocampal sclerosis in TLE patients with co-morbid affective illness [45–48].

In the basal ganglia (i.e., caudate, putamen, or globus pallidus) subjects with BPD generally have not shown morphometric differences relative to controls (reviewed in [21]). These data appear consistent with the reported absence of N-acetyl-aspartate (NAA) abnormalities in the basal ganglia of BPD samples [49–51]. Nevertheless, a *post mortem* study of a combined MDD and BPD sample reported volumetric reductions of the left accumbens, bilateral pallidum, and right putamen [52].

There has, however, been some suggestion of striatal enlargement in adult and pediatric samples with BPD (reviewed in [21]). As in the case of the hippocampus, these analyses may conceivably be confounded by treatment effects. Enlargement of basal ganglia structures is a well-known effect of antipsychotic drugs [53–56], and notably three of the studies reporting basal ganglia enlargement made use of partially manic samples treated with antipsychotic medication [57–59].

Enlargement of the third and lateral ventricles has commonly been observed in BPD (reviewed in [21]). Many studies reporting ventriculomegaly

included subjects with early age of onset. Nevertheless, the extent to which chronic alcohol abuse [60], incipient neurological disorders with prodromal depression, or cerebrovascular disease [61–63] (see ensuing section on white matter abnormalities) contributed to ventricular enlargement has not been established.

Neuromorphological MRI abnormalities in BPD: white matter pathology

In morphological MRI studies, an elevation in the incidence of white matter hyperintensities (WMH), especially in the deep frontal cortex and basal ganglia, commonly has been reported in BPD and in late-onset MDD samples [64–68]. Seen as high intensity signals on T2-weighted MRI scans, WMH are caused by circumscribed increases in water content, that putatively indicate a decrease in white matter density due to demyelination, atrophy of the neuropil, ischemia-associated microangiopathy, or other causes [69]. This phenomenon normally is prevalent in elderly, non-depressed populations [70], but shows an abnormally high prevalence in MDD cases with a late age of onset and in BPD samples of all ages.

The incidence of WMH may relate in part to cerebrovascular disease (reviewed in [71]). BPD is associated with a significantly increased prevalence of cardiovascular disease risk factors such as smoking, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia (reviewed in [72,73]). Hypertension [74, 75], obesity [76], smoking [77] and diabetes mellitus [78] have in turn been directly associated with the development of WMH. Although most published studies of BPD attempt to exclude patients with such potentially confounding conditions, the whole gamut of risk conditions is rarely controlled for, raising the possibility that WMH in BPD are an artifact of medical co-morbidity or some obscure ischemic risk factor. Moreover, drug abuse is prevalent in BPD populations and stimulant drug-induced vasoconstriction may lead to WMH [79, 80]. Notably, marijuana use also may interact in an additive fashion with WMH to predispose to depressive symptomatology [81]. In addition, Lenze and colleagues [82] and Nemeroff and colleagues [83] speculated that excess depression-associated secretion of serotonin by blood platelets [84, 85] facilitates platelet aggregation and thereby predisposes to thrombotic events and vasoconstriction. Finally, cerebrovascular reactivity, which describes the compensatory dilatory capacity of arterioles to dilatory stimuli, is reportedly reduced in acutely depressed patients without any neurological, cardiac, or vascular risk factors [86], raising the possibility that impaired regulation of vascular tone also plays a role in the pathogenesis of WMH in BPD.

Nevertheless, studies that attempted to match patients and controls for the presence of cardiovascular risk factors still find elevated rates of WMH in their depressed samples (reviewed in [21]). Moreover, the hypothesis that WMH reflect cerebrovascular disease fails to account for the white matter pathology

noted in pediatric BPD samples [87–89] as well as the high concentration of WMH in both BPD subjects and their unaffected relatives [90]. A significant minority of young BPD patients with a relatively typical age-of-onset show white matter abnormalities on MRI scans (reviewed in [21]). Thus, while a proportion of adults with BPD with significant white matter pathology will present with risk factors for cerebrovascular disease, WMH may also less commonly arise in pediatric or young adult BPD samples due to developmental insults or via some as yet unknown pathophysiological mechanism.

Obstetric complications are well known to be associated with schizophrenia [91], but with a few exceptions [92, 93], appear less salient in BPD. Nevertheless, it is possible that perinatal hypoxic events precipitate BPD in a vulnerable minority [94].

Another possible explanation for demyelination as evidenced by WMH in BPD may be changes in oligodendrocyte function. *Post mortem* studies have reported a down-regulation of oligodendrocyte-related gene expression of genes impacting myelin or oligodendrocyte function and decreased oligodendrocyte density in both BPD and MDD [95–100]. As reviewed in [101–103] variants of some of these genes such as oligodendrocyte lineage transcription factor 2 (*OLIG2*) [NCBI accession number 10215], Neuregulin 1 (*NRG1*) [3084], and v-erb-a erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*) [2066] have been directly associated with mood disorders and may determine how resilient these cells are to environmental stressors. White matter is decreased in the genu of the corpus callosum in both adults with BPD or MDD and their high-risk child and adolescent offspring (particularly in females), and is also decreased in the splenium of the corpus callosum in adults with BPD or MDD. Finally, the high incidence of familial WMH seen in the Ahearn and colleagues [90] sample supports a role for genetic factors, and suggests that genetic variance in genes related to oligodendrocyte function may contribute to the development of WMH in BPD.

An unresolved issue is whether the relationship between white matter pathology and mood disorders is one of cause or effect. Certainly, new cases of BPD may be precipitated by subcortical infarcts [104]. Moreover, depressive and bipolar syndromes are relatively common sequelae of the genetic disorder cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [105, 106]. The deep frontal white matter pathology commonly seen in mood disorders conceivably may result in a disruption of the pathways linking subcortical regions such as the striatum to functionally homologous regions of the PFC, giving rise to dysregulation of emotional behavior in BPD [107–109].

Neurophysiological imaging in bipolar depression

Many regions where structural abnormalities are apparent in mood disorders also contain abnormalities of cerebral blood flow (CBF) and glucose metabo-

lism (Tab. 1; Fig. 1). In most of these structures, and particularly those that form the extended visceromotor network, the basal activity appears abnormally increased during the depressed phase of BPD. In MDD this pattern of differences also has been demonstrated in cross-sectional studies of depressed MDD subjects relative to controls, longitudinal studies of patients imaged before *versus* after treatment (e.g., [8], and challenge studies of remitted patients scanned before *versus* during depressive relapse (e.g., [110, 111]).

Nevertheless, the reduction in gray matter volume in some structures is sufficiently prominent to produce partial volume effects in functional brain images due to their relatively low spatial resolution, yielding complex relationships between physiological measures and depression severity. For example, relative to controls, depressed BPD and MDD subjects show metabolic activity that appears *reduced* in the sgACC [13, 112]. However, when this volumetric deficit is taken into account by correcting the metabolic data for the partial volume averaging effect associated with the corresponding gray matter reduction (which range in magnitude from ~20% to ~50% across studies of MDD and BPD), metabolism instead appears *increased* in the sgACC in the unmedicated-depressed phase and normal in the medicated-remitted phase [7]. Consistent with these data, activity is decreased in the remitted *versus* the depressed phase of mood disorders in the sgACC, as assessed following effective treatment [8, 9, 113, 114]. Conversely, metabolic activity is increased in the sgACC in remitted MDD cases during depressive relapse induced by tryptophan depletion or catecholamine depletion [110, 111]. The volumetric reductions in the OFC and VLPFC may also contribute to the complexity of relationships observed between metabolism and illness severity, as metabolism appears elevated in depressed samples of mild-to-moderate severity, but reduced in more severe, treatment-refractory cases (reviewed in [115]).

Although the pattern of activity in the extended visceromotor network generally is one in which metabolism is elevated during the depressed *versus* the remitted phases, the relationship between activity and symptom severity differs in valence across some structures, compatible with preclinical evidence that distinct structures are involved in opponent processes with respect to emotion modulation [116]. Regions where metabolism correlates positively with depression severity include the amygdala, sgACC, and ventromedial frontal polar cortex [7, 111]. Metabolism and flow decrease in these regions during effective treatment [8, 9]. Conversely, in recovered MDD cases who experience depressive relapse under serotonin or catecholamine depletion, metabolic activity generally increases in these regions as depressive symptoms return [110, 111, 117], although such studies have not been extended to BPD.

In the amygdala, abnormal elevations of resting metabolism can be seen in depressed samples categorized as having BPD, familial pure depressive disease (FPDD), MDD-melancholic type, or MDD that responds to a night of total sleep deprivation (reviewed in [118]). In such cases amygdala metabolism decreases toward normative levels during effective antidepressant treat-

ment [8]. In BPD these findings of increased baseline amygdalar activity have largely been limited to adults [119–123], in whom resting activity has correlated positively with severity of depression [119]. Furthermore, increased hemodynamic responses of the amygdala to negatively valenced faces have been reported in BPD subjects relative to healthy controls [124–127].

In the accumbens, medial thalamus, and posterior cingulate cortex the metabolism is abnormally elevated in the depressed phase of MDD and BPD [10, 121,123]. In the OFC, Blumberg and colleagues [128] showed that manic patients have reduced rCBF, while induction of a sad mood through psychological means resulted in decreased rCBF to the medial OFC in euthymic but not depressed BPD subjects *versus* controls [129]. Finally, reductions in metabolism and in the hemodynamic responses to various cognitive-behavioral tasks have been reported in dorsolateral PFC regions located outside the OMPFC (reviewed in [3]).

Implications for treatment mechanisms

Elevated glutamatergic function is thought to support the neurophysiological activation of visceromotor networks in depression. The anatomical projections between the OMPFC, striatum, and amygdala implicated in mood disorders are formed by predominantly excitatory projections [4]. Because cerebral glucose metabolism largely reflects the energy requirements associated with glutamatergic transmission [130], the elevated metabolism evident in limbic-thalamo-cortical circuits in depression implies that glutamatergic transmission is increased in these circuits [131]. Compatible with this hypothesis, *post mortem* studies of the NMDA receptor complex in suicide victims found evidence suggesting that glutamatergic transmission had been increased in the PFC *antemortem*, and implicated disturbances in glutamate metabolism, NMDA, and mGluR1,5 receptors in depression and suicide [132].

Notably, antidepressant and mood stabilizing drugs that have diverse primary pharmacological actions are hypothesized to have a final common pathway of reducing NMDA receptor sensitivity and/or transmission, and many of these agents also increase GABA levels or transmission [132, 133]. Compatible with these data, during effective antidepressant drug or electroconvulsive therapy, glucose metabolic activity decreases in the regions of the extended visceromotor network (Tab. 1; reviewed in [10, 121]), which would be expected if treatment-induced NMDA receptor desensitization resulted in reduced glutamatergic transmission [132]. As described in the ensuing sections, elevated glutamatergic transmission within discrete anatomical circuits may partly explain the targeted nature of grey matter changes within mood disorders (e.g., affecting left more than right sgACC) [7, 134], so one important mechanism of effective treatment in bipolar depression may involve the reduction of excessive excitatory transmission mediated via NMDA receptor stimulation [134].

Neuropathological correlations in mood disorders

Most regions where MRI studies demonstrated volumetric abnormalities in BPD also have been shown to contain histopathological changes or grey matter volumetric reductions in *post mortem* studies of MDD and BPD. For example, reductions of grey matter volume, thickness, or wet weight have been reported in the subgenual ACC, posterolateral orbital cortex, and ventral striatum in MDD and/or BPD subjects relative to controls [52, 135–137]. The histopathological correlates of these abnormalities included reductions in glial cells with no equivalent loss of neurons, reductions in synapses or synaptic proteins, elevations in neuronal density, and reductions in neuronal size in MDD and/or BPD samples [99, 136, 138, 139]. Reductions in glial cell counts and density, and/or glia-to-neuron ratios additionally were found in MDD subjects *versus* controls in the pregenual ACC (pgACC [BA24]) [140], the dorsal anterolateral PFC (BA9) [97, 99], and the amygdala [98, 141]. Finally, the density of non-pyramidal neurons was decreased in the ACC and hippocampus in BPD [142, 143], and in the dorsal anterolateral PFC (BA9) of MDD [139]. Reductions in synapses and synaptic proteins were evident in BPD subjects in the hippocampal subiculum/ventral CA1 region [138, 144].

The glial type that specifically differed between mood disordered and control samples in many of these studies was the oligodendrocyte (e.g., [98, 99]). Oligodendroglia are best characterized for their role in myelination, and the reduction in oligodendrocytes may conceivably arise secondary to an effect on myelin, either through demyelination, abnormal development, or atrophy in the number of myelinated axons. Notably, myelin basic protein concentration was found to be decreased in the frontal polar cortex (BA 10) [145], and the expression of genes related to oligodendrocyte function (i.e., genes that encoded structural components of myelin, enzymes involved in the synthesis of myelin constituents or in the regulation of myelin formation, transcription factors regulating other myelination-related genes, or factors involved in oligodendrocyte differentiation) was decreased in the middle temporal gyrus in MDD subjects relative to controls [96].

Compatible with these data, myelin staining was decreased in the deep white matter of the dorsolateral PFC in MDD and BPD subjects [146], and the white matter volume of the genual and splenial portions of the corpus callosum were abnormally reduced in MDD and BPD (e.g., [147]). These regions of the corpus callosum were also smaller in child and adolescent offspring of women with MDD who had not yet developed a mood disorder, relative to age-matched controls, suggesting that the reduction in white matter in MDD reflects a developmental defect that exists prior to illness onset [148].

Finally, satellite oligodendrocytes were also implicated in the pathophysiology of mood disorders by an electron microscopic study of the PFC in BPD, which revealed decreased nuclear size, clumping of chromatin, and other types of damage to satellite oligodendrocytes, including indications of both apoptotic and necrotic degeneration [100, 149]. Satellite oligodendrocytes are

immunohistochemically reactive for glutamine synthetase, suggesting that they function like astrocytes to take up synaptically released glutamate for conversion to glutamine and cycling back into neurons [150].

In other brain regions, reductions in astroglia have been reported by *post mortem* studies of mood disorders. In the frontal cortex one study found that four forms of the astrocytic product glial fibrillary acidic protein (GFAP) were decreased in mood disordered subjects relative to controls, although it was not determined whether this decrement reflected a reduction in astrocyte density or GFAP expression [151]. However, another study that used immunohistochemical staining for GFAP did not find significant differences in cortical astrocytes between controls and MDD or BPD cases [152]. Other studies also did not find differences in GFAP between mood disorder cases and controls (reviewed in [153]).

Factors that may conceivably contribute to a loss of oligodendroglia in mood disorders include elevated glucocorticoid secretion and glutamatergic transmission evident during depression and mania. Glucocorticoids affect both glia and neurons [154] and elevated glucocorticoid concentrations and repeated stress decrease the proliferation of oligodendrocyte precursors [155, 156]. Moreover, oligodendrocytes express AMPA and kainate type glutamate receptors, and are sensitive to excitotoxic damage from excess glutamate (reviewed in [98]). The targeted nature of the reductions in grey matter volume and glial cells to specific areas of the limbic-cortical circuits that show increased glucose metabolism during depressive episodes is noteworthy given the evidence reviewed below that the glucose metabolic signal is dominated by glutamatergic transmission.

Correlations with rodent models of chronic and repeated stress

In regions that appear homologous to the areas where grey matter reductions are evident in humans with BPD (i.e., medial PFC, hippocampus), repeated stress results in dendritic atrophy and reductions in glial cell counts or proliferation in rodents [134, 156–159]. In contrast, in the basolateral amygdala (BLA), chronic, unpredictable stress also produced dendritic atrophy, but chronic immobilization stress instead *increased* dendritic branching [160, 161].

Dendritic atrophy would be reflected by a decrease in the volume of the neuropil, which occupies most of the grey matter volume. The similarities between the histopathogical changes that accompany stress-induced dendritic atrophy in rats and those found in humans suffering from depression thus led to hypotheses that homologous processes underlie the reductions in grey matter volume in hippocampal and PFC structures in MDD and BPD [134]. In rats the stress-induced dendritic atrophy in the medial PFC was associated with impaired modulation (i.e., extinction) of behavioral responses to fear-conditioned stimuli [162, 163]. Notably, healthy humans with thinner ventromedial

PFC tissue also show a greater galvanic skin response to conditioned stimuli during extinction learning [164]. Finally, when rats were subjected to repeated stress beyond 4 weeks, the dendritic atrophy could be reversed by lithium [134], resembling the effects on sgACC volume in depressed humans.

In rodent stress models, these dendritic reshaping processes depend on interactions between increased N-methyl-D-aspartate (NMDA) receptor stimulation and glucocorticoid secretion associated with repeated stress [134, 158]. Elevations of glutamate transmission and cortisol secretion in mood disorders also may contribute to reductions in gray matter volume and synaptic markers by inducing dendritic atrophy in some brain structures, as the depressive subtypes (e.g., BPD, FPDD) who show regional reductions in grey matter volume also show evidence of cortisol hypersecretion (reviewed in [8]) and increased glutamate transmission. Subjects with familial BPD also show elevations of glucose metabolism, which largely reflect glutamate transmission (see above), in the medial and orbital PFC, amygdala, and cingulate cortex regions that show reductions in grey matter volume and cellular elements. The findings that grey matter reductions appear to occur specifically in regions that show hypermetabolism during BPD thus raise the possibility that excitatory amino acid transmission plays a role in the neuropathology of BPD.

Neuroreceptor imaging in bipolar depression

Of the neurochemical systems that modulate neural transmission within the visceromotor network, mood disorders have been associated with abnormalities of serotonergic, dopaminergic, noradrenergic, cholinergic, glutamatergic, GABA-ergic, glucocorticoid, and peptidergic (e.g., corticotrophin releasing factor (CRF)) function. Some receptors of the monoaminergic neurotransmitter systems have been imaged in BPD using PET or SPECT and radioligands.

Serotonergic system

The central serotonin (5-HT) system has received particular interest in depression research because selective serotonin reuptake inhibitors (SSRIs) exert antidepressant effects, and most other antidepressant drugs also increase serotonin (especially post-synaptic 5-HT_{1A} receptor) transmission [165]. This effect of antidepressant drugs may augment an endogenous elevation of serotonin release during the stress of depression, analogous to the enhanced serotonergic transmission that occurs in some brain regions during stress in rodents (reviewed in [166, 167]). Enhancement of serotonin transmission in MDD also may compensate for abnormalities in density and sensitivity of some serotonin receptor subtypes evidenced by *post mortem*, neuroimaging, and pharmacological challenge studies of depression [165, 168]. For example, *postsynaptic* 5-HT_{1A} receptor binding or mRNA expression is decreased in the insula, cin-

gulate, parieto-occipital, and orbital/ventrolateral prefrontal cortices in some neuroimaging studies of MDD and BPD (reviewed in [165]).

It remains unclear whether the reduction in 5-HT_{1A} receptor function and expression in mood disorders constitutes a neurodevelopmental or an acquired abnormality. This issue is of interest because interruption of 5-HT_{1A} receptor function during neurodevelopment persistently alters the function of emotion-modulating systems in genetically engineered mice [169]. Nevertheless, the reduction in 5-HT_{1A} receptor binding and mRNA expression in depression may arise secondarily to cortisol hypersecretion [170], as 5-HT_{1A} receptor mRNA expression and density are tonically inhibited by glucocorticoid receptor stimulation. In experimental animals the elevated CORT secretion during chronic or repeated stress results in reduced 5-HT_{1A} receptor density and mRNA expression [170, 171]. Moreover, the mood disordered subgroups with reduced 5-HT_{1A} receptor binding may be limited to those with a diathesis to hypersecrete cortisol (e.g., [165, 170, 172]).

Altered serotonin transporter (5-HTT) function is also thought to play a role in the pathophysiology of mood disorders (reviewed in [168, 173]). For example, depressed BPD subjects showed elevated 5-HTT binding in the striatum, thalamus, and insula, as well as reduced binding in the vicinity of the pontine raphe [166, 173] (Fig. 3). PET studies performed using 5-HTT radioligands with high selectivity for 5-HTT sites, such as [^{11}C]DASB, similarly reported abnormally increased 5-HTT binding in the striatum, thalamus, insula, and ACC of individuals with early-onset MDD and/or those MDD patients with negativistic attitudes; however, the reduction in 5HTT binding in the pontine raphe found in individuals with bipolar depression did not extend to MDD cases [166]. Finally, genetic polymorphisms involving 5-HTT regulatory sites reportedly increase the vulnerability for developing BPD as well as MDD (reviewed in [166]).

Dopamine receptor imaging

Neuroimaging studies have discovered abnormalities involving multiple aspects of the central dopaminergic system in depression, which converge with other types of evidence to implicate this system in the pathophysiology of mood disorders. However, few of these studies specifically assessed bipolar depression. With respect to dopamine D1 receptors, Suhara and colleagues [174] reported that binding of [^{11}C]SCH-23990 was decreased in the frontal cortex of BPD subjects studied in various illness phases, a finding that awaits replication using more selective D_1 receptor ligands. In addition, Pearlson and colleagues [175] showed that *psychotic* individuals with BPD had increased striatal uptake of the dopamine D2/D3 receptor ligand [^{11}C]- N-methylspiperone relative to healthy controls and non-psychotic individuals with BPD, but that the non-psychotic BPD cases did not differ from healthy controls. Similarly, a SPECT-[^{123}I]IBZM study found no difference in striatal dopamine

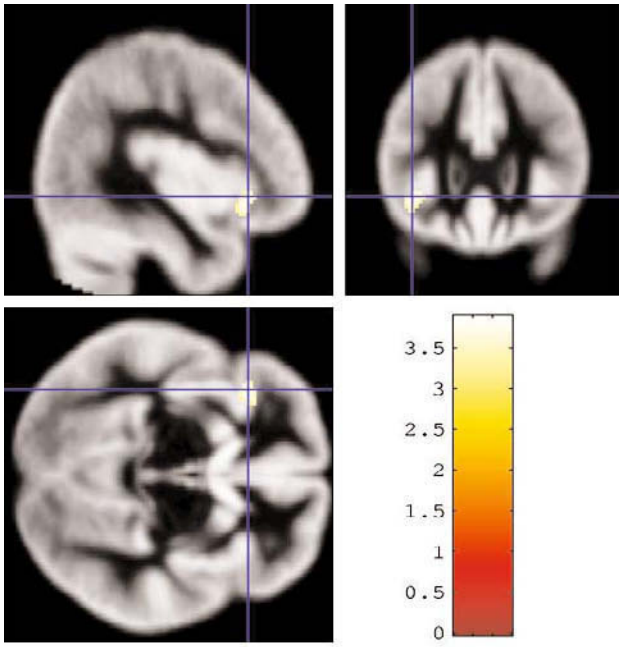


Figure 2. Lateral orbitofrontal cortical area (approximately sulcal BA 47 l/47 s) [4] where peak effect size of grey matter reduction was located in BPD. The image sections shown are from a voxel-based morphometric analysis that compared MRI measures of grey matter volume between depressed subjects with BPD and healthy controls. Anterior or left is to left. Reproduced with permission from [19].

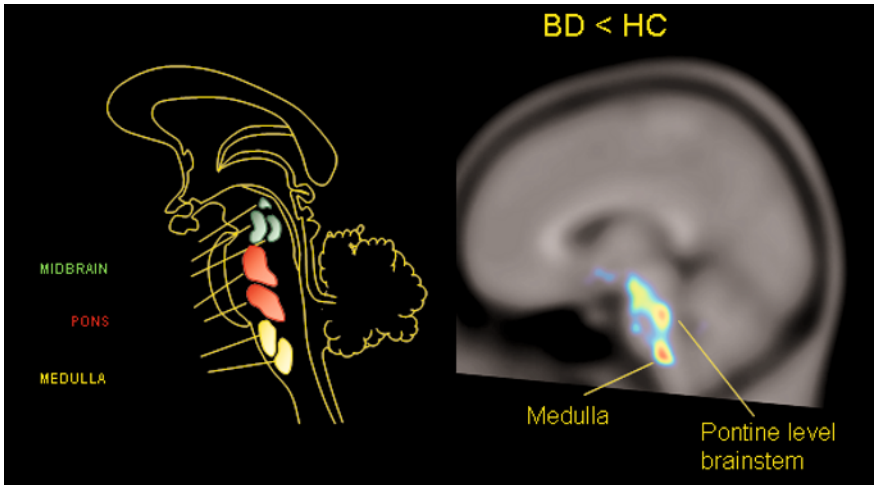


Figure 3. Serotonin transporter binding is reduced in bipolar depression. This section from a voxel-wise analysis of [^{11}C]DASB parametric binding potential images shows regions where individuals with BPD have reduced serotonin transporter (5-HTT) binding relative to controls at $p < 0.05$ (right panel), together with a schematic illustration showing approximate locations of the raphe-nuclei within the brainstem (left panel; after [190]). Reproduced with permission from [173].

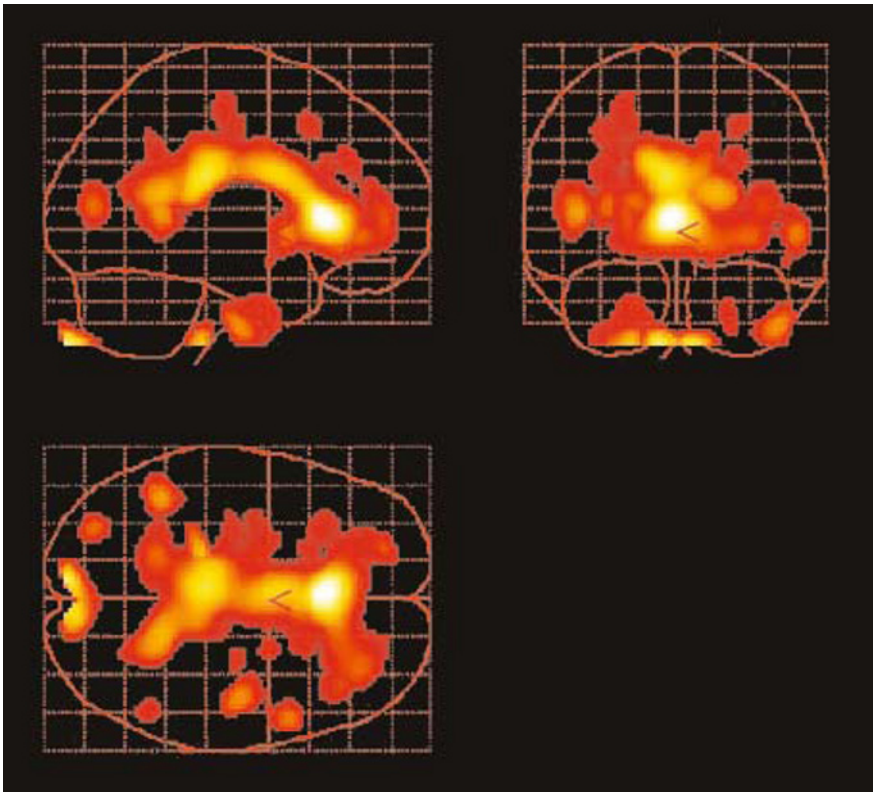


Figure 4. Reduced muscarinic type 2 (M2) receptor binding in the cingulate cortex in individuals with bipolar depression relative to healthy controls. The statistical parametric map shows voxel t-values corresponding to areas where the uptake of [^{18}F]FP-TZTP, a PET radioligand that selectively binds M2 receptors, was significantly reduced (at $p < 0.005$) in individuals with bipolar depression relative to healthy controls. The areas of maximal difference between groups were located in the anterior cingulate cortex. Reproduced from [180].

D2/D3 receptor binding at baseline, and no difference in the change in [^{123}I]IBZM binding under amphetamine challenge between medicated, euthymic BPD patients and healthy controls [176].

Cholinergic system

The cholinergic system is also implicated in the pathophysiology of mood disorders, with evidence indicating that the muscarinic cholinergic system is overactive or hyper-responsive in depression. Janowsky and colleagues [177] reported that increasing cholinergic activity using the acetylcholine-esterase inhibitor physostigmine, resulted in the rapid induction of depressive symptoms in currently manic BPD subjects, and in a worsening of symptoms in

individuals with MDD. The administration of the M_2R antagonist, procaine, elicits emotional responses in humans ranging from sadness, fear, and severe anxiety to euphoria, and results in increased physiological activity of the cingulate cortex [178, 179], a region densely innervated by cholinergic projections. Moreover, in individuals with bipolar depression, decreased M_2R binding has been reported in the cingulate cortex [180] (Fig. 4). Multiple M_2R gene polymorphisms are associated with increased risk for developing major depressive episodes (reviewed in [180]), but thus far these SNPs have not been associated with BPD. Finally, the muscarinic cholinergic receptor antagonist, scopolamine, exerts rapid and robust antidepressant effects in depressed MDD and BPD patients, although the ~24 h delay in onset of these effects raises the possibility that a secondary mechanism of action underlies the antidepressant response [181].

Implications for neurocircuitry models of depression

The neuropathological, neurochemical, and neurophysiological abnormalities extant within the extended visceromotor network may impair this network's modulation of autonomic, endocrine, neurotransmitter, emotional, and behavioral responses to aversive and reward-related stimuli or contexts [4], potentially accounting for the disturbances within these domains seen in BPD (Fig. 5). The neuroimaging abnormalities in the VLPFC, OFC, sgACC, pgACC, amygdala, ventral striatum, and medial thalamus evident in BPD implicate a limbic-thalamo-cortical circuit involving the amygdala, the mediodorsal nucleus of the thalamus (MD), and the OMPFC, and a limbic-striatal-pallidal-thalamic circuit involving related parts of the striatum and ventral pallidum along with the components of the other circuit [131].

The first of these circuits can be conceptualized as an excitatory triangular circuit (Fig. 5) whereby the BLA and the OMPFC are interconnected by excitatory (especially glutamatergic) projections with each other and with the MD [7], so increased glucose metabolism in these structures would presumably reflect increased synaptic transmission through the limbic-thalamo-cortical circuit. The limbic-striatal-pallidal-thalamic circuit constitutes a disinhibitory side loop between the amygdala or PFC and the MD. The amygdala and the PFC send excitatory projections to overlapping parts of the ventromedial striatum [182]. This part of the striatum sends an inhibitory projection to the ventral pallidum which in turn sends GABA-ergic, inhibitory fibers to the MD (reviewed in [131]). Because the pallidal neurons have relatively high spontaneous firing rates, activity in the PFC or amygdala that activates the striatum and in turn activates the ventral pallidum may release the MD from the inhibitory pallidal influence, potentially disinhibiting transmission through the limbic-thalamo-cortical circuitry (reviewed in [131]). Notably, repeated stress results in hyperexcitability in the BLA in rodents [183], although whether the mechanisms underlying these changes involve changes

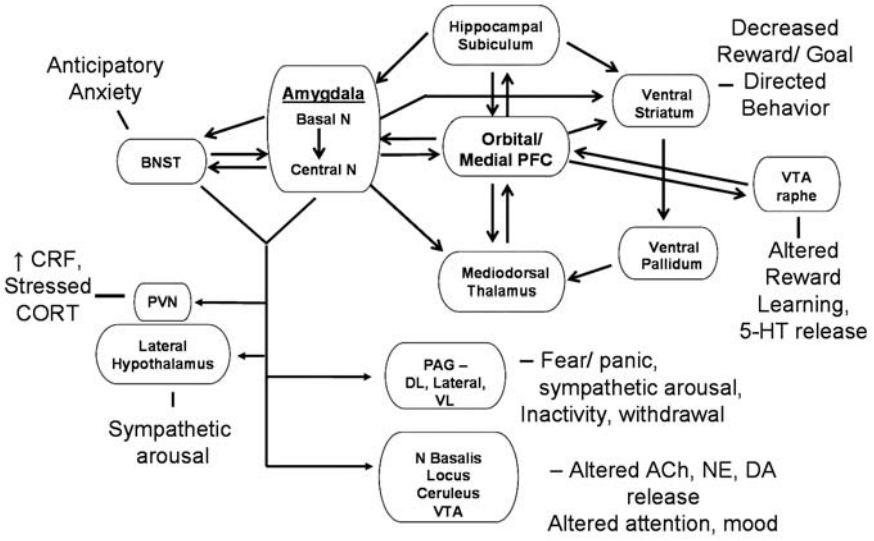


Figure 5. Anatomical circuits involving the orbitomedial PFC (OMPFC) and amygdala reviewed within the context of a model in which OMPFC dysfunction results in disinhibition of limbic transmission through the amygdala, yielding the emotional, cognitive, endocrine, autonomic, and neurochemical manifestations of depression. The basolateral amygdala sends efferent projections to the central nucleus of the amygdala (ACe) and the bed nucleus of the stria terminalis (BNST). The efferent projections from these structures to the hypothalamus, periaqueductal grey (PAG), nucleus basalis, locus coeruleus, raphe, and other diencencephalic and brainstem nuclei then organize the neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli [184, 185]. The OMPFC shares reciprocal projections with all of these structures (although only the connections with the amygdala are illustrated), which function to modulate each component of emotional expression [4]. Impaired OMPFC function thus may disinhibit or dysregulate limbic outflow through the ACe and BNST. Solid white lines indicate some of the major anatomical connections between structures, with closed arrowheads indicating the direction of projecting axons. Solid yellow lines show efferent pathways of the ACe and BNST, which are generally monosynaptic, but in some cases are bisynaptic connections (e.g., [189]). Other abbreviations: 5-HT – serotonin; ACh – acetylcholine; DA – dopamine; DL – dorsolateral column of PAG; N – nucleus, NE – norepinephrine; NTS – nucleus tractus solitarius; PVN – paraventricular N of the hypothalamus; VL – ventrolateral column of PAG; VTA – ventral tegmental area. Reproduced with permission from [188].

in afferent modulation of the amygdala or alterations in synaptic plasticity remains unclear.

The BLA sends anatomical projections to the central nucleus of the amygdala (ACe) and the BNST, and projections from these structures to the hypothalamus, PAG, locus coeruleus, raphe, nucleus basalis, and other diencencephalic and brainstem nuclei play major roles in organizing neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli [184, 185]. The OMPFC sends overlapping projections to each of these structures and to the amygdala that function to modulate each component of emotional expression [186]. The neuropathological changes evident in the OMPFC in BPD and mood disorders arising secondary to neurological

disorders thus may impair the modulatory role of the OMPFC over emotional expression, disinhibiting, or dysregulating limbic responses to stressors and emotional stimuli (reviewed in [7]). These data suggest that during depressive episodes the increased activity seen within some OMPFC areas reflects a compensatory response that modulates depressive symptoms, and impaired function of these regions (possibly due to the neuropathological changes in BPD) may result in more severe and treatment-refractory illness.

Summary

Convergent results from studies conducted using neuroimaging, lesion analysis and *post mortem* techniques support models in which the signs of BPD emanate from dysfunction within an extended visceromotor network that interferes with this system's modulation of emotional behavior. Mood stabilizing and antidepressant therapies may compensate for this dysfunction by attenuating the pathological limbic activity that putatively mediates depressive symptoms [8] and increasing expression of neurotrophic/neuroprotective factors that preserve the function of the OMPFC [187].

References

1 The World Health Organization (WHO) (2001) *The World Health Report 2001*. Geneva, Switzerland
2 Kessler RC, Chiu WT, Demler O, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 62: 617–627
3 Phillips ML, Drevets WC, Rauch SL, Lane R (2003) Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54: 515–528
4 Ongur D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 460: 425–449
5 Nauta WJH, Domesick V (1984) Afferent and efferent relationships of the basal ganglia. In: D Evered, M O'Conner (eds): *Function of the basal ganglia*. Pitman Press, London
6 Folstein MF, Robinson R, Folstein S, McHugh PR (1985) Depression and neurological disorders. New treatment opportunities for elderly depressed patients. *J Affect Disord* Suppl 1: S11–14
7 Drevets WC, Price JL (2005) Neuroimaging and neuropathological studies of mood disorders. In: JWM Licinio (ed.): *Biology of depression: from novel insights to therapeutic strategies*. Wiley-VCH Verlag GmbH & Co., Weinheim, Germany, 427–466
8 Drevets WC, Bogers W, Raichle ME (2002) Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12: 527–544
9 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. *Neuron* 45: 651–660
10 Drevets WC, Gadde K, Krishnan KRR (2004) Neuroimaging studies of depression. In: DS Charney, BJ Bunney (eds): *The neurobiological foundation of mental illness: Second Edition*. Oxford University Press, New York, 461–490
11 Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD (2002) Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry* 51: 342–344
12 Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC (2005) Subgenual prefrontal cortex

volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am J Psychiatry* 162: 1706–1712
13 Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386: 824–847
14 Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, Yurgelun-Todd D, Zarate C, Kikinis R, Jolesz FA et al (1999) Subgenual cingulate cortex volume in first-episode psychosis. *Am J Psychiatry* 156: 1091–1093
15 Haznedar MM, Roversi F, Pallanti S, Baldini-Rossi N, Schnur DB, Licalzi EM, Tang C, Hof PR, Hollander E, Buchsbaum MS (2005) Fronto-thalamo-striatal gray and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. *Biol Psychiatry* 57: 733–742
16 Lyoo IK, Kim MJ, Stoll AL, Demopulos CM, Parow AM, Dager SR, Friedman SD, Dunner DL, Renshaw PF (2004) Frontal lobe gray matter density decreases in bipolar I disorder. *Biol Psychiatry* 55: 648–651
17 Drevets WC, Savitz J (2008) Mood disorders and the subgenual anterior cingulate cortex. *CNS Spectr* 13: 663–681
18 Drevets WC, Todd RD (2005) Depression, mania and related disorders. In: E Rubin, C Zorumski (eds): *Adult psychiatry, Second Ed.* Blackwell Publishing, Oxford, 91–129
19 Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, Zarate CA, Pine DS, Price JL, Drevets WC (2006) Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *Neuroimage* 30: 485–497
20 Cecil KM, DelBello MP, Morey R, Strakowski SM (2002) Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. *Bipolar Disord* 4: 357–365
21 Savitz J, Drevets WC. Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev*; *in press*
22 Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH (2005) The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. *Biol Psychiatry* 58: 859–864
23 Dickstein DP, Milham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, Leibenluft E (2005) Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. *Arch Gen Psychiatry* 62: 734–741
24 Lochhead RA, Parsey RV, Oquendo MA, Mann JJ (2004) Regional brain gray matter volume differences in patients with bipolar disorder as assessed by optimized voxel-based morphometry. *Biol Psychiatry* 55: 1154–1162
25 Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS et al (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 159: 2072–2080
26 Sheline YI, Gado MH, Kraemer HC (2003) Untreated depression and hippocampal volume loss. *Am J Psychiatry* 160: 1516–1518
27 Kim JS, Chang MY, Yu IT, Kim JH, Lee SH, Lee YS, Son H (2004) Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both *in vitro* and *in vivo*. *J Neurochem* 89: 324–336
28 Son H, Yu IT, Hwang SJ, Kim JS, Lee SH, Lee YS, Kaang BK (2003) Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. *J Neurochem* 85: 872–881
29 Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000) Lithium-induced increase in human brain grey matter. *Lancet* 356: 1241–1242
30 Manji HK, Moore GJ, Chen G (2000) Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 48: 740–754
31 Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, Trakhtenbroit M, Glahn DC, Brambilla P, Sassi RB et al (2007) Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol Psychiatry* 62: 7–16
32 Beyer JL, Kuchibhatla M, Payne ME, Moo-Young M, Cassidy F, Macfall J, Krishnan KR (2004) Hippocampal volume measurement in older adults with bipolar disorder. *Am J Geriatr Psychiatry* 12: 613–620
33 Sassi RB, Brambilla P, Hatch JP, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2004) Reduced left anterior cingulate volumes in untreated bipolar patients. *Biol Psychiatry* 56: 467–475

34 Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT, Macqueen GM (2008) Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology* 33: 361–367
35 Hao Y, Creson T, Zhang L, Li P, Du F, Yuan P, Gould TD, Manji HK, Chen G (2004) Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis. *J Neurosci* 24: 6590–6599
36 Mark RJ, Ashford JW, Goodman Y, Mattson MP (1995) Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca^{2+} deregulation, and cytoskeletal pathology. *Neurobiol Aging* 16: 187–198
37 McEwen BS, Magarinos AM, Reagan LP (2002) Structural plasticity and tianeptine: cellular and molecular targets. *Eur Psychiatry* 17 Suppl 3: 318–330
38 McEwen BS, Olie JP (2005) Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol Psychiatry* 10: 525–537
39 Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS (1992) Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol* 222: 157–162
40 Stewart CA, Reid IC (2000) Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. *Psychopharmacology (Berl)* 148: 217–223
41 Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59: 1116–1127
42 Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, Wilkins J, Gerner R, Mintz J (2000) An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biol Psychiatry* 48: 147–162
43 Brambilla P, Harenski K, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2003) MRI investigation of temporal lobe structures in bipolar patients. *J Psychiatr Res* 37: 287–295
44 Krishnamoorthy ES (2007) A differential role for the hippocampus and amygdala in neuropsychiatric disorders. *J Neurol Neurosurg Psychiatry* 78: 1165–1166
45 Tebartz Van Elst L, Baeumer D, Lemieux L, Woermann FG, Koepp M, Krishnamoorthy S, Thompson PJ, Ebert D, Trimble MR (2002) Amygdala pathology in psychosis of epilepsy: A magnetic resonance imaging study in patients with temporal lobe epilepsy. *Brain* 125: 140–149
46 Baxendale SA, Thompson PJ, Duncan JS (2005) Epilepsy & depression: the effects of comorbidity on hippocampal volume – a pilot study. *Seizure* 14: 435–438
47 Briellmann RS, Hopwood MJ, Jackson GD (2007) Major depression in temporal lobe epilepsy with hippocampal sclerosis: clinical and imaging correlates. *J Neurol Neurosurg Psychiatry* 78: 1226–1230
48 Richardson EJ, Griffith HR, Martin RC, Paige AL, Stewart CC, Jones J, Hermann BP, Seidenberg M (2007) Structural and functional neuroimaging correlates of depression in temporal lobe epilepsy. *Epilepsy Behav* 10: 242–249
49 Kato T, Hamakawa H, Shioiri T, Murashita J, Takahashi Y, Takahashi S, Inubushi T (1996) Choline-containing compounds detected by proton magnetic resonance spectroscopy in the basal ganglia in bipolar disorder. *J Psychiatry Neurosci* 21: 248–254
50 Hamakawa H, Kato T, Murashita J, Kato N (1998) Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. *Eur Arch Psychiatry Clin Neurosci* 248: 53–58
51 Ohara K, Isoda H, Suzuki Y, Takehara Y, Ochiai M, Takeda H, Igarashi Y, Ohara K (1998) Proton magnetic resonance spectroscopy of the lenticular nuclei in bipolar I affective disorder. *Psychiatry Res* 84: 55–60
52 Baumann B, Danos P, Krell D, Diekmann S, Leschinger A, Stauch R, Wurthmann C, Bernstein HG, Bogerts B (1999) Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a postmortem study. *J Neuropsychiatry Clin Neurosci* 11: 71–78
53 Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL (1991) Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 48: 881–890
54 Swayze VW, Andreasen NC, Alliger RJ, Yuh WT, Ehrhartdt JC (1992) Subcortical and temporal lobe structures in affective disorder and schizophrenia: A magnetic resonance imaging study. *Biol Psychiatry* 31: 221–240
55 Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M (1995) Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 345: 456–457
56 Frazier JA, Giedd JN, Kaysen D, Albus K, Hamburger S, Alaghband-Rad J, Lenane MC,

McKenna K, Breier A, Rapoport JL (1996) Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 153: 564–566
57 Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, Shear P, Adler CM (2002) Ventricular and periventricular structural volumes in first- *versus* multiple-episode bipolar disorder. *Am J Psychiatry* 159: 1841–1847
58 DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM (2004) Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord* 6: 43–52
59 Wilke M, Kowatch RA, DelBello MP, Mills NP, Holland SK (2004) Voxel-based morphometry in adolescents with bipolar disorder: first results. *Psychiatry Res* 131: 57–69
60 Anstey KJ, Jorm AF, Reglade-Meslin C, Maller J, Kumar R, von Sanden C, Windsor TD, Rodgers B, Wen W, Sachdev P (2006) Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosom Med* 68: 778–785
61 Salerno JA, Murphy DG, Horwitz B, DeCarli C, Haxby JV, Rapoport SI, Schapiro MB (1992) Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension* 20: 340–348
62 Goldstein IB, Bartzokis G, Guthrie D, Shapiro D (2002) Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology* 59: 713–719
63 Knopman DS, Mosley TH, Catellier DJ, Sharrett AR (2005) Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology* 65: 876–881
64 Krishnan KR, Doraiswamy PM, Figiel GS, Husain MM, Shah SA, Na C, Boyko OB, McDonald WM, Nemeroff CB, Ellinwood EH Jr (1991) Hippocampal abnormalities in depression. *J Neuropsychiatry Clin Neurosci* 3: 387–391
65 Figiel GS, Krishnan KR, Rao VP, Doraiswamy M, Ellinwood EH Jr, Nemeroff CB, Evans D, Boyko O (1991) Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. *J Neuropsychiatry Clin Neurosci* 3: 18–22
66 Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B (1995) Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry* 37: 151–160
67 Steffens DC, Helms MJ, Krishnan KR, Burke GL (1999) Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* 30: 2159–2166
68 Hannestad J, Taylor WD, McQuoid DR, Payne ME, Krishnan KR, Steffens DC, Macfall JR (2006) White matter lesion volumes and caudate volumes in late-life depression. *Int J Geriatr Psychiatry* 21: 1193–1198
69 Ovbiagele B, Saver JL (2006) Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. *Cerebrovasc Dis* 22: 83–90
70 Kertesz A, Black SE, Tokar G, Benke T, Carr T, Nicholson L (1988) Periventricular and subcortical hyperintensities on magnetic resonance imaging. 'Rims, caps, and unidentified bright objects'. *Arch Neurol* 45: 404–408
71 Drevets WC, Gadde K, Krishnan KRR (2008) Neuroimaging studies in depression. In: DS Charney, EJ Nestler (eds): *The neurobiological foundation of mental illness*. Oxford University Press, New York, 461–490
72 Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL (2004) Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord* 6: 368–373
73 Newcomer JW (2006) Medical risk in patients with bipolar disorder and schizophrenia. *J Clin Psychiatry* 67 Suppl 9: 25–30; discussion 36–42
74 Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, Alperovitch A, Tzourio C (2001) Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology* 56: 921–926
75 Gunstad J, Cohen RA, Tate DF, Paul RH, Poppas A, Hoth K, Macgregor KL, Jefferson AL (2005) Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Press* 14: 353–358
76 Gustafson DR, Steen B, Skoog I (2004) Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. *Int Psychogeriatr* 16: 327–336
77 Dager SR, Friedman SD (2000) Brain imaging and the effects of caffeine and nicotine. *Ann Med* 32: 592–599
78 Novak V, Last D, Alsop DC, Abduljalil AM, Hu K, Lepicovsky L, Cavallerano J, Lipsitz LA

(2006) Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. *Diabetes Care* 29: 1529–1534
79 Dupont RM, Jernigan TL, Butters N, Delis D, Hesselink JR, Heindel W, Gillin JC (1990) Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Clinical and neuropsychological significance. *Arch Gen Psychiatry* 47: 55–59
80 Lyoo IK, Streeter CC, Ahn KH, Lee HK, Pollack MH, Silveri MM, Nassar L, Levin JM, Sarid-Segal O, Ciraulo DA et al (2004) White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. *Psychiatry Res* 131: 135–145
81 Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF (2007) Depressive symptoms in adolescents: associations with white matter volume and marijuana use. *J Child Psychol Psychiatry* 48: 592–600
82 Lenze E, Cross D, McKeel D, Neuman RJ, Sheline YI (1999) White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. *Am J Psychiatry* 156: 1602–1607
83 Nemeroff CB, Musselman DL (2000) Are platelets the link between depression and ischemic heart disease? *Am Heart J* 140: 57–62
84 Biegon A, Essar N, Israeli M, Elizur A, Bruch S, Bar-Nathan AA (1990) Serotonin 5-HT2 receptor binding on blood platelets as a state dependent marker in major affective disorder. *Psychopharmacology (Berl)* 102: 73–75
85 Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, Marzec U, Harker LA, Nemeroff CB (1996) Exaggerated platelet reactivity in major depression. *Am J Psychiatry* 153: 1313–1317
86 de Castro AG, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P (2008) Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res* 42: 78–82
87 Botteron KN, Vannier MW, Geller B, Todd RD, Lee BC (1995) Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. *J Am Acad Child Adolesc Psychiatry* 34: 742–749
88 Lyoo IK, Lee HK, Jung JH, Noam GG, Renshaw PF (2002) White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr Psychiatry* 43: 361–368
89 Pillai JJ, Friedman L, Stuve TA, Trinidad S, Jesberger JA, Lewin JS, Findling RL, Swales TP, Schulz SC (2002) Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. *Psychiatry Res* 114: 51–56
90 Ahearn EP, Steffens DC, Cassidy F, Van Meter SA, Provenzale JM, Seldin MF, Weisler RH, Krishnan KR (1998) Familial leukoencephalopathy in bipolar disorder. *Am J Psychiatry* 155: 1605–1607
91 Cannon M, Jones PB, Murray RM (2002) Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 159: 1080–1092
92 Kinney DK, Yurgelun-Todd DA, Levy DL, Medoff D, Lajonchere CM, Radford-Paregol M (1993) Obstetrical complications in patients with bipolar disorder and their siblings. *Psychiatry Res* 48: 47–56
93 Kinney DK, Yurgelun-Todd DA, Tohen M, Tramer S (1998) Pre- and perinatal complications and risk for bipolar disorder: a retrospective study. *J Affect Disord* 50: 117–124
94 Pavuluri MN, Henry DB, Nadimpalli SS, O'Connor MM, Sweeney JA (2006) Biological risk factors in pediatric bipolar disorder. *Biol Psychiatry* 60: 936–941
95 Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S (2003) Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 362: 798–805
96 Aston C, Jiang L, Sokolov BP (2005) Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry* 10: 309–322
97 Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP (2002) Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex* 12: 386–394
98 Hamidi M, Drevets WC, Price JL (2004) Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. *Biol Psychiatry* 55: 563–569
99 Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI (2004) Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* 67: 269–275

100 Vostrikov VM, Uranova NA, Orlovskaya DD (2007) Deficit of perineuronal oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. *Schizophr Res* 94: 273–280
101 Carter CJ (2007) EIF2B and oligodendrocyte survival: where nature and nurture meet in bipolar disorder and schizophrenia? *Schizophr Bull* 33: 1343–1353
102 Carter CJ (2007) Multiple genes and factors associated with bipolar disorder converge on growth factor and stress activated kinase pathways controlling translation initiation: implications for oligodendrocyte viability. *Neurochem Int* 50: 461–490
103 Sokolov BP (2007) Oligodendroglial abnormalities in schizophrenia, mood disorders and substance abuse. Comorbidity, shared traits, or molecular phenocopies? *Int J Neuropsychopharmacol* 1–9
104 Starkstein SE, Robinson RG (1989) Affective disorders and cerebral vascular disease. *Br J Psychiatry* 154: 170–182
105 Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, Krebs MO, Julien J, Dubois B, Ducrocq X et al (1995) Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet* 346: 934–939
106 Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP (1999) The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke* 30: 1230–1233
107 Adler CM, Holland SK, Schmithorst V, Wilke M, Weiss KL, Pan H, Strakowski SM (2004) Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. *Bipolar Disord* 6: 197–203
108 Geschwind N (1965) Disconnexion syndromes in animals and man. I. *Brain* 88: 237–294
109 Geschwind N (1965) Disconnexion syndromes in animals and man. II. *Brain* 88: 585–644
110 Neumeister A, Nugent AC, Waldeck T, Geraci M, Schwarz M, Bonne O, Bain EE, Luckenbaugh DA, Herscovitch P, Charney DS et al (2004) Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry* 61: 765–773
111 Hasler G, Fromm S, Carlson PJ, Luckenbaugh DA, Waldeck T, Geraci M, Roiser JP, Neumeister A, Meyers N, Charney DS, Drevets WC (2008) Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and health subjects. *Arch Gen Psychiatry* 65: 521–531
112 Kegeles LS, Malone KM, Slifstein M, Ellis SP, Xanthopoulos E, Keilp JG, Campbell C, Oquendo M, Van Heertum RL, Mann JJ (2003) Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Am J Psychiatry* 160: 76–82
113 Holthoff VA, Beuthien-Baumann B, Zundorf G, Triemer A, Ludecke S, Winiecki P, Koch R, Fuchtner F, Herholz K (2004) Changes in brain metabolism associated with remission in unipolar major depression. *Acta Psychiatr Scand* 110: 184–194
114 Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, Mann JJ (2001) Decreased regional brain metabolism after ect. *Am J Psychiatry* 158: 305–308
115 Ketter TA, Drevets WC (2002) Neuroimaging studies of bipolar depression: functional neuropathology, treatment effects, and predictors of clinical response. *Clinical Neuroscience Research* 2: 182–192
116 Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ (2006) Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn Mem* 13: 728–733
117 Neumeister A, Hu XZ, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, Herscovitch P, Goldman D, Drevets WC, Charney DS (2006) Differential effects of 5-HTTLPR genotypes on the behavioral and neural responses to tryptophan depletion in patients with major depression and controls. *Arch Gen Psychiatry* 63: 978–986
118 Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol* 11: 240–249
119 Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Benson BE, Willis MW, Danielson A, Frye MA, Herscovitch P et al (2001) Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry* 49: 97–109
120 Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA (2001) Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50: 651–658
121 Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002) Glucose metabolism

in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71: 431–447
122 Bauer M, London ED, Rasgon N, Berman SM, Frye MA, Altshuler LL, Mandelkern MA, Bramen J, Voytek B, Woods R et al (2005) Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Mol Psychiatry* 10: 456–469
123 Mah L, Zarate CA Jr, Singh J, Duan YF, Luckenbaugh DA, Manji HK, Drevets WC (2007) Regional cerebral glucose metabolic abnormalities in bipolar II depression. *Biol Psychiatry* 61: 765–775
124 Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD (2000) fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord* 2: 237–248
125 Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML (2004) Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry* 55: 578–587
126 Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E (2006) Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc Natl Acad Sci USA* 103: 8900–8905
127 Pavuluri MN, O'Connor MM, Harral E, Sweeney JA (2007) Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. *Biol Psychiatry* 62: 158–167
128 Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, Epstein J, Isenberg N, McBride PA, Kemperman I et al (1999) Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. *Am J Psychiatry* 156: 1986–1988
129 Kruger S, Seminowicz D, Goldapple K, Kennedy SH, Mayberg HS (2003) State and trait influences on mood regulation in bipolar disorder: blood flow differences with an acute mood challenge. *Biol Psychiatry* 54: 1274–1283
130 Shulman RG, Rothman DL, Behar KL, Hyder F (2004) Energetic basis of brain activity: implications for neuroimaging. *Trends Neurosci* 27: 489–495
131 Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992) A functional anatomical study of unipolar depression. *J Neurosci* 12: 3628–3641
132 Paul IA, Skolnick P (2003) Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci* 1003: 250–272
133 Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, Epperson CN, Goddard A, Mason GF (2002) Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol Psychiatry* 7 Suppl 1: S71–80
134 McEwen BS, Magarinos AM (2001) Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. *Hum Psychopharmacol* 16: S7–S19
135 Bowen DM, Najlerahim A, Procter AW, Francis PT, Murphy E (1989) Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proc Natl Acad Sci USA* 86: 9504–9508
136 Ongur D, Drevets WC, Price JL (1998) Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA* 95: 13290–13295
137 Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 45: 1085–1098
138 Eastwood SL, Harrison PJ (2000) Hippocampal synaptic pathology in schizophrenia, bipolar disorder and major depression: a study of complexin mRNAs. *Mol Psychiatry* 5: 425–432
139 Rajkowska G, Miguel-Hidalgo JJ (2007) Gliogenesis and glial pathology in depression. *CNS Neurol Disord Drug Targets* 6: 219–233
140 Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 58: 545–553
141 Bowley MP, Drevets WC, Ongur D, Price JL (2002) Low glial numbers in the amygdala in major depressive disorder. *Biol Psychiatry* 52: 404–412
142 Benes FM, Vincent SL, Todtenkopf M (2001) The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. *Biol Psychiatry* 50: 395–406
143 Todtenkopf MS, Vincent SL, Benes FM (2005) A cross-study meta-analysis and three-dimensional comparison of cell counting in the anterior cingulate cortex of schizophrenic and bipolar brain. *Schizophr Res* 73: 79–89

144 Czeh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *Eur Arch Psychiatry Clin Neurosci* 257: 250–260
145 Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ (1999) Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience* 91: 1247–1255
146 Regenold WT, Phatak P, Marano CM, Gearhart L, Viens CH, Hisley KC (2007) Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Res* 151: 179–188
147 Brambilla P, Nicoletti M, Sassi RB, Mallinger AG, Frank E, Keshavan MS, Soares JC (2004) Corpus callosum signal intensity in patients with bipolar and unipolar disorder. *J Neurol Neurosurg Psychiatry* 75: 221–225
148 Martinez P, Ronsaville D, Gold PW, Hauser P, Drevets WC (2002) Morphometric abnormalities in adolescent offspring of depressed mothers. *Soc Neurosci Abstr* 32: 498–504
149 Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V, Rachmanova V (2001) Electron microscopy of oligodendroglia in severe mental illness. *Brain Res Bull* 55: 597–610
150 Janus C, D'Amelio S, Amitay O, Chishti MA, Strome R, Fraser P, Carlson GA, Roder JC, St George-Hyslop P, Westaway D (2000) Spatial learning in transgenic mice expressing human presenilin 1 (PS1) transgenes. *Neurobiol Aging* 21: 541–549
151 Johnston-Wilson NL, Sims CD, Hofmann JP, Anderson L, Shore AD, Torrey EF, Yolken RH (2000) Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. *Mol Psychiatry* 5: 142–149
152 Webster MJ, Knable MB, Johnston-Wilson N, Nagata K, Inagaki M, Yolken RH (2001) Immunohistochemical localization of phosphorylated glial fibrillary acidic protein in the prefrontal cortex and hippocampus from patients with schizophrenia, bipolar disorder, and depression. *Brain Behav Immun* 15: 388–400
153 Cotter DR, Pariante CM, Everall IP (2001) Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Res Bull* 55: 585–595
154 Cheng JD, de Vellis J (2000) Oligodendrocytes as glucocorticoids target cells: functional analysis of the glycerol phosphate dehydrogenase gene. *J Neurosci Res* 59: 436–445
155 Alonso G (2000) Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* 31: 219–231
156 Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. *Neuropsychopharmacology* 29: 450–460
157 Czeh B, Pudovkina O, van der Hart MG, Simon M, Heilbronner U, Michaelis T, Watanabe T, Frahm J, Fuchs E (2005) Examining SLV-323, a novel NK1 receptor antagonist, in a chronic psychosocial stress model for depression. *Psychopharmacology (Berl)* 180: 548–557
158 Wellman CL (2001) Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol* 49: 245–253
159 Radley JJ, Rocher AB, Rodriguez A, Ehlenberger DB, Dammann M, McEwen BS, Morrison JH, Wearne SL, Hof PR (2008) Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. *J Comp Neurol* 507: 1141–1150
160 Vyas A, Bernal S, Chattarji S (2003) Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Res* 965: 290–294
161 Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S (2002) Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci* 22: 6810–6818
162 Izquierdo A, Wellman CL, Holmes A (2006) Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. *J Neurosci* 26: 5733–5738
163 Miracle AD, Brace MF, Huyck KD, Singler SA, Wellman CL (2006) Chronic stress impairs recall of extinction of conditioned fear. *Neurobiol Learn Mem* 85: 213–218
164 Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL (2005) Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proc Natl Acad Sci USA* 102: 10706–10711
165 Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, Mathis C (2007)

Serotonin-1A receptor imaging in recurrent depression: replication and literature review. *Nucl Med Biol* 34: 865–877
166 Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC (2007) Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [^{11}C]DASB; comparison with bipolar disorder. *Biol Psychiatry* 62: 870–877
167 Barton DA, Esler MD, Dawood T, Lambert EA, Haikerwal D, Brenchley C, Socratous F, Hastings J, Guo L, Wiesner G et al (2008) Elevated brain serotonin turnover in patients with depression: effect of genotype and therapy. *Arch Gen Psychiatry* 65: 38–46
168 Stockmeier CA (2003) Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *J Psychiatr Res* 37: 357–373
169 Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R (2002) Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 416: 396–400
170 Lopez JF, Chalmers DT, Little KY, Watson SJ (1998) A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol Psychiatry* 43: 547–573
171 Flugge G (1995) Dynamics of central nervous 5-HT1A-receptors under psychosocial stress. *J Neurosci* 15: 7132–7140
172 Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C (1999) PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 46: 1375–1387
173 Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, Klaver JM, Charney DS, Manji HK, Drevets WC (2006) Serotonin transporter binding in bipolar disorder assessed using [^{11}C]DASB and positron emission tomography. *Biol Psychiatry* 60: 207–217
174 Suhara T, Nakayama K, Inoue O, Fukuda H, Shimizu M, Mori A, Tateno Y (1992) D1 dopamine receptor binding in mood disorders measured by positron emission tomography. *Psychopharmacology (Berl)* 106: 14–18
175 Pearlson GD, Wong DF, Tune LE, Ross CA, Chase GA, Links JM, Dannals RF, Wilson AA, Ravert HT, Wagner HN Jr, et al (1995) *In vivo* D2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch Gen Psychiatry* 52: 471–477
176 Anand A, Verhoeff P, Seneca N, Zoghbi SS, Seibyl JP, Charney DS, Innis RB (2000) Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am J Psychiatry* 157: 1108–1114
177 Janowsky DS, Overstreet DH, Nurnberger JIJ (1994) Is cholinergic sensitivity a genetic marker for the affective disorders? *Am J Med Genet* 54: 335–344
178 Benson BE, Carson RE, Kiesewetter DO, Herscovitch P, Eckelman WC, Post RM, Ketter TA (2004) A potential cholinergic mechanism of procaine's limbic activation. *Neuropsychopharmacology* 29: 1239–1250
179 Ketter TA, Andreason PJ, George MS, Lee C, Gill DS, Parekh PI, Willis MW, Herscovitch P, Post RM (1996) Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Arch Gen Psychiatry* 53: 59–69
180 Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, Rollis D, Drevets M, Gandhi S, Solorio G et al (2006) Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. *Arch Gen Psychiatry* 63: 741–747
181 Furey ML, Drevets WC (2006) Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63: 1121–1129
182 Russchen FT, Bakst I, Amaral DG, Price JL (1985) The amygdalostriatal projections in the monkey. An anterograde tracing study. *Brain Res* 329: 241–257
183 Shekhar A, Truitt W, Rainnie D, Sajdyk T (2005) Role of stress, corticotrophin releasing factor (CRF) and amygdala plasticity in chronic anxiety. *Stress* 8: 209–219
184 Davis M, Shi C (1999) The extended amygdala: are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear *versus* anxiety? *Ann N Y Acad Sci* 877: 281–291
185 LeDoux J (2003) The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol* 23: 727–738
186 Drevets WC, Price JL, Furey ML (2008) Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Function* 213: 93–118

187 Manji HK, Drevets WC, Charney DS (2001) The cellular neurobiology of depression. *Nature Medicine* 7: 541–547
188 Drevets WC (2007) Orbitofrontal cortex function and structure in depression. *Ann N Y Acad Sci* 1121: 499–527
189 Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20: 78–84
190 Carpenter M, Sutin J (1983) *Human Neuroanatomy, Eighth Edition*. Williams and Wilkins, Baltimore, MD

Section C:
Acute and long-term treatment of bipolar disorder

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Pharmacological treatment of acute bipolar depression

Gary S. Sachs, Louisa G. Sylvia and Hannah G. Lund

Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, USA

Abstract

Acute depression is the condition for which bipolar patients most often seek treatment. The foundation of evidence-based practice is the practitioner's obligation to inform the patient of proven therapies that may exist to treat their condition. The best guidance for meeting this obligation in clinical practice comes from double-blind, placebo-controlled trials with adequate sample size, referred to in this chapter as Category A evidence. This level of evidence is currently available for only four pharmacological treatments, lamotrigine, olanzapine plus fluoxetine, olanzapine monotherapy, and quetiapine. Interestingly, the most common treatment for bipolar depression – the adjunctive use of standard antidepressants along with lithium or valproate – has not been shown to be effective in any Category A study. Additional treatments for bipolar depression are needed for the many depressed bipolar patients who do not respond adequately to currently available treatments. Several classes of medications show promise for these patients. Exploring the variety of mechanisms by which these medications work may shed light on the pathophysiology of bipolar disorder.

Introduction

The debate over litigation arising from the care of a patient with bipolar disorder suffering from depression played an important role in the ascension of evidence-based practice. Lessons illustrated by this case remain relevant to care nearly two decades later. As articulated by Klerman [1] in testimony and publications, American psychiatrists began referring to the right of patients to be informed about evidence-based treatments. The resulting perspective helped move psychiatric practice from a position where any school of thought could be cited as sufficient basis for justifying care given to patients to a position that granted primacy to clinical trial data. Today, proven treatments are preferred over unproven treatments, even while we acknowledge that unproven does not mean that a treatment is necessarily ineffective.

Bipolar depression remains a clinical challenge, and debate over its treatment continues into the 21st century. Although abnormal mood elevation is the cardinal diagnostic feature of bipolar disorder, depression is more than three

times as common as episodes of mood elevation and represents the doorway through which bipolar patients most often enter treatment [2].

This chapter will review the state of evidence supporting pharmacological treatments for bipolar depression. Management of the acute phase of bipolar depression remains controversial. While this largely reflects a continued scarcity of high quality studies, the past decade has seen the publication of the first fully-powered, placebo-controlled trials for bipolar depression as well as a number of new therapeutic agents.

State of the evidence

All published evidence is not created equal. The best guidance for clinical decision-making comes from double-blind, randomized, placebo-controlled trials with adequate samples. Studies meeting these criteria are referred to here as category A studies [3]. Table 1 offers a simple grading system intended to help the reader draw distinctions between these studies. Over the past 5 years, clinicians treating bipolar disorder have seen a healthy increase in the number of agents with Category A evidence. Comparison between these agents, however, is not as simple as comparing outcomes across studies or calculating an

Table 1. Categories of clinical evidence

A:	Double-blind, placebo-controlled trials with adequate sample size
B:	Double-blind, controlled trials without placebo or without adequate sample size; controlled studies without randomization
C:	Naturalistic or open-label trials/non-experimental descriptive studies or case control studies
D:	Uncontrolled observations, case series, and single case reports
E:	Absence of published studies. However, Category A evidence supports a class effect

effect size. Direct head-to-head studies are required to confidently compare medications.

Approach to clinical management

Recognition of bipolar depression

Patients with bipolar depression, by definition, meet criteria for a current major depressive episode and a lifetime history of bipolar disorder. To make the diagnosis, a clinician must determine whether the patient has experienced clinically significant abnormal mood elevation in the past. Confident diagno-

sis of bipolar depression requires the identification of at least one specific episode meeting criteria for mania or hypomania. Thus, the pathway to appropriate treatment requires recognition of a clinical state other than that observed at the time the patient presents for treatment. Guidelines and quality standards are beginning to recognize the importance of inquiring about a past personal or family history of mania in the assessment of every patient with acute depression [4]. While data from DSM field trials show high rates of agreement for acute mania and reasonably good rates for acute depression [5], these studies do not guide clinical practice on the reliability of eliciting a past history of mania or hypomania from a currently depressed patient. Bipolar disorder cannot be ruled out in the absence of input from collateral sources, particularly in the face of severe acute depression [6]. Care of bipolar depression can be greatly facilitated by clear documentation in the medical record of an index episode of hypomania or mania.

Initiation of sequential measurement-based treatment

The patient's right to evidence-based treatment necessitates that clinicians be aware of treatments supported by adequate clinical trial data (Category A evidence) and that these be offered to patients. Where multiple treatment options are supported by high quality evidence, it is appropriate to present these options to patients as a menu of reasonable choices [3]. Revicki [7] has shown that bipolar patients are generally able to weigh the risk benefit tradeoffs presented by clinicians, which is requisite for patient participation as collaborators in formulating their treatment plan. Thus, patients who are non-responsive to a treatment can be offered each of the reasonable options sequentially based on the patient's preference.

Integrating routine outcome measurement

After patients have agreed to use a medication, it is useful for patients and their doctors to agree on how progress will be measured [8, 9]. While formal depression severity scales such as the Hamilton Depression Rating Scale (HAM-D) or self report scales like the Inventory of Depressive Symptoms (IDS) have the virtue of generating numbers, even raw symptom counts provide serviceable aides to navigating a complex and changing clinical course. The clinical monitoring form and waiting room self-report form, used at the Massachusetts General Hospital Bipolar Clinic are available at *www.manicdepressive.org*. Using these measures facilitates individualized management in which beneficial treatments are continued, and ineffective or intolerable treatments are withdrawn. The pitfalls of repetitious indecisive trials can be avoided by carrying out each intervention with sufficient dose and duration to declare a definitive outcome (beneficial, ineffective, or intolerable).

Options supported by Category A Evidence (at least one positive adequately powered double-blind, placebo-controlled, clinical trial)

Lamotrigine

Calabrese and colleagues [10] first demonstrated the efficacy of lamotrigine for treating bipolar depression. In this 7-week, multicenter, double-blind, fixed-dose study, 195 patients were treated with lamotrigine (50 or 200 mg/day) or placebo. The trend favoring lamotrigine on the primary outcome measure (mean change in HAM-D score) fell just short of statistical significance; however, significant improvements over placebo were found for key secondary endpoints, such as change in Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-BP (Clinical Global Impression for Bipolar Disorder Scale) mean scores. Lamotrigine was not associated with an increased risk of Treatment Emergent Affective Switch (TEAS) compared to placebo. Although subsequent Glaxo-sponsored studies of lamotrigine for bipolar depression resulted in failed trials, trends in these results have consistently favored lamotrigine. In a recent meta-analysis of monotherapy studies lamotrigine did demonstrate efficacy in the acute treatment of bipolar depression, despite results not reaching statistical significance in four out of five placebo-controlled studies [11].

Nierenberg and colleagues [12] randomized Bipolar I and II patients with depression who were unresponsive to at least two trials of standard antidepressants combined with mood stabilizers to receive open treatment with lamotrigine (150–250 mg), risperidone (up to 1–6 mg), or inositol (10–25 g). This Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized, open-label study reported positive results for lamotrigine (24% 'recovered') compared with risperidone (5% 'recovered'). Outcomes for inositol (17% recovered) did not significantly differ from either risperidone or lamotrigine.

Van der Loos and colleagues showed a statistically significant benefit for lamotrigine over placebo as an adjunct to lithium for bipolar depression [13]. In addition, Brown and colleagues randomized bipolar depressed patients to receive either lamotrigine or combined treatment with olanzapine and fluoxetine (OFC) [14]; although response rates were generally comparable between the groups, lamotrigine was associated with significantly less weight gain, sedation, dry mouth, and tremor than combined treatment with OFC.

Olanzapine and OFC

The only fully-powered, placebo-controlled trial examining these agents is particularly valuable because it involves a direct comparison between two active arms and a placebo control. Tohen and colleagues [15] randomized Bipolar I depressed subjects to receive placebo (n = 355), olanzapine (n = 352), or OFC (n = 82) and reported a statistically significant advantage

for olanzapine over placebo. OFC was found to have superior efficacy to olanzapine monotherapy as well as placebo. The groups did not differ in treatment-emergent antidepressant switch (TEAS) rates. The study by Brown and colleagues [14] mentioned above was a double-blind, 7-week, controlled trial that randomized Bipolar I depressed patients (n = 205) to OFC or lamotrigine. Although response rates did not differ significantly between treatment groups, time to 50% reduction in their MADRS score was significantly shorter with OFC. There was no significant difference in rates of TEAS between groups, although OFC was associated with significantly more weight gain, somnolence, dry mouth, and tremor.

Quetiapine

There are five adequately-powered, double-blind, placebo-controlled trials demonstrating the efficacy of quetiapine for bipolar depression. The first of these [16] was a double-blind trial (BOLDER I) that randomized 542 patients with bipolar depression to placebo, quetiapine 300 mg, or quetiapine 600 mg [9]. Both dosages of quetiapine resulted in significantly higher response rates (58%) compared to placebo (36%) at 8 weeks, as well as a significant advantage over placebo on mean change from baseline in MADRS score. No differences between the groups were found in TEAS rates. These results have recently been replicated by two subsequent trials with similar design (one of which used the extended release form of quetiapine). Two additional studies used variations on the same design with the addition of an active control; one study used lithium and the other used paroxetine. These yielded results for placebo and quetiapine that were similar to the prior study outcomes, but neither of the active control groups differed from placebo.

Importantly, the overall study results include outcomes for patients with Bipolar I and Bipolar II disorder [16, 17]. Because most other studies excluded patients with Bipolar II disorder, it is worth noting that quetiapine is the only agent that has shown a statistically significant benefit in the treatment of Bipolar II depression [16, 17] and has the largest effect size (.91 and 1.09, for 300 and 600 mg/day of quetiapine in the BOLDER I study, respectively) observed in any trial for Bipolar I disorder. Slightly lower effect sizes were observed in subsequent studies, likely reflecting the impact of expectancy following BOLDER I and the tendency of trials with more arms to have higher placebo response rates.

Standard antidepressant medications

Until recently, clinical management of bipolar depression was extrapolated from accumulated experience and research in treating unipolar depression due to the dearth of evidence for bipolar patients. More than two dozen agents have

been approved by the US Food and Drug Administration, or other regulatory authorities, for treating unipolar depression. The appropriateness of these agents for bipolar patients cannot be determined based on studies of unipolar depression, because the mechanisms by which these drugs act remain poorly understood and because the trials establishing the efficacy of these agents typically excluded bipolar patients.

In this century, a total of five Category A studies have been reported involving imipramine (one study), paroxetine (three studies) and bupropion (one study) with bipolar patients (see Fig. 1).

The first Category A study for bipolar depression was reported by Nemeroff and colleagues [18]. This study randomized depressed Bipolar I subjects treated with lithium (0.5–1.2 mmol per liter) to double-blind adjunctive treatment with placebo, paroxetine, or imipramine. Overall, this study found no benefit for paroxetine or imipramine over placebo on any of the efficacy measures. Among the subgroup with lithium levels between 0.5 and 0.8 mmol/L, however, there was a significant advantage for patients receiving paroxetine. No differences were found between the groups in the rate of TEAS. Unfortunately, confidence in this finding is limited, because the study had no formal rating scale to assess mood elevation and was likely insensitive to TEAS.

The largest placebo-controlled study of standard antidepressants was carried out by STEP-BD. This National Institute of Mental Health sponsored double-blind study randomized 366 patients to receive treatment with a mood stabilizer (lithium, carbamazepine, valproate) and placebo or a mood stabilizer

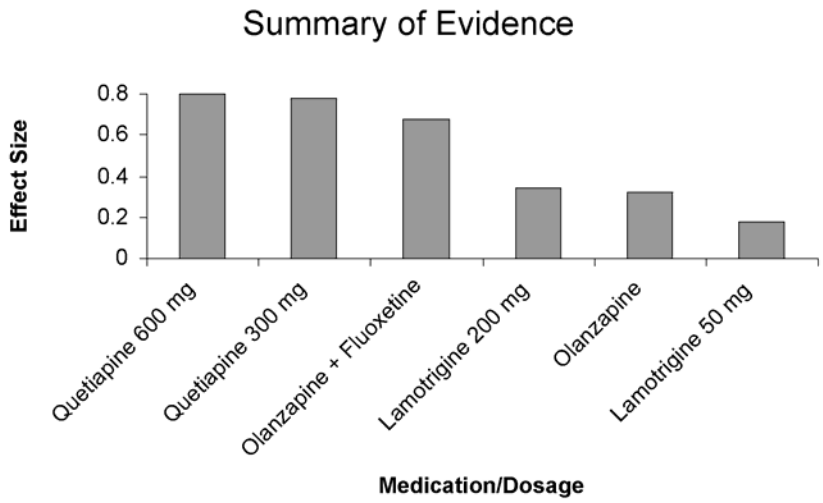


Figure 1. In a pooled analysis of patients with Bipolar I disorder from two randomized controlled trials (BOLDER I and II), effect sizes were 0.78 and 0.80 for quetiapine 300 and 600 mg/daily dosages, respectively [39]. In a study of olanzapine *versus* olanzapine + fluoxetine (OFC) in combination, effect sizes were .32 and .68, respectively [15]. When lamotrigine 200 mg and 50 mg were compared *versus* placebo, effect sizes were .18 and .34, respectively [10].

and an antidepressant (bupropion or paroxetine) [19]. There were no group differences in regards to subjects' likelihood of achieving a durable recovery (eight consecutive weeks euthymic) (27% in placebo group and 24% in antidepressant groups), their TEAS scores (10–11%, both groups), or other outcome measures. Thus, there was evidence of neither benefit nor harm in adjunctive use of bupropion or paroxetine.

In summary, no Category A study has found a statistically significant benefit to adding a standard antidepressant to lithium, carbamazepine, or valproic acid. OFC was superior to treatment with placebo and superior to treatment with olanzapine monotherapy, but this single study represents the only available high-quality evidence supporting the practice of administering a standard antidepressant medication to depressed patients with bipolar disorder [15]. The degree to which this finding generalizes to combining fluoxetine with other agents, or the possibility that olanzapine might potentiate other agents, is unclear.

Studies without placebo control

The Stanley Foundation Bipolar Network (SFBN) conducted a randomized, double-blind comparison of adjunct bupropion, sertraline, or venlafaxine to ongoing mood stabilizer treatment in 159 patients with bipolar disorder [20, 21]. Overall TEAS into hypomania and mania occurred in 11.4% and 7.9%, respectively, of acute treatment trials (10 weeks), and in 21.8% and 14.9% of the continuation trials (1-year duration). The rate of TEAS was higher in patients with Bipolar I disorder (30.8%) than in those with Bipolar II disorder (18.6%). The risk of switch into hypomania or mania was significantly increased in subjects treated with venlafaxine (15%) compared to bupropion (4%) or sertraline (7%).

In a 6-week, randomized, single-blind trial, Vieta and colleagues [22] compared the efficacy of mood stabilizers with adjunctive paroxetine (n = 30) to mood stabilizers with adjunctive venlafaxine (n = 30), and found no significant differences in terms of treatment response rates between the groups (paroxetine 43%, venlafaxine 47%). Rates of TEAS were 3% in the paroxetine group and 13% in the venlafaxine group. Silverstone and colleagues [23] compared the antidepressant efficacy of moclobemide (n = 81), and imipramine (n = 75) in patients with bipolar disorder, 64% of whom were prescribed concomitant mood stabilizers. No statistically significant differences between the two groups were found on any of the efficacy measures. The trend for higher rates of study withdrawal due to TEAS did not reach statistical significance (moclobemide = 3.7%, imipramine = 11%).

Amsterdam and colleagues [24] evaluated the efficacy of fluoxetine in a randomized, double-blind, placebo-controlled study (n = 34). Significant reductions in mean HAM-D and MADRS ratings, without an increase in YMRS scores, were reported in the active and placebo groups. These investigators also

reported that in patients with bipolar depression who received 8 weeks of open-label fluoxetine treatment, 48% showed a HAM-D reduction of greater than 50%, while 7.3% developed TEAS (YMRS ≥8) [25]. Other small double-blind studies of standard antidepressant use in bipolar depression include those of add-on tranylcypromine [26, 27] and desipramine *versus* bupropion [28].

Studies without randomization

Altshuler and colleagues [29] reported quasi-experimental results from the SFBN. Among the 1,078 patients with bipolar disorder, about 50% became depressed and had a standard antidepressant added to their treatment regimen. 15% of these patients, for whom there was a clinical intent-to-treat with a standard antidepressant, achieved remission. A comparison of remitted patients (depending on whether antidepressants were continued for more than 6 months or discontinued before 6 months) revealed that 20–25% experienced a relapse into depression over the first 4 months regardless of whether or not antidepressants were continued. Significantly lower rates of relapse into depression over 1 year were observed for those who remained on antidepressants (36%) compared with those who discontinued (70%). However, when interpreting this finding one must consider that the reasons for antidepressant discontinuation are not apparent; for example, treatments may have been discontinued due to lack of efficacy. A similarly designed study [30] reported 1-year outcome rates of antidepressant treatment in 59 patients with bipolar depression and found comparable results, which are also subject to the same limitations.

A STEP-BD study reported a quasi-experimental comparison of outcomes for 1,000 patients with bipolar disorder treated openly and followed prospectively for 1 year. In this sample, 18% of patients experienced the onset of a new depressive episode, including 5% who had multiple depressive episodes [31]. Outcome analysis for the first depressive episode revealed no statistically significant advantage to adding standard antidepressant medications compared to subjects managed without a standard antidepressant. Rates of TEAS were 14.6% irrespective of the use of standard antidepressants.

Meta-analyses and systematic reviews

Gijsman and colleagues [32] reported a meta-analysis of 12 randomized, controlled trials on the efficacy and safety of antidepressants for the short-term treatment of bipolar depression, and found antidepressants to be significantly more effective than placebo. A similar analysis for the TEAS data from these studies indicated that, overall, antidepressants did not cause higher rates of TEAS than placebo, but an association was found for the subgroup treated with tricyclic antidepressants. Several caveats pertain to translating these meta-analysis findings into clinical use. Chief among these is that the results do not

support the use of any one antidepressant. The 'response rates' used in the meta-analysis were overestimates of drug effectiveness because the studies based response solely on depression outcomes; thus the count includes successful responses cases in which a switch to mania had occurred. For instance, about 25% of the responders in the tranylcypromine and imipramine studies became manic [26]. The TEAS findings are also limited by the lack of any formal assessment for TEAS in most studies. Meta-analyses are most appropriate as a means of pooling underpowered homogeneous studies and are less desirable when high-quality, fully-powered studies are available.

Lithium

The American Psychiatric Association (APA) Guidelines recommend lithium as an initial treatment for bipolar depression of mild to moderate severity. There is, however, little statistical evidence comparing the antidepressant efficacy of lithium to placebo. Prior to 2008, relevant studies were limited to small placebo-controlled studies, crossover studies, or non-randomized samples. The recently completed AstraZeneca-sponsored comparison of lithium, quetiapine, and placebo showed no benefit for lithium compared to placebo. While the assay sensitivity of this trial was ostensibly established based on its success in detecting a substantial benefit for the groups treated with quetiapine (300 mg and 600 mg), the trial design may have inadvertently disadvantaged lithium relative to quetiapine; lithium is widely used by the eligible population and lithium-responsive subjects would have been unlikely to enroll. In addition, lithium and placebo would be disadvantaged to the extent that quetiapine's sedative qualities and other adverse effects may have unblinded raters.

Studies intended to test other adjunctive treatments in which subjects in all treatment groups received lithium cannot prove lithium's efficacy, but may nonetheless be instructive for clinical practice. The efficacy of lithium can be estimated to some extent based on the aforementioned double-blind trial by Nemeroff and colleagues [18], in which no overall benefit was found for the addition of standard antidepressants to lithium compared with lithium monotherapy at lithium levels ≥0.8 mEq/l. Where lithium was dosed at levels ≤0.8 mEq/L, add-on antidepressant treatment was more beneficial than lithium monotherapy [18]. This finding suggests that subtherapeutic lithium levels are less effective than therapeutic lithium levels, but does not allow any conclusions to be drawn about the relative efficacy of lithium compared with antidepressants or placebo.

Valproate

Evidence supporting the antidepressant properties of valproate is limited. Three small placebo-controlled trials suggest valproate may have beneficial

effects for bipolar depression [33–35]. As with lithium, enthusiasm for use of valproate in bipolar depression is often muted by historical perspectives that may not apply to contemporary clinical nomenclature. When analyzing treatment effect in a large, open case-series, Lambert (1966) found moderate improvement in only 22% of 103 'manic-depressive' patients treated with valpromide; this likely discouraged use of valproate in a manner similar to Cade's reported impression that lithium was ineffective for depression [36]. Because Lambert's series also largely comprised subjects who would be classified as having unipolar depression according to DSM-IV criteria, the question of valproate's antidepressant efficacy for bipolar patients remains open.

Carbamazepine

Controlled studies supporting the efficacy of carbamazepine in bipolar depression are scarce. Post and colleagues [37] published a randomized, double-blind study of 35 patients with bipolar depression. They found at least mild improvement in symptoms (CGI ratings) in 57%, and a more substantial improvement in 34.3% of patients treated with carbamazepine. This group also conducted a meta-analysis of carbamazepine treatment in unipolar and bipolar depression (including several small, open-label, and controlled studies), reporting that response rates to carbamazepine treatment were observed in 56% of open-label trials and 44% of controlled studies [38].

Conclusion

The right of patients to be made aware of evidence-based treatment options carries with it a need for practicing clinicians to be aware of the treatment options supported by Category A evidence. Currently, only four medications meet Category A criteria for use in bipolar depression: lamotrigine, olanzapine, OFC, and quetiapine. Regardless of whether patients accept these treatments, a measurement-based approach provides a systematic means of working towards individualized treatment.

Finally, this chapter has focused on the acute treatment of bipolar depression with currently available therapeutics. Chapter 12 of this volume, by Zarate and Manji, explores the utility of novel therapeutics currently under investigation for the treatment of bipolar depression.

References

1 Klerman GL (1990) The psychiatric patient's right to effective treatment: implications of Osheroff v. Chestnut Lodge. *Am J Psychiatry* 147: 409–418

2 Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, Endicott J, Keller M (2003)

Long-term symptomatic status of bipolar I *versus* bipolar II disorders. *Int J Neuropsychopharmacol* 6: 127–137
3 Sachs GS (2007) Bipolar disorder clinical synthesis: where does the evidence lead? *Focus* V: 1–11
4 Johnson SL, Brickman AL (2006) Diagnostic inconsistency: a marker of service utilization in bipolar disorder. *Manag Care Interface* 19: 41–45
5 Keller MB, Hanks DL, Klein DN (1996) Summary of the DSM-IV mood disorders field trial and issue overview. *Psychiatr Clin North Am* 19: 1–28
6 Bowden CL (2001) Strategies to reduce misdiagnosis of bipolar depression. *Psychiatr Serv* 52: 51–55
7 Revicki DA, Hanlon J, Martin S, Gyulai L, Nassir Ghaemi S, Lynch F, Mannix S, Kleinman L (2005) Patient-based utilities for bipolar disorder-related health states. *J Affect Disord* 87: 203–210
8 Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ et al (2006) Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 31: 1841–1853
9 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R et al (2003) The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 54: 573–583
10 Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD (1999) A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 60: 79–88
11 Calabrese J, Huffman RF, White R, Edwards S, Thompson T, Ascher J, Monaghan E, Leadbetter R (2008) Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 10: 323–333
12 Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, Miyahara S, Bauer MS, Thase ME, Wisniewski SR et al (2006) Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 163: 210–216
13 van der Loos ML, Kolling P, Knoppert-van der Klein EA, Nolen W (2007) Lamotrigine in the treatment of bipolar disorder. A review. *Tijdschr Psychiatr* 49: 95–103
14 Brown EB, McElroy SL, Keck PE, Jr, Deldar A, Adams DH, Tohen M, Williamson DJ (2006) A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination *versus* lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 67: 1025–1033
15 Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW et al (2003) Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60: 1079–1088
16 Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J (2005) A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162: 1351–1360
17 Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR (2006) Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 26: 600–609
18 Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD (2001) Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 158: 906–912
19 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 356: 1711–1722
20 Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, Kupka RW, Denicoff KD, Nolen WA, Grunze H et al (2006) Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 163: 232–239
21 Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD et al (2006) Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 189: 124–131
22 Vieta E, Martinez-Aran A, Goikolea JM, Torrent C, Colom F, Benabarre A, Reinares M (2002) A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed

patients taking mood stabilizers. *J Clin Psychiatry* 63: 508–512
23 Silverstone T (2001) Moclobemide *versus* imipramine in bipolar depression: a multicentre double-blind clinical trial. *Acta Psychiatr Scand* 104: 104–109
24 Amsterdam JD, Shults J, Brunswick DJ, Hundert M (2004) Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression – low manic switch rate. *Bipolar Disord* 6: 75–81
25 Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Schweizer E, Beasley C (1998) Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 18: 435–440
26 Himmelhoch JM, Thase ME, Mallinger AG, Houck P (1991) Tranylcypromine *versus* imipramine in anergic bipolar depression. *Am J Psychiatry* 148: 910–916
27 Nolen WA, Kupka RW, Hellemann G, Frye MA, Altshuler LL, Leverich GS, Suppes T, Keck PE Jr, McElroy S, Grunze H et al (2007) Tranylcypromine *versus* lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. *Acta Psychiatr Scand* 115: 360–365
28 Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF (1994) A double-blind trial of bupropion *versus* desipramine for bipolar depression. *J Clin Psychiatry* 55: 391–393
29 Altshuler L, Suppes T, Black D, Nolen WA, Keck PE Jr, Frye MA, McElroy S, Kupka R, Grunze H, Walden J et al (2003) Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry* 160: 1252–1262
30 Joffe RT, MacQueen GM, Marriott M, Trevor Young L (2004) A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disord* 6: 62–66
31 Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, Miklowitz DJ, Sachs GS, Thase ME (2007) Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 164: 1348–1355
32 Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM (2004) Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 161: 1537–1547
33 Davis LL, Bartolucci A, Petty F (2005) Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord* 85: 259–266
34 Sachs G, Altshuler L, Ketter T, Suppes T, Rasgon N, Frey M, Collins M (2001) Divalproex *versus* placebo for treatment of Bipolar depression. 40th American College of Neuropsychopharmacology (ACNP), Waikoloa, Hawaii; December 9–13, 2001
35 Ghaemi SN, Gilmer WS, Goldberg JF, Zablotsky B, Kemp DE, Kelley ME, Bauer AD, Fleck J, Filkowski MM, Stan VA et al (2007) Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry* 68: 1840–1844
36 Lambert PA, Carraz G, Borselli S, Carbel S (1966) Action neuro-psychotrope d'un nouvel antiépileptique: le Dépamide [Neuropsychotropic action of a new antiepileptic: valpromide]. *Ann Med Psychol Paris* 124: 707–710
37 Post RM, Uhde TW, Roy-Byrne PP, Joffe RT (1986) Antidepressant effects of carbamazepine. *Am J Psychiatry* 143: 29–34
38 Post R, Ketter T, Uhde T, Ballenger JC (2007) Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. *CNS Drugs* 21: 47–71
39 Weisler RH, Hirschfeld R, Cutler AJ, Gazda T, Ketter TA, Keck PE, Swann A, Kalali A (2006) Extended-release carbamazepine capsules as monotherapy in bipolar disorder: pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs* 20: 219–231

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Pharmacological treatment of the maintenance phase of bipolar depression: focus on relapse prevention studies and the impact of design on generalizability

Keming Gao, David E. Kemp and Joseph R. Calabrese

Department of Psychiatry, Bipolar Disorder Research Center in Mood Disorders Program, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106, USA

Abstract

The goal of pharmacological treatment of bipolar disorder is to prevent future occurrences of mood episodes. To achieve this goal, medications must demonstrate efficacy in the prevention of both manic/hypomanic and depressive relapses/recurrences. Currently, the efficacy of most pharmacological agents in the maintenance treatment of bipolar disorder has been studied using relapse prevention designs, in which only patients who tolerate and respond to a studied drug(s) in the acute phase (mania or depression) can enter the maintenance phase. Subsequently, the results from relapse prevention studies are not generalizable, not only because of the design, but also because of different index mood episodes. So far, however, only lithium and lamotrigine, and to some extent divalproex, have been investigated in both manic and depressive index episodes, while olanzapine and aripiprazole have been evaluated in manic index episodes. To facilitate the application of currently available data, this chapter will systematically examine randomized, blinded, controlled maintenance studies enrolling ≥100 patients and lasting ≥6 months.

Introduction

Symptomatic patients with Bipolar I disorder experience depressive symptoms three to four times more commonly than manic symptoms [1], while symptomatic patients with Bipolar II disorder experience depressive symptoms approximately 39 times more commonly than hypomanic symptoms [2]. In a prior report of 593 subjects who screened positive for bipolar disorder, moderate to extreme impairment in work, social life, and family interactions occurred significantly more often from depressive than manic symptoms [3]. In addition, significant psychosocial impairment during illness-free periods was more strongly predicted by the number of past depressive episodes than past manias [4, 5]. Moreover, there is a higher risk for suicide in bipolar disorder than in other major psychiatric disorders, particularly during depressive episodes [6–8].

From these findings, it is evident that the prevention of acute major depressive episodes is critical in order to reduce the morbidity and mortality associated with bipolar disorder. This necessarily involves the discovery and implementation of more effective treatments during the maintenance phase. Disappointingly, the prevention of bipolar depression during maintenance treatment is less well studied compared with the prevention of mania. More importantly, most maintenance studies have used relapse prevention designs instead of prophylaxis designs. "In the prophylaxis design, any patient who is euthymic, regardless of how that person got well, is eligible to be randomized to drug *versus* placebo or a comparator. In the relapse prevention design, only those patients who respond acutely to the drug being studied are eligible to enter the maintenance phase, when they are randomized to remain on the drug or be switched (usually abruptly) to placebo and/or an active comparator…Thus results from a prophylactic design are generalizable, whereas those from a relapse prevention trial are not." (p. 709) [6]. Evidence suggests the index mood episode often predicts the polarity of future relapse at different times after remission [9], but it also may predict different responses to treatment (see below) [10]. Likely, results from patients initially presenting with mania may not be applicable to those initially presenting with depression or *vice versa*. Even results from studies with the same index mood polarity may not be generalizable because of differences in inclusion and exclusion criteria or other variations in study designs. Therefore, an understanding of these differences is important when considering generalizability to clinical practice. To achieve this goal, we will provide an overview of the various trial methodologies and summarize key efficacy findings from existing bipolar maintenance studies.

Methodology in bipolar maintenance research

Although there is little consensus on the methodology of bipolar maintenance studies, the methods that have evolved the most include study enrollment, study design, outcome measures, and statistical analysis [6, 11]. These components can directly affect interpretation of the results and will be reviewed independently.

Study enrollment

Due to different inclusion and exclusion criteria, selection biases stemming from study enrollment are unavoidable. Most early maintenance studies published between 1970 and 1976 tended to evaluate small cohorts of patients, typically from 5 to 40 patients per arm. Most studies only enrolled patients who were hospitalized. At the time of these early studies, concepts such as Bipolar II disorder, secondary bipolar disorder, and rapid cycling were not yet

introduced into practice; only mood-congruent psychotic features were allowed. Furthermore, the use of hospitalization to confirm a diagnosis of mania was commonly employed. Consequently, patients with mania enrolled into the early studies tended to have classic euphoric mania. After redefining the criteria for the diagnosis of mania in DSM-III in 1980 and permitting outpatients into the study, more recent maintenance studies probably included less-impaired patients who were more likely to respond to placebo treatment [11].

Study design (crossover versus *parallel)*

Crossover designs were used in some early lithium maintenance studies. In a typical crossover study, each patient's response under treatment A is compared with his or her response under treatment B. The advantage of this design is the increased homogeneity of the study population. The primary disadvantage associated with the use of a crossover design is the increased risk for false-positive results due to abrupt discontinuation of the initial treatment [11].

In a parallel study design, all patients are randomized to different treatments at the beginning of the study. The advantage of the parallel design is that it is less dependent on the crossover design's assumption that each individual patient has a similar disease process prior to and during a treatment, and generally produces a lower dropout rate because each patient is exposed to only one treatment. The primary disadvantage of the parallel design is the disturbance caused by spontaneous remissions or erratic, short-lived fluctuations in mood states. Most maintenance studies have used an open label stabilization phase in which all patients receive active drug(s), followed by random assignment to different treatment arms in a parallel fashion. The 'enriched' nature of the sample tends to increase homogeneity, similar to the crossover design. Like the crossover scheme, the parallel discontinuation design used in most recent maintenance studies might also inflate the response of the studied drugs.

Outcome measures

Most early lithium studies did not measure mood severity with standardized rating scales, such as the Hamilton Rating Scale of Depression (HAM-D) or the Young Mania Rating Scale (YMRS). Typically, these trials evaluated efficacy through general indices of outcome during the study period. Such outcomes included the number of manic and depressive episodes, the probability of relapsing into a manic or depressive episode, experiencing a relapse severe enough for hospitalization, or experiencing a relapse severe enough for a pharmacological intervention. More recent maintenance studies have used standardized rating scales to quantify the minimum severity for an index episode or DSM-IV criteria for a mood episode. The advantage of using rating scales

is that they can detect rather minor changes in illness severity. However, they are limited by their cross-sectional assessment of a period of 7 days prior to the completion of the rating scale. Some recent studies have used the time to intervention as a primary outcome measure, but each individual study has its own criteria for intervention [11].

Statistical analyses

Early maintenance studies used responder analyses with little or no distinction between primary and secondary outcome measures. The proportion of patients who experienced a relapse or recurrence was commonly compared [12–14] with the exception of one study that used additional Kaplan-Meier life table analysis [15]. This approach is inadequate for a maintenance study because it does not consider the length of time that patients remain well before relapsing. A further drawback of this method is that the number of patients withdrawing prematurely without experiencing a relapse is either ignored or analyzed incorrectly.

The use of survival analysis has become the standard method of examining data from bipolar disorder maintenance studies. Relapse prevention trials typically assess the length of time after open stabilization, starting at the point of randomization and ending when relapse or recurrence has occurred. These survival data are commonly depicted with a Kaplan-Meier curve, which can also be used to demonstrate median survival (the time at which 50% of patients have relapsed/recurred). There are several methods available to conduct significance testing on time-to-event data, including log rank, Cox proportional hazards, and the Wilcoxon two-sample test. The log rank test is the most commonly used method and was used in the lamotrigine/Lamictal® [16–18], aripiprazole/Abilify® [19], and olanzapine/Zyprexa® maintenance studies [20]. Cox regression testing was used in the other olanzapine maintenance studies, presumably because of its flexibility, which permits the use of multiple predictors and covariates [21, 22]. In the divalproex/Depakote® maintenance study, life-table methods were constructed to compare survival curves using the Wilcoxon test because of this method's sensitivity to early group differences [23]. However, the primary problems with survival analysis techniques derive from sample size and drop-outs. As the sample size decreases over time due to drop-outs, a survival analysis is most valid for the earlier portion of the curves, where there are a larger number of patients in the study [6].

The index mood episode

In relapse prevention studies, an index mood episode (a presenting mood episode) is commonly used to start a trial of a study drug, although each study has its own severity requirement (Tab. 1). The importance of the index mood

Table 1. Summary of the characteristics of maintenance studies during open-label phase

Open label enrichment	Study index severity	Open-label treatment (s)	Enrollment		Stabilization Criteria	Randomization scheme	Randomized treatments
			Entry (N)	Completion N (%)			
Agents studied in both mania and depression index episodes							
Lithium or Imipramine [12][¶]							
	Bipolar depression or Unipolar depression Hospitalized	Antidepressant or ECT first, then Lithium (0.5–1.4 mEq/L) or Imi (50–200 mg/day)	122	–	After remission	Abrupt discontinuation Parallel assignment	Li Imi PBO
Lithium [13][¶]							
	Acute mania Hospitalized	Li (0.5–1.4 mEq/L)	205	–	After remission	Abrupt discontinuation Parallel assignment	Li PBO
Lithium and Imipramine [15][*]							
	Acute mania, bipolar depression or unipolar depression RSDMS ≥ 7, GAS ≤ 60 Inpatients (42%) and outpatients	Treatment of choice first, then Imi (75–150 mg/day) plus Li (0.6–0.9 mEq/L) for 2 months	216	117 (54.2)	RSDMS < 7, GAS > 60 for 2 months	Abrupt discontinuation Parallel assignment	Li + Imi Li Imi
Lamotrigine [16]							
	Bipolar I depression A current DSM-IV MDE or MDE within 6 months but symptomatic at enrollment	LTG (100–200 mg/day) adjunctive or monotherapy for 8–16 weeks	966	480 (49.7)	CGI-S ≤ 3 for ≥4 weeks	Abrupt discontinuation Parallel assignment lithium with 3 weeks[§]	LTG Li PBO

(Continued on next page)

Table 1. (Continued)

Open label enrichment	Study index severity	Open-label treatment (s)	Enrollment		Stabilization Criteria	Randomization scheme	Randomized treatments
			Entry (N)	Completion N (%)			
Lamotrigine [17]							
	Bipolar I disorder Current mania/hypomania or mania/hypomania with 60 days but symptomatic at enrollment	LTG (100–200 mg/day) adjunctive or monotherapy for 8–16 weeks	349	175 (50.1)	CGI-S ≤ 3 for ≥4 weeks	Abrupt discontinuation Parallel assignment lithium with 3 weeks[§]	LTG Li PBO
Lithium and Divalproex [18]							
	Bipolar I or II disorder Rapid cycling in last 12 months Mania, hypomania, mixed state within last 3 months	Li (≥ 0.8 mEq/L) Val (≥ 50 μg/ml) for 12–20 weeks	254	60 (23.6)	HAM-D-24 ≤ 20, YMRS ≤ 12, GAS ≥ 51 for ≥4 weeks	Gradual discontinuation for average 6 weeks	Li + PBO Val + PBO
Agents only studied in Mania Index Episode							
Aripiprazole [19]							
	Bipolar I disorder, mania or mixed YMRS ≥ 20	ARIP (15 or 30 mg/day) for 6–18 weeks	567	206 (36.3)	YMRS ≤ 10, MADRS ≤ 13 for ≥6 weeks	Abrupt discontinuation Parallel assignment	ARIP PBO
Lithium and Olanzapine [20]							
	Bipolar I disorder, mania or mixed YMRS ≥ 20 Inpatients and outpatients	OLZ (5–20 mg/day) Li (0.6–1.2 mEq/L) for 6–12 weeks	543	431 (79.4)	YMRS ≤ 12, HAM-D-21 ≤ 8	Gradual discontinuation for 4 weeks	OLZ + PBO Li + PBO

(Continued on next page)

Table 1. (Continued)

Open label enrichment	Study index severity	Open-label treatment (s)	Enrollment Entry (N)	Enrollment Completion N (%)	Stabilization Criteria	Randomization scheme	Randomized treatments
Olanzapine [21]							
	Bipolar I disorder, mania or mixed YMRS ≥ 20	OLZ (5–20 mg/day) for 6–12 weeks	731	361 (49.4)	YMRS ≤ 12, HAM-D-21 ≤ 8 2 consecutive weekly visit	Abrupt discontinuation Parallel assignment	OLZ PBO
Lithium or Valproate and Olanzapine [22][**]							
	Bipolar I disorder, mania or mixed YMRS ≥ 16 Inadequate response to Li or Val for 2 weeks	Li (0.6–1.2 mEq/L) Val (50–125 µg/ml) OLZ (5–20 mg/day) for 6 weeks	229	99 (43)	YMRS ≤ 12, HAM-D-21 ≤ 8 Syndromic remission[***]	Abrupt discontinuation Parallel assignment	Li/Val + OLZ Li/Val + PBO
Divalproex, Lithium or both, others, or none [23]							
	Bipolar I disorder, manic or partially recovered from mania or euthymic after mania	Val, Lithium, or both, others or none for ≤ 3 months	571	372 (65.1)	MAR ≤ 11, DSS ≤ 13, GAS ≥ 60 for ≥6 days	Gradual discontinuation Parallel assignment for 2 weeks	Val Li PBO

[¶] Relapsed patients were allowed to continue the study; [§] For those taking lithium during open-label phase, the dosage was tapered over at least 3 weeks and discontinued a minimum of 1 week prior to randomization; [#] Research Diagnostic Criteria for primary major depressive disorder or manic disorder; [**] Olanzapine was a part of blinded acute treatment for mania; [***] Syndromic remission was defined as 1) DSM-IV 'A' criteria for current manic episode no worse than mild, 'B' criteria no worse than mild, and no more than 2 'B' criteria that were mild; 2) All DSM-IV 'A' criteria for current major depressive episode no worse than mild, and no more than 3 'A' criteria mild. Abbreviations: ARIP, aripiprazole, CGI-S, Clinical Global Impression – Severity scale; DSS, Depression Severity scale; GAS, Global Assessment scale; HAM-D-21, Hamilton Depression Rating scale 21 items; HAM-D-24, Hamilton Depression Rating scale 24 items; Imi, imipramine; Li, lithium; LTG, lamotrigine; MADRS, Montgomery – Asberg Depression Rating Scale; MAR, Mania Rating Scale; MDE, major depressive episode; n, number of patients; OLZ, olanzapine; PBO, placebo; RSDMS, Raskin Severity of Depression and Mania Scale; Val, valproate or divalproex; YMRS, Young Mania Rating Scale.

episode is that not only may it bring patients into acute treatment; it may also predict the mood polarity of future relapses, as well as treatment response. After reviewing 11 published articles, Calabrese and colleagues concluded that patients presenting with depression for a maintenance study tended to relapse into depression, and that those presenting with mania tended to relapse into a manic, hypomanic, or mixed episode with a ratio of about 2:1 to 3:1; this was particularly true during the first few months after randomization [24]. However, the polarity of a new mood episode differed depending on the time after randomization from an index mood episode. Relapses within the first 90 days were more likely to be of the same polarity as the index mood episode, while relapses after 180 days were more likely to be of the opposite polarity as the index mood episode [9]. Furthermore, in a *post hoc* analysis of a bipolar maintenance study [10], Shapiro and colleagues found that lithium monotherapy or the combination of lithium and imipramine were superior to imipramine alone in prevention of relapses in patients presenting with mania, but not in those presenting with depression.

Clearly, any drug must be studied with different index mood episodes, and the study must last long enough to show a spectrum of efficacy in the prevention of early and later mood relapses. However, due to the nature of bipolar disorder, no consensus has been achieved for the ideal duration of a bipolar maintenance study. Investigators have purported that 'pure' maintenance efficacy of maintenance studies cannot be established if the study duration is shorter than 6 months [6, 25]. Therefore, in this chapter, randomized, blinded, controlled trials with an index episode of mania or depression enrolling ≥100 patients and lasting more than 6 months will be systematically reviewed.

Agents studied in both manic and depressive mood episodes

So far, only lithium and lamotrigine have been studied in patients presenting with a manic or depressive episode. In most early studies, patients were 'enriched' with lithium monotherapy or a lithium + imipramine/Tofranil® combination before they were randomized. In recent studies, patients have been 'enriched' with lamotrigine (Tabs 1 and 2).

Lithium or lithium + imipramine (mildly enriched)

Lithium's observed acute antimanic efficacy led to mania being studied as the index episode for a number of early maintenance studies. In response to criticisms raised over the use of crossover designs in some early lithium studies and the skepticism relating to its maintenance efficacy, Prien and colleagues (1973) published two randomized, single-blinded (rater-blinded) prospective maintenance studies [12, 13]. In these studies, hospitalized manic patients were stabilized with lithium (*lithium-enrichment*) and hospitalized depressed

Table 2. Summary of maintenance studies during randomized, blinded, controlled phase

Enrichment Index mood episode Randomization criteria	Randomized treatments	Duration	Completion (%)	Primary outcome measure	Median time to intervention/relapse (Active arm *versus* PBO for PBO-controlled trials) or (Active *versus* active for active comparator trials)			Rates of relapse/recurrence (%) (Active arm *versus* PBO for PBO-con trolled trials) or (Active *versus* active for active comparator trials)		
					Any mood	Mania	Depression	Any mood	Mania	Depression
Agents studied in both mania and depression index episodes										
Lithium or Imipramine [12]										
Depression	Li (0.5–1.4 mEq/L), n = 18	24 months	45*	Occurrence of affective	—	—	—	†28¥	11	22¥
After remission	Imi (50–200 mg/day), n = 13			episodes (hospitalization				†77	54	31
	PBO, n = 13			or supplementary drug)	—	—	—	†77	38	62
Lithium [13]										
Mania	Li (0.5–1.4 mEq/L), n = 101	24 months	59*	Frequency and severity of	—	—	—	42¥	32¥	16
After remission	PBO, n = 104			relapse				80	68	26
				(hospitalization-"severe" relapse, supplementary drug-"moderate")	—	—	—			
Lithium and Imipramine [15]**										
Depression or mania	Li (0.45–1.1 mEq/L) +	30 months	17***	Occurrence of affective	—	—	—	—	28	22
RSDMS < 7,	Imi (75–150 mg/day), n = 36			episodes						
GAS > 60	Li (0.45–1.1 mEq/L), n = 42			(RDC Criteria of MDE or	—	—	—	—	26	29
for 2 months	Imi (75–150 mg/day), n = 36			ME and GAS ≤ 60)	—	—	—	—	53	28

(Continued on next page

Table 2. (Continued)

Enrichment Index mood episode Randomization criteria	Randomized treatments	Duration	Completion (%)	Primary outcome measure	Median time to intervention/relapse			Rates of relapse/recurrence (%)		
					Any mood	Mania	Depression	Any mood	Mania	Depression
Lamotrigine [16]										
Depression CGI-S ≤ 3 for at least 4 weeks	LTG (50, 200, 400 mg/day), n = 221	76 weeks	17	Time to intervention (additional pharmacotherapy or electroconvulsive therapy)	200 days, p = 0.029	p = ns	Longer, p = 0.047	50	16	35
	Li (0.8–1.1 mEq/L), n = 121		17		170 days, p = 0.029	Longer, p = 0.026	p = ns	47	8	38
	PBO, n = 121		10		93 days			56	16	40
Lamotrigine [17]										
Mania CGI-S ≤ 3 for at least 4 weeks	LTG (100–400 mg/day), n = 59	76 weeks	5	Time to intervention (additional pharmaco therapy or electroconvulsive therapy)	141 days, p = 0.02	NE, p = ns	NE, P = 0.02	48	35	14
	Li (0.8–1.1 mEq/L), n = 46		2		292 days, p = 0.003	NE, p = 0.006	NE, p = ns	41	18	23
	PBO, n = 70		0		85 days	203 days	269 days	71	41	30
Lithium and divalproex [18]										
Mania/hypomania in 3 months	Li (0.92 mEq/L), n = 32	20 months	16	Time to treatment for a mood episode	18 weeks, p = ns	NE, p = ns	NE, p = ns	56	22	34
HAM-D-24 ≤ 20, YMRS ≤ 12, GAS ≥ 51 for ≥ 4 weeks	Val (77 μg/ml), n = 28		29	(emerging symptoms of a relapse judging by Investigator or a full relapse)	45 weeks	NE	36 weeks	50	22	29

(Continued on next page)

Table 2. (Continued)

Enrichment Index mood episode Randomization criteria	Randomized treatments	Duration	Completion (%)	Primary outcome measure	Median time to intervention/relapse			Rates of relapse/recurrence (%)		
					Any mood	Mania	Depression	Any mood	Mania	Depression
Agents studied only in mania index episode										
Aripiprazole [19]										
Mania YMRS ≤ 10,	ARIP (15 or 30 mg/day), n = 78	100 weeks	18	Time to relapse for a mood episode	Longer, p = 0.011	Longer, p = 0.005	p = ns	33[¥]	12[¥]	14
MADRS ≤ 13 for ≥ 6 weeks	PBO, n = 83		19	(Manic, depressed, or mixed, discontinuation due to lack of efficacy)				52	23	16
Lithium and Olanzapine [20]										
Mania YMRS ≤ 12,	OLZ (13.5 ± 4 mfg/day), n = 217	52 weeks	47	Symptomatic mood episode recurrence	Longer, p = 0.07	—	—	30	14[¥]	16
HAM-D-21 ≤ 8	Li (0.697 ± 0.14 mEq/L), n = 214		33	(YMRS ≥ 15, HAM-D-21 ≥ 15)		—	—	39	23	11
Olanzapine [21]										
Mania YMRS ≤ 12,	OLZ (5–20 mg/day), n = 225	48 weeks	21	Time to symptomatic relapse	174 days, p = 0.001	[£]NE, p < 0.001	[£]49 days, p < 0.001	47[¥]	12[¥]	30
HAM-D-21 ≤ 8 for 2 consecutive weekly visit	PBO, n = 136		7	(YMRS ≥ 15, HAM-D-21 ≥ 15 or hospitalization for any mood)	22 days	[£]26 days	[£]18 days	80	32	39
Lithium or Valproate and Olanzapine [22]										
Mania Syndromic remission	Li (0.76 mEq/L) or Val (67.8 µg/ml) + OLZ (8.6 mg/day), n = 51	18 months	31	Syndromic relapse (DSM-IV criteria for a manic, mixed or depressive episode) & symptomatic relapse (YMRS ≥ 15, HAM-D-21 ≥ 15)	[§]163 days, p = ns	172 days, p = ns	163 days, p = 0.071	37	20	23
	Li (0.74 mEq/L) or Val (66.3 µg/ml) + PBO, n = 48		10		42 days	59 days	55 days	55	29	40

(Continued on next page)

Table 2. (Continued)

Enrichment Index mood episode Randomization criteria	Randomized treatments	Duration	Completion (%)	Primary outcome measure	Median time to intervention/relapse			Rates of relapse/recurrence (%)		
					Any mood	Mania	Depression	Any mood	Mania	Depression
Divalproex, lithium or both, others, or none [23]										
Mania, partially recovered from	Val (71–125 μg/L), n = 187	12 months	[#]38	Time to any mood episode	275 days,[£] p = ns	> 365 days,[£] p = ns	126 days, p = ns	—	—	27[¶]
mania, euthymic after mania	Li (0.8–1.2 mEq/L), n = 91		[#]24	(MRS ≥ 16 or requiring hospitalization) or	189 days, p = ns	[£]293 days, p = ns	[£]81 days, p = ns	—	—	28[¶]
MAR ≤ 11, DSS ≤ 13, GAS ≥ 60 for ≥6 days	PBO, n = 94		[#]25	(antidepressant use or discontinuation because of depressive symptoms)	173 days	[£]189 days	[£]101 days	—	—	26[¶]

[*] Relapsed patients were allowed to continue the study; [†] Data from a reanalysis of the original study [14]; [¥] Significant difference (P < 0.05 to <0.001); [**] Research Diagnostic Criteria for primary major depressive disorder or manic disorder; [***] Excluding those terminated while in good clinical state during year 1 (13%), terminated while in good clinical state during year 2 (3%), and remained well for the study duration (22%); [£] Estimated 25% time to relapse; [§] there was also no significant difference between combination therapy and monotherapy in delaying the time to syndromic relapse, 94 days *versus* 41 days, p = 0.742; [#] Patients receiving antidepressants for depression were allowed to continue the study; [¶] Data from a *post hoc* analysis of the original study [26].

Abbreviations: ARIP, aripiprazole, CGI-S, Clinical Global Impression – Severity scale; DSS, Depression Severity scale; GAS, Global Assessment scale; HAM-D-21, Hamilton Depression Rating scale 21 items; HAM-D-24, Hamilton Depression Rating scale 24 items; Imi, imipramine; Li, lithium; LTG, lamotrigine; MADRS, Montgomery – Asberg Depression Rating Scale; MAR, Mania Rating Scale; MDE, major depressive episode, ME, mood episode; n, number of patients; NE, not evaluable; ns, no significance; OLZ, olanzapine; PBO, placebo; RSDMS, Raskin Severity of Depression and Mania Scale; Val, valproate or divalproex; YMRS, Young Mania Rating Scale.

(bipolar or unipolar) patients were stabilized with lithium-imipramine (*lithium-imipramine-enrichment)* after the remission of an acute episode, and prior to discharge from the hospital (Tab. 1). After stabilization, depressed patients were randomized to receive lithium, imipramine, or placebo [12]. In the primary outcome analysis, bipolar patients treated with placebo or imipramine experienced more episodes than patients receiving lithium. However, the differences were statistically significant during months 5 to 24, but not at the 4 month endpoint. The superiority of lithium in preventing any mood episode relapse compared to imipramine and placebo was further demonstrated when the 24-month data were analyzed as a whole [14]. The difference between the lithium and the imipramine groups was due almost entirely to the higher incidence of manic episodes in the imipramine group. However, the difference between the lithium and placebo groups was due to both manic and depressive episodes (Tab. 2).

In the mania study [13], patients were randomized to receive lithium or placebo after stabilization. 70 of 104 patients on placebo had at least one severe relapse compared to only 31 of 101 on lithium ($p < 0.001$), but no significant difference was found in the rate of moderate relapses between the two groups. Analysis of first or second year results yielded similar findings. Despite the fact that stabilizations were carried out after remissions (mild enrichments) of the acute episodes for both studies, these results may not be generalizable to modern clinical practice due to the unstructured diagnostic criteria for bipolar disorder. Furthermore, as with other early prospective studies, the abrupt discontinuation of lithium in the placebo or imipramine group might have inflated the effect of lithium.

In order to provide more definitive data regarding the long-term preventive treatment of recurrent affective illness, Prien and colleagues (1984) published a double-blinded study of lithium, imipramine, or both in a mixed group of patients with mania, bipolar depression, or unipolar depression [15]. In contrast to the prior studies that enrolled only hospitalized patients, this study permitted the inclusion of outpatients. In addition, diagnoses were based on the Research Diagnostic Criteria (RDC), which were used to define major depressive or manic episodes. Subjects were also required to have a Global Assessment Scale (GAS) score of ≤60, but hospitalization was not required (Tabs 1 and 2).

The primary analysis showed no difference in the rates of depressive recurrence among the three groups (Tab. 2). However, there was a significantly higher rate of manic recurrence in the imipramine monotherapy group than in the lithium monotherapy group (Tab. 2). The Kaplan-Meier life-table analysis showed that lithium alone and lithium in combination with imipramine were superior to imipramine monotherapy in delaying the recurrences of mood episodes. When analyzed by the study index mood episode, patients with a manic or mixed episode responded much better to lithium alone or in combination with imipramine as compared with imipramine alone, with corresponding success rates of 53%, 47%, and 8% respectively. By contrast, there were

no significant differences among the three treatments for patients with a depressive index episode, with corresponding success rates of 22% for lithium, 18% for the combination, and 9% for imipramine alone.

Allowing outpatients into the study and using less restricted treatment during the open-label phase made the results of this study more generalizable. However, like many other early studies of lithium, the time to relapse into mania or depression was not used as a primary outcome. Again, the abrupt discontinuation of lithium in the imipramine alone group might have increased the risk of relapse for this group.

In a *post hoc* analysis of this study that used Kaplan-Meier survival analysis (product-limit method) and a Cox regression model [10], Shapiro and colleagues not only replicated the initial findings, but also determined that patients with a manic index episode who took imipramine were almost 11 times more likely to have a recurrence than subjects taking lithium, and five times more likely than those taking the combination. More importantly, among patients with a depressive index episode, the treatments differed significantly. The combination was significantly superior to imipramine, but it failed to reach statistical superiority to lithium alone. Patients with a depressive index episode taking imipramine were three times more likely to suffer a recurrence than those taking the combination. During a 24 month period, the estimated median time in remission for those with a manic index episode was not calculable for the lithium alone group because fewer than half of patients relapsed; time in remission was 14.8 months for those patients taking the combination, and 3.1 months for those taking imipramine alone. The median time in remission for those with a depressive index episode was 3.4 months for lithium, 7.6 months for combination, and 4.8 months for imipramine, respectively. This *post hoc* analysis highlighted the limitations of statistical analyses performed in previous studies.

Lamotrigine (moderately enriched)

The efficacy of lamotrigine in the maintenance treatment of bipolar disorder was compared with lithium and placebo among patients with both mania and depression index episodes [16, 17]. The design of these two studies was quite similar except for the study index mood episode (Tabs 1 and 2). Patients were 'enriched' by responding to open treatment with lamotrigine adjunctively or as monotherapy prior to randomization. In the depression study [16], the median times to treatment intervention were 93 days for placebo, 170 days for lithium, and 200 days for lamotrigine (combined 200 mg/day and 400 mg/day). Both lithium and lamotrigine were superior to placebo in prolonging the time to intervention for any mood episode (Tab. 2). Lithium and lamotrigine did not differ from each other on this measure. The median times to depression intervention were similar between lithium and placebo, but significantly longer with lamotrigine as compared with placebo. On the other hand, the median

time to mania intervention was significantly longer in lithium- than placebo-treated subjects. Once again there was no significant difference between lithium and lamotrigine. The rates of depression relapse were lower in the lamotrigine group, but rates of manic relapse were lower in the lithium group (Tab. 2).

In the mania study [17], both lamotrigine and lithium were significantly superior to placebo on the median time to intervention for any mood episode (141 days for lamotrigine, 292 days for lithium, and 85 days for placebo). Lamotrigine and lithium did not differ from each other on this measure. Lamotrigine, but not lithium, was superior to placebo at prolonging the time to a depressive episode. Lamotrigine and lithium did not differ on this measure. In contrast, lithium, but not lamotrigine, was superior to placebo at prolonging time to a manic/hypomanic/mixed episode. A trend favored lithium over lamotrigine on this parameter ($p = 0.09$). There were fewer incidences of depressive relapse in the lamotrigine group, but fewer incidences of manic relapse in the lithium group (Tab. 2).

These trials represent the first studies ever conducted in a Bipolar I population in which lithium differentiated from placebo using DSM-IV criteria and modern survival analytic methods, providing some of the strongest evidence available for the efficacy of lithium in the maintenance treatment of bipolar disorder. By using time to intervention for an emerging mood episode as the primary outcome measure, the threshold for detecting a treatment 'failure' was essentially lowered, improving the overall sensitivity for mood worsening [16]. Both studies also slowly tapered lithium for those subjects who received lithium during the open-label phase, rather than abruptly discontinuing the dose. However, these studies have several methodological limitations. In the depression study, comparisons between lithium and lamotrigine are problematic because of the unbalanced design and because the *a priori* primary efficacy analysis combined lamotrigine 200 mg/day and 400 mg/day. As with other studies, in both studies patients with co-morbid anxiety disorders (except for generalized anxiety disorder), substance use disorders, or those who were currently suicidal were excluded. In addition, both studies employed an 'enriched' double-blind discontinuation design, and only about half of patients entering the open-label phase were randomized with completion rates of ≤20% (Tabs 1 and 2).

Lithium and divalproex (moderately enriched)

The efficacy of lithium in the maintenance treatment of bipolar disorder was also compared with divalproex in a lithium-divalproex 'enriched' group with rapid cycling Bipolar I or II disorder. Although a history of at least one episode of hypomania, mania, or a mixed episode within 3 months of the study was required (Tab. 1), 58% of patients presented with depression, 36% with hypomania/mania/mixed state, and 7% with euthymia at the screening visit [18].

The primary analysis did not find significant differences between lithium and divalproex in the time to treatment for a mood episode, the time to premature discontinuation for any reason, the time to treatment for depression, and the time to treatment for a hypomanic/manic/mixed episode. The rates of mood episode relapse were also similar between the two groups (Tab. 2).

Several aspects of the study design were innovative. The open-label stabilization extended up to 6 months, which was longer than any of the previously conducted maintenance studies. The results from the combination of divalproex and lithium, two commonly used treatments for bipolar disorder, are likely to be clinically meaningful. The 20-month duration of the maintenance phase of this study was also longer than most recently conducted maintenance studies in bipolar disorder. More importantly, this study included 62% of patients with Bipolar II disorder that other recent maintenance studies did not include. However, the study had several limitations: 1) the sample size was modest; 2) lithium levels were kept at a minimum of 0.8 mEq/L and divalproex levels at a minimum of 50 μg/ml, which might have disadvantaged the divalproex arm; 3) because the combination of lithium and divalproex possessed better acute and continuation efficacy for mania/hypomania than depression, more patients with depressive episodes not responsive to the combination might have been excluded from the maintenance phase; and 4) this study only included patients with rapid cycling. Therefore, the results might not be applicable to other populations.

Agents only studied in manic episodes

The trend of using mania as a study index episode for maintenance trials has continued unabated in recent years (Tabs 1 and 2). In addition to the limitations of relapse prevention trials, the data from a manic index mood episode may not be applicable to patients presenting with a depressive episode [10] (although lithium and lamotrigine have been studied in both index mood episodes, showing similar results regardless of the index mood state [16, 17]). However, a discussion of these mania studies may shed light on the efficacy of these agents in preventing depressive relapses.

Aripiprazole (highly enriched)

Aripiprazole is the second atypical antipsychotic to be studied in the maintenance treatment of bipolar disorder with a manic index mood episode [19]. This study used the most stringent criteria to date to define stability before randomization, i.e., YMRS total score ≤10 and MADRS score of ≤13 maintained for at least six consecutive weeks (Tabs 1 and 2). At the end of week 26, the time to relapse was significantly longer for the aripiprazole group. A secondary analysis determined that aripiprazole was superior to placebo in delaying

manic relapse, but no significant difference was observed in the time to depressive relapse (Tab. 2). Overall, aripiprazole-treated patients had significantly fewer mood relapses and manic relapses than placebo-treated patients, but there was no significant difference in rates of depressive relapses between the two groups (Tab. 2). The double-blind phase was extended to an additional 74 weeks. At the end of 100 weeks, the results were similar. In addition to other potential limitations (Tabs 1 and 2), this study was limited by the fact that only 36% of patients completed the open-label treatment, the lowest in a non-rapid cycling population.

Olanzapine (highly enriched)

Among antipsychotics, olanzapine is the most studied antipsychotic in the maintenance treatment of bipolar disorder [20–22]. The studied population was either 'enriched' with olanzapine monotherapy [21], olanzapine combination therapy with lithium [20], or olanzapine adjunctive therapy to mood stabilizers [22]. All olanzapine maintenance studies were extensions of acute mania studies in which only those patients who tolerated and responded to the treatments were randomized (Tabs 1 and 2). In the monotherapy study [21], the estimate median time to symptomatic relapses was significantly longer in patients treated with olanzapine compared to that of placebo (Tab. 2). For relapse into mania or depression alone, the estimated 25th percentile time to relapse was significantly longer in the olanzapine group than in the placebo. The rates of symptomatic relapse into any mood were significantly lower in olanzapine-treated patients. However, olanzapine was more effective in preventing manic relapse than depressive relapse (Tab. 2). Similar results were also observed among those subjects who received a combination of olanzapine and lithium during the open-label treatment [20]. Olanzapine and lithium did not significantly differ in the proportion of patients who had a depressive recurrence. However, significantly fewer olanzapine-treated patients had the recurrence of a manic or mixed episode. In contrast, in patients who had inadequate response to mood stabilizer during the first two weeks, the efficacy of adjunctive olanzapine to mood stabilizer was not robust even in the prevention of manic relapses [22] (Tab. 2).

These three olanzapine maintenance studies possess unique features. In the monotherapy study [21], the time to symptomatic relapse was used as the primary outcome measure, which may detect patients with symptoms before clinical intervention. In addition, hazard ratios were calculated to quantify the magnitude of difference between olanzapine and placebo in the odds of relapsing into a mood episode. In the lithium-olanzapine enriched study [20], a 4-week period of discontinuation was employed to minimize the withdrawal effect associated with the discontinuation of lithium and olanzapine. Potential limitations of the three studies are summarized in Tables 1 and 2.

Lithium, divalproex, or both (mildly enriched)

In the first maintenance study employing modern methods such as DSM-III diagnostic criteria for bipolar disorder, time to intervention as a primary outcome, and survival analysis methodology [23], the efficacy of divalproex was compared with lithium and placebo in Bipolar I patients who had a recent manic episode (Tab. 1). In the primary analyses, the time to development of any mood episode did not differ significantly among the treatment groups, although a trend was observed favoring divalproex over lithium ($p = 0.06$). Some secondary outcome measures also favored divalproex over lithium (Tab. 2).

One should interpret these negative results cautiously. First, the lithium group had a larger proportion of patients who dropped out of the study due to intolerance or to non-compliance with treatment. Second, fewer patients were randomized to the lithium group than to divalproex because of a 2:1:1 ratio of assignment, which reduced the power for lithium-placebo comparisons. Another factor that might have contributed to the surprisingly good outcomes in the placebo group was that patients with milder forms of bipolar disorder were selected for this group; thus, the disease burden was milder in the randomized patients than the non-randomized. Although the treatment during the open-label phase was at the discretion of clinicians, the sample was somewhat 'enriched' with divalproex, lithium, or both.

Conclusions and clinical implications

Data from these relapse prevention trials have shown that lamotrigine and lithium are effective in preventing depressive and manic relapses, respectively, regardless of the index mood episode polarity. Both olanzapine and aripiprazole are effective in preventing manic, but not depressive relapses when patients present with mania. The efficacy of divalproex in maintenance treatment requires further study. Obviously, the generalizability of these results is limited, not only because of differences inherent to each individual trial, but also because of the universal exclusion of patients with co-morbid conditions such as substance use disorders, anxiety disorders, and those with severe suicidality. Therefore, when choosing an agent for maintenance treatment of bipolar disorder, it should always be kept in mind that most maintenance studies to date only enrolled patients with Bipolar I disorder during a manic episode, and that all these results were biased in some way because of the relapse prevention design.

Although results from a relapse prevention study are not generalizable, this design will continue to be used because of regulatory requirements for approving new drugs or indications, commercial interests in bipolar research, and the feasibility of conducting a study [11]. There will never be a perfect study even with a prophylaxis design. Future studies should not only focus on efficacy, but should also strive for improved generalizability. The generalizability of a

relapse prevention study can be increased by broadening the inclusion criteria of the study and using less 'enriched' treatments during the open-label phase.

Furthermore, the restricted inclusion criteria of most published studies to date can often exclude patients with severe illness. Because placebo response rates in less-impaired patients are higher, it is difficult to detect differences between a study drug and placebo if only less severely ill patients are enrolled into the study. However, the inclusion of the severely ill may pose legal and ethical challenges. Use of randomized add-on designs such as those employed in the epilepsy studies may help relieve this problem [11]. Gradual discontinuation of open-label drugs may reduce 'false' efficacy of the studied drugs whether it is a crossover or a parallel scheme. Because the polarities of mood episodes are different from the index mood episode at different times after randomization [9], the duration of any study – prophylaxis or relapse prevention – should last long enough (at least 12 months), and analyses should be divided into the first 6 months and afterward so that a spectrum of efficacy in the prevention of early and later relapses can be demonstrated. These early and late relapses may represent different pathological processes. In terms of analysis, the time to event survival analysis data and rate of occurrence of manic or depressive episodes should be reported; this will provide information on how fast, how often, and what kind of mood episodes occur. In addition, hazard ratios should be calculated to quantify the magnitude of difference between a drug and placebo on the odds of relapsing into a mood episode.

In conclusion, it is clear that more longitudinal maintenance studies for bipolar depression are urgently needed, especially in patients presenting with an index depressive episode. Achieving adequate methodological rigor without sacrificing overall study feasibility has become an important scientific focus.

Acknowledgements
This manuscript is supported in part by the National Institute of Mental Health P20 MH-66054 and the NARSAD.

References

1 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537
2 Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 60: 261–269
3 Calabrese JR, Hirschfeld RMA, Frye MA, Reed ML (2004) Impact of depressive symptoms compared with manic symptoms in bipolar disorder: Results of a U.S. community-based sample. *J Clin Psychiatry* 65: 1499–1504
4 MacQueen GM, Young LT, Joffe RT (2001) A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatr Scand* 103: 163–170
5 MacQueen GM, Young LT, Robb JC, Marriott M, Cooke RG, Joffe RT (2000) Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. *Acta Psychiatr Scand* 101: 374–381
6 Goodwin F, Jamison K (eds): (2007) *Manic-depressive illness: bipolar disorder and recurrent depression*, 2nd edition. Oxford University Press, New York

7 Isometsä ET, Henriksson MM, Aro HM, Lönnqvist JK (1994) Suicide in bipolar disorder in Finland. *Am J Psychiatry* 151: 1020–1024
8 Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Tsai-Dilsaver Y, Krajewski KJ (1997) Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure- mania. *Psychiatry Res* 73: 47–56
9 Calabrese JR, Goldberg JF, Ketter TA, Suppes T, Frye M, White R, DeVeaugh-Geiss A, Thompson TR (2006) Recurrence in bipolar I disorder: a *post hoc* analysis excluding relapses in two double-blind maintenance studies. *Biol Psychiatry* 59: 1061–1064
10 Shapiro DR, Quitkin FM, Fleiss JL (1989) Response to maintenance therapy in bipolar illness. Effect of index episode. *Arch Gen Psychiatry* 46: 401–405
11 Calabrese JR, Rapport DJ, Shelton MD, Kimmel SE (2001) Evolving methodologies in bipolar disorder maintenance research. *Br J Psychiatry* 178 (Suppl 41): S157–163
12 Prien RF, Klett CJ, Caffey EM Jr (1973) Lithium carbonate and imipramine in prevention of affective episodes: A comparison in recurrent affective illness. *Arch Gen Psychiatry* 29: 420–425
13 Prien RF, Caffey EM Jr, Klett CJ (1973) Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Arch Gen Psychiatry* 28: 334–337
14 Prien RF, Klett CJ, Caffey EM Jr (1974) Lithium prophylaxis in recurrent affective illness. *Am J Psychiatry* 131: 198–203
15 Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Arch Gen Psychiatry* 41: 1096–1104
16 Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N et al (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 64: 1013–1024
17 Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 60: 392–400
18 Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL (2005) A 20-month, double-blind, maintenance trial of lithium *versus* divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* 162: 2152–2161
19 Keck PE, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, Carlson BX, Marcus RN, Sanchez R; for the Aripiprazole Study Group (2007) Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study *versus* placebo. *J Clin Psychiatry* 68: 1480–1491
20 Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, Koukopoulos A, Cassano GB, Grunze H, Licht RW et al (2005) Olanzapine *versus* lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry* 162: 1281–1290
21 Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, Baker RW, Chou JC, Bowden CL (2006) Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry* 163: 247–256
22 Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, Sachs GS, Kupfer DJ, Ghaemi SN, Feldman PD et al (2004) Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabilizer v. mood stabilizer alone. *Br J Psychiatry* 184: 337–345
23 Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG Jr, Chou JC, Keck PE Jr, Rhodes LJ et al (2000) A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 57: 481–489
24 Calabrese JR, Vieta E, El-Mallakh R, Findling RL, Youngstrom EA, Elhaj O (2004) Mood state at study entry as predictor of the polarity of relapse in bipolar disorder. *Biol Psychiatry* 56: 957–963
25 Ghaemi SN, Pardo RR, Hsu DJ (2004) Strategies for preventing the recurrence of bipolar disorder. *J Clin Psychiatry* 65 (Suppl 10): 16–23
26 Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, Chou JC, Wassef A, Risch CS, Hirschfeld RM et al (2003) Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology* 28: 1374–1382

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Non-pharmacological somatic treatments for bipolar depression

Harold A. Sackeim

Departments of Psychiatry and Radiology, College of Physicians and Surgeons of Columbia University, New York, USA

Abstract

Non-pharmacological somatic treatments have a long history in the care of patients with bipolar disorder. Indeed, electroconvulsive therapy (ECT) is the biological intervention with the longest history of continuous use in psychiatry, and it remains the most effective acute treatment available for either unipolar or bipolar depression or mania. This chapter discusses the therapeutic properties of ECT in the acute treatment of bipolar depression, mania, and unipolar depression. It also reviews the essential limitations of ECT – its adverse cognitive effects and high rates of relapse. The chapter introduces new developments in this field that have created forms of ECT administration that dramatically reduce the frequency and severity of adverse cognitive effects. These include critical alterations in the administration of ECT, such as the use of ultrabrief electrical stimuli, and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST). Additional novel interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) are also reviewed.

Introduction

The pharmacological treatment of bipolar disorder has always presented key challenges. Results of the recent national study of unipolar depression, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) have generally indicated that response and remission rates are disappointingly low and that large percentages of patients do not achieve substantial improvement if they have not benefited from two adequate treatment trials [1]. Furthermore, relapse is both more rapid and more likely in patients who prospectively manifest treatment resistance during sequential pharmacological trials. Similarly, the national study of bipolar depression, Systematic Treatment Enhancement Program for Bipolar Depression (STEP-BP) found disappointingly low rates of sustained recovery when paroxetine or buproprion were added to a mood-stabilizing agent, and these rates did not differ from the group receiving a mood-stabilizing agent and placebo [2].

In addition to high rates of treatment resistance in bipolar depression, pharmacological management has been beset by two other major conundrums.

There is considerable concern that exposure to antidepressant medications may induce or exacerbate symptoms of agitation in bipolar patients and in some cases result in a switch into a hypomanic or manic state. For example, 44% of the first 500 patients to enter the STEP-BP study retrospectively reported a switch to a hypomanic, manic, or mixed states within 12 weeks of starting antidepressant treatment [3]. This seemed especially likely in patients with short duration of illness, exposure to multiple antidepressant trials, and a previous history of switching. An independent concern was raised during the era when tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the mainstays of antidepressant treatment. It was suggested that these agents, while often effective in the acute treatment of bipolar depression, could accelerate the progression of illness, resulting in shorter periods of euthymia and, in some cases, inducing rapid-cycling [4]. These concerns about the limitations of pharmacological treatment in bipolar depression are accentuated with respect to the management of bipolar mania, where there is a high rate of morbidity and mortality and an especially great need for rapid and effective treatment.

Non-pharmacological somatic treatments have a long history in the care of patients with bipolar disorder. Indeed, electroconvulsive therapy (ECT) is the biological intervention with the longest history of continuous use in psychiatry, and it remains the most effective acute treatment available for either unipolar or bipolar depression or mania [5]. That is a powerful statement, as it suggests that ECT is one of the few treatments with therapeutic properties in the acute treatment of either bipolar depression or mania, and, even more remarkably, that it is likely the most effective acute treatment available for either condition. The essential limitations of ECT – its adverse cognitive effects and high rates of relapse – are discussed below [6–8]. However, new developments in this field have created forms of ECT administration that dramatically reduce the frequency and severity of adverse cognitive effects. These include critical alterations in the administration of ECT, such as the use of ultrabrief electrical stimuli [9], and the development of new forms of convulsive therapy, particularly Magnetic Seizure Therapy (MST) [10] and Focal Electrically Administered Seizure Therapy (FEAST) [11].

ECT has developed to the point that the total exposure of the brain to an electrical stimulus over a complete course of treatment may be less than 1/10th of a second. The electrical stimulus that is applied is less than one amp at the scalp surface and markedly less than that in neuronal tissue. Thus, a weak and remarkably transient electrical stimulus results in the most profound acute antidepressant and antimanic effects seen in bipolar disorder. Because the intensity of the electrical stimulus is known not to result in neuronal injury, and because this stimulus is ‘ephemeral’, having no ‘metabolites’, residue, or other long-term physical existence in the brain, the therapeutic properties of ECT must result from the brain’s response to being stimulated in this fashion. In essence, ECT is a paradigm for how endogenous neural processes can produce profound antidepressant and antimanic effects, if triggered in an appropriate fashion.

This observation provides the essential rationale for a host of other brain stimulation technologies that do not rely on seizure induction as part of their therapeutic mechanisms of action. ECT is a model where an intense single train of stimulation produces an ictal event that, in turn, results in a large set of neurochemical, neurophysiological, and neuroanatomic alterations, some of which are targeted at seizure suppression, some of which are intrinsic to the electrical stimulation (independent of whether a seizure occurs), and others that may be seizure-induced, but are not critical in seizure termination. In other words, it has become apparent in recent years that electrical stimulation of the brain, independent of whether seizures are produced, results in neurochemical release; the specifics of the magnitude and type of neurotransmitter and peptides involved depends on the intensity and patterns of stimulation. Beyond neurochemical alterations, electrical stimulation of the brain can enhance or block signal transmission, and perhaps in some cases, improve signal-to-noise ratios compromised by damage in distal regions. Consequently, the field of brain stimulation, currently in its initial development, opens the possibility for focal control of neurochemical alterations, second messenger processes, and modulation of brain communication systems in ways that have never been achieved with pharmacological interventions. This chapter reviews both what is known about current brain stimulation technologies in the treatment of bipolar depression, and highlights potential new developments.

Electroconvulsive therapy

Ladislas von Meduna, acting under a view common at the time that there was an intrinsic antagonism between epilepsy and schizophrenia, introduced convulsive therapy. While others had tried blood transfusion across these illnesses, von Meduna tested the bold concept that exogenously-induced seizures might reduce symptoms in patients with schizophrenia. Using camphor in oil as the induction method, he reported that a remarkable number of patients with a diagnosis of schizophrenia showed marked symptomatic improvement with this method [12]. This assertion proved controversial, because the predominant view at the time in biological psychiatry was that the major forms of mental illness were due to congenital or degenerative conditions and could not be ameliorated, even palliatively, by any intervention. As a result of taking this position, von Meduna lost his academic post. His method of chemical seizure induction was quickly replaced by the use of Metrazol, a gamma aminobutyric acid (GABA) antagonist that more reliably resulted in seizures. Convulsive therapy was widely adopted worldwide.

In 1938, Cerletti and Bini in Rome demonstrated that electrical stimulation was the preferred method of seizure induction. It had the advantages of ensuring that only one seizure occurred, whereas recirculation was always possible with chemical induction; more critically, seizure induction was instantaneous after application of the electrical stimulus. This advantage was critical because

chemical methods often involved a substantial delay, frequently resulting in full panic attacks prior to seizure onset, and subsequent refusal of treatment. The electrical stimulus itself was poorly conceived and basically varied only as a function of the amplitude of the sine wave voltage waveform output by the standard electrical grid, with crude control over the duration of exposure. There was little consideration about whether this type of electrical signal was optimal for neural tissue. Subsequent developments during the 1950s introduced the use of muscle relaxants (first curare and then succinylcholine) to block the convulsive motor manifestations of seizures. This innovation markedly reduced the rate of vertebral fractures, but required the introduction of general anesthesia. Whereas the application of the electrical stimulus invariably resulted in loss of consciousness (for the most part, regardless of whether a seizure was induced), the pre-application of a muscle paralyzing agent, and the subsequent inability to breathe without assistance, necessitated for psychological reasons the use of general anesthesia.

Soon after the introduction of ECT it was recognized that the intervention had greater success in the treatment of mood disorders than schizophrenia, at least in the short-term. Of course, diagnosis at the time had questionable reliability, but the general consensus has been that in the middle of the 20th century, mood disorders were under-recognized and schizophrenia over-diagnosed in the US. Thus, the observation that mood disorders responded at remarkably high rates to ECT, and more so than patients with schizophrenia, if anything, likely underestimated the true difference. Early on, Kalinowsky and others would claim that approximately 80–90% of patients with depressive illness would achieve remission after receiving approximately 6–12 treatments with ECT [13].

This estimate, extending across unipolar and bipolar depressive conditions, has not been realized in recent years. Regardless of treatment methods, remission rates with ECT are somewhat more modest [8, 9, 14–16]. This shift is likely due to the fact that when ECT was introduced there were few, if any, competing treatments, and ECT was commonly used at the outset. Today, resistance to pharmacological treatments is the leading indication for the use of ECT. Several, but not all, studies have found that degree of medication resistance is predictive of ECT outcome, and that, in general, patients who have not benefited from adequate psychopharmacology and/or who have long durations of their current episode of depression have somewhat inferior outcomes [15, 17]. Thus, remission rates on the order of 60–70% may be a more realistic estimate, especially if remission is defined as maintaining nearly complete symptomatic improvement for at least 1 week following the end of the treatment course.

The extent of expected clinical improvement with ECT exceeds that of any other known antidepressant treatment [5]. Typically, in ECT research the bar is set higher for what is defined as response or remission than in standard pharmacological trials, and yet the response and remission rates are higher, despite the concentration of patients with treatment resistance who receive ECT. For

example, in the STAR*D study, remission rates among unipolar depressed patients who had not achieved adequate benefit after two pharmacological treatments were roughly 10% [1]. Such patients would be expected to remit at substantially higher rates if treated with ECT.

There is no evidence that the distinction between bipolar and unipolar depression affects the likelihood of achieving response or remission with ECT. Retrospective and prospective comparisons have generally indicated that both forms of depression respond or remit at approximately the same rates. However, there are two caveats to this claim. First, it has been shown that patients with bipolar depression require fewer treatments to achieve response or remission than patients with unipolar depression. This was first reported in samples treated in randomized protocols at the New York State Psychiatric Institute (NYSPI), with the observation that, on average, patients with bipolar depression who responded or remitted required approximately 1.5 fewer treatments than unipolar patients meeting the same outcome criteria [18]. This observation was subsequently replicated in a very large naturalistic study of patients treated in community settings [19].

This observation reflects a large effect, given that the bulk of clinical gains with ECT are usually obtained within the first six treatments. Bipolar depressed patients appear to achieve this benefit more rapidly. The only factor known to have substantial impact on the speed of response with ECT is the extent to which dosage exceeds seizure threshold, with higher dosage leading to more rapid improvement [14]. However, multiple studies have failed to find a difference in initial seizure threshold in bipolar and unipolar depression, and in the studies at NYSPI, dosage was always adjusted to a specific level relative to seizure threshold for all patients in a treatment condition. Bipolar patients appeared to improve more rapidly regardless of whether they received right unilateral or bilateral ECT or the particular dosage that was applied. This would suggest that the neurophysiological response to exogenous seizure induction may differ in bipolar and unipolar depression. For example, it has long been speculated that it is the endogenous anticonvulsant response of the brain in terminating the seizure that is critical to achieving antidepressant effects [20], while others have noted that ECT results in remarkably rapid onset of neuroplastic changes, including neurogenesis [21]. Thus, there are a variety of avenues needing exploration to account for the more rapid onset of benefit in bipolar depression.

The second area in which efficacy in bipolar depression may be altered pertains to the subset of patients with psychotic or delusional depression. It has often been stated that psychotic features are over-represented in patients with bipolar relative to unipolar depression, although this is not firmly established. Regardless, most studies that have compared the efficacy of ECT in patients with and without psychotic features have found higher rates of response and remission in psychotic depression [5]. Until the advent of atypical antipsychotic medications, only a very small minority of patients with psychotic depression had received an adequate combined pharmacological trial prior to

ECT; the dosage of antipsychotic medication considered adequate was often intolerable, especially in the elderly, and especially when combined with the available antidepressant medications [22]. Relatively low rates of established medication resistance continue to characterize patients whose depression has psychotic features, as treatment with ECT is also often considered due to clinical urgency, history of response, and patient preference.

Two principal issues distinguish the management of the patient with bipolar depression during ECT. The first pertains to concomitant pharmacological agents and the second to the emergence of hypomania or mania. In general, in the United States it had long been recommended that all patients be withdrawn from psychotropic agents during ECT, with the exception of antipsychotics in patients with psychotic features [5]. There was little evidence that concomitant antidepressant medications enhanced clinical outcome, and some concern that concomitant anxiolytics, especially benzodiazepines and perhaps anticonvulsants, interfered with the therapeutic process.

Recently, a large, multi-site study randomized unipolar and bipolar depressed patients to concomitant treatment with placebo, nortriptyline, or venlafaxine during the course of ECT (unpublished data). There was significant enhancement of the therapeutic benefit in patients treated with nortriptyline or venlafaxine relative to placebo, and some evidence that concurrent nortriptyline reduced the cognitive side effects of ECT. Over 20% of the 319 participants in this study had bipolar depression and there was no evidence that these results differed with polarity. Thus, this recent evidence may lead to a revision of the longstanding view that antidepressants should be stopped during the administration of ECT. For instance, in the intent-to-treat sample, the remission rates following ECT among unipolar patients for those treated with nortriptyline or placebo were 61.2% and 43.7%, respectively. The comparable remission rates for bipolar depressed patients were 72.0% and 59.3%. This reflects substantial outcome enhancement.

Research in schizophrenia has supported the safety and clinical utility of combining antipsychotic medications and ECT, with evidence for synergistic clinical effects [23]. However, as regards mood disorders, there has long been concern that agents with anticonvulsant properties, especially benzodiazepines, may interfere with the seizure process and diminish efficacy. The evidence for diminished efficacy is entirely circumstantial, stemming mainly from naturalistic, retrospective studies. It is possible that the most agitated patients are the most likely to receive the highest doses of these agents, thus confounding these observations. Nonetheless, it is prudent to limit both benzodiazepine and anticonvulsant use during ECT. Because ECT has profound anticonvulsant properties, often leading to a decrease in anticonvulsant dosage in epilepsy patients, and because improvement is usually marked and rapid in psychic anxiety, these dosage limitations are usually well tolerated. Another problematic issue is exposure to lithium during ECT. It is well-established that a minority of individuals will develop a severe organic brain syndrome when the two are combined, which diminishes rapidly once the lithium is stopped. For this reason,

most expert groups recommend discontinuation of lithium during an acute ECT course, or, at minimum, withholding doses the evening before a treatment [5].

The major limitations associated with ECT are its side effects, rates of relapse, and patient acceptability. There is always the concern that treatment of the patient in a mixed state or in bipolar depression will provoke a hypomanic or manic reaction. This certainly does happen with ECT. However, careful examination of the outcomes of hundreds of patients prospectively followed at NYSPI show that such reactions occurred at remarkably small rates. The reasons for this are unknown, but may reflect the antimanic properties of the treatment and/or its marked anticonvulsant effects. There is little consensus on how to manage emergent mania during ECT. Many practitioners will continue the treatment if the symptoms are mild, but others terminate the ongoing course of ECT, institute a new pharmacological regimen, and observe the patient for the emergence of severe manic symptoms.

Only in recent years have the adverse long-term effects of ECT on memory been documented. Both randomized and naturalistic studies have shown that methods of ECT administration may substantially differ in their impact on the degree of retrograde amnesia observed 6 months following treatment [7, 9]. Indeed, recent work has, for the first time, shown that the objective findings can co-vary with patients' subjective reports of deficits [24]. It has become evident that *how* ECT is administered can radically alter the likelihood of long-term negative effects. For instance, the introduction of an ultrabrief form of stimulation, when coupled with the right unilateral electrode placement, substantially reduces cognitive effects at all time points [9]. There is evidence that older bipolar patients may at baseline have greater cognitive impairment, especially memory deficits, than similarly aged unipolar patients, presumably because of their history of more frequent episodes [25]. However, there is no evidence that bipolar patients are more at risk than unipolar patients with respect to ECT's cognitive side effects.

ECT is one of the only psychiatric treatments that is discontinued once effective. Relapse is common following ECT-induced remission, and modern prospective studies document that approximately 50% of remitted patients relapse despite aggressive continuation therapy with pharmacological agents or ECT; not surprisingly, medication resistance is a strong predictor of relapse [9, 15, 16, 26]. However, as the STAR*D study highlighted, durability of benefit appears to be a significant and general problem in the management of depression, regardless of which treatment patients receive. Furthermore, and although sample sizes have been generally small, there is no evidence that relapse risk following ECT differs in unipolar and bipolar depression.

Magnetic Seizure Therapy (MST)

It has been established that the current paths of the ECT stimulus and the dosing within those paths have profound effects on the efficacy and side effects of

the treatment [14, 15, 27]. Yet, with traditional ECT, the high impedance of the skull and other anatomic reasons limit the capacity to restrict current paths. A treatment method that offers superior control over anatomic distributions of the current, and greater precision in intracerebral dosing (current densities) should be a major advance. Sackeim (1994) proposed that use of a time-varying train of magnetic pulses might achieve these goals, and termed the intervention, Magnetic Seizure Therapy (MST) [10]. Theoretically, the transparency of the scalp and skull to the magnetic field would allow for greater anatomic precision, and the fact that dosage was primarily determined by distance from the coil would limit deep stimulation and allow for greater dosing precision.

The future of this modality is uncertain. Preliminary studies are underway and have generally shown a relatively low level of cognitive side effects but uncertain efficacy [28, 29]. From an engineering standpoint, the major limitation to MST is that it has not been possible to develop MST systems sufficiently powerful to elicit seizures from regions in frontal cortex using coils that maximize focality of stimulation. This limitation is especially problematic because the extent that dosage is substantially above seizure threshold can be a critical determinant of efficacy.

Focal Electrically Applied Seizure Therapy (FEAST)

FEAST is a new intervention that also offers the possibility of greater anatomic precision in the site of seizure initiation. Sackeim (2004) reasoned that by using unidirectional current flow, thus having a consistent anode and cathode, and by altering the geometry of the electrodes, one could achieve greater precision in the anatomic distribution of currents paths [11]. The basic principles underlying FEAST have been validated in limited research with non-human primates and in a small open pilot investigation.

Repetitive Transcranial Magnetic Stimulation (rTMS)

One can induce current in neural tissue by exposing the tissue to a time-varying magnetic field. With a magnetic coil placed on the surface of the head, anatomic resolution and distribution will be determined mainly by coil geometry and detectable current densities can generally reach two centimeters deep. A large number of open and blinded studies have raised the possibility that repetitive stimulation at high frequency (>5 Hz) over the left dorsolateral prefrontal cortex (DLPFC) has antidepressant effects. A smaller number of studies suggest that slow stimulation (≤1 Hz) over the right DLPFC may have similar effects. Several meta-analyses have concluded that randomized sham-controlled trials have shown consistent antidepressant effects [30], and a large industry-sponsored multi-site trial also reported generally positive findings [31].

Despite this evidence, there is controversy about the role of rTMS as an antidepressant treatment, and it has yet to be approved by the FDA for routine clinical use. The evidence is convincing that rTMS has a very strong safety profile, with transient pain at site of stimulation. However, some question whether the magnitude of the antidepressant effect is of clinical consequence, and there have been methodological concerns regarding the adequacy of blinding and other technical issues. Fundamentally, there is a need to amplify rTMS's antidepressant effects. This may occur through patient selection factors. For instance, in the industry trial, patients with the lowest levels of medication resistance showed a robust clinical effect that was much diminished in more resistant patients. Alternatively, there has been very little work optimizing rTMS stimulation parameters to amplify the clinical signal. As yet there is no evidence that patients with bipolar depression differ in response to rTMS from patients with unipolar depression.

Vagus Nerve Stimulation (VNS)

VNS is approved by the FDA specifically for treatment-resistant depression (either unipolar or bipolar). 80% of the fibers in the vagus nerve are afferent to brain, and basic research has shown that repetitive electrical stimulation of the vagus nerve can have widespread effects on brain physiology and neurochemistry. In 1997, VNS was approved as a treatment for epilepsy due to its anticonvulsant properties. Subsequently, an initial pilot study in 60 patients suggested that VNS had clinically significant long-term effects for depressed patients with marked medication resistance [32]. A subsequent randomized, sham-controlled, multi-site study failed to detect a difference between active and sham VNS after a 10-week treatment period [33]. However, as in the pilot study, a substantial number of patients were improved after a year. Notably, it also seemed that VNS had remarkable durability of benefit [34]. A surprisingly large percentage of patients who showed clinical benefit after starting VNS maintained that benefit for periods of up to 2 years. Thus, it is possible that this intervention may take a considerable amount of time to show antidepressant effects, and a high capacity to maintain benefit when achieved. As yet, there is no evidence that unipolar and bipolar depressed patients differ in response to VNS.

The absence of controlled data establishing the claims of late onset of action and strong durability of benefit have limited patient access to VNS, due to the reluctance of insurers to reimburse for the procedure. New studies are being planned to address these challenges.

Deep Brain Stimulation (DBS)

Stimulation through electrodes indwelling in specified locations in the brain offers unique opportunities to modulate specific pathways for therapeutic ben-

efit. DBS is a FDA-approved treatment for dystonia, essential tremor, and tremor in Parkinson's disease. Evidence gleaned from the treatment of these disorders suggest that there may be multiple entry points to modulate a network for therapeutic purpose, and that these networks differ anatomically among the movement disorders [35].

DBS in mood disorders is an experimental procedure with a small knowledge base. The morbidity/mortality risk of DBS is significant due to the invasiveness of the procedure. Therefore, DBS in individuals with mood disorders is only conducted in a research setting in patients with markedly resistant and severe major depression. The experience so far has been limited to small, open-label pilot studies. The targets for stimulation have been the anterior cingulate in the work led by Mayberg [36], and the anterior limb of the internal capsule in the work led by Greenberg [37].

Mood and movement disorders may differ in how rapidly treatment paradigms are developed. First, knowledge of specific circuitry is less advanced in the case of mood disorders. Second, the nuclei targeted within the striatum are relatively small in the case of movement disorders, and yet specific location within a nucleus is critical to outcome. In the case of major depression, the structures most often implicated as targets for modulation are large gray matter areas like the anterior cingulate or right orbital frontal cortex. However, in most contexts the DBS signal does not broadcast well over wide regions of tightly packed grey matter. Thus, it is difficult to modulate over broad areas and there is little knowledge to guide targeting to lower volume areas. Consequently, the work by Mayberg and colleagues [36] has involved stimulating the white matter under the anterior cingulate, hoping to modulate activity within the cingulate itself. Similarly, the group stimulating in the internal capsule [37] are also stimulating white matter tracks that may act at distant structures. Indeed, initial observations with this target suggest that therapeutic effects in major depression may be contingent on use of high intensities of stimulation.

The initial experience with DBS in treatment-resistant major depression has been largely positive. Despite small sample sizes, unblinded and uncontrolled trials, and many other caveats, both groups conducting this research have achieved encouraging clinical outcomes, including the durability of the treatment response. Other pilot studies of DBS have implicated the accumbens as a target to specifically modulate anhedonia in depression. Randomized, blinded, sham-controlled trials of DBS in treatment-resistant depression are now being planned.

References

1 Rush AJ (2007) STAR*D: what have we learned? *Am J Psychiatry* 164: 201–204
2 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant

treatment for bipolar depression. *N Engl J Med* 356: 1711–1722
3 Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, Thase ME, Sachs GS (2007) Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J Clin Psychiatry* 68: 1472–1479
4 Wehr TA, Goodwin FK (1979) Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36: 555–559
5 American Psychiatric Association (2001) *The practice of ECT: recommendations for treatment, training and privileging. Second Edition.* American Psychiatric Press, Washington DC
6 Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001) Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 285: 1299–1307
7 Sackeim H, Prudic J, Fuller RB, Keilp J, Lavori PW, Olfson M (2007) The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 32: 244–254
8 Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA (2004) Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry* 55: 301–312
9 Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, Berman RM, Brakemeier EL, Perera TD, Devanand DP (2008) Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation* 1: 71–83
10 Sackeim, HA (1994) Magnetic stimulation therapy and ECT. *Convulsive Ther* 10: 255–258
11 Sackeim HA (2004) The convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation. *Clin Neurosci Rev* 4: 39–57
12 Meduna LJ (1935) Versuche über die biologische Beeinflussung des Abaufes der Schizophrenie: I. Campher und Cardiozolkrämpfe. *Z Neurol Psychr* 152: 235–262
13 Kalinowsky LB, Hoch PH (1946) *Shock treatments and other somatic procedures in psychiatry.* Grune & Stratton, New York
14 Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, Mcelhiney MC, Coleman EA, Settembrino JM (1993) Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy *N Engl J Med* 328: 839–846
15 Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 57: 425–434
16 Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, Mueller M, Bernstein HJ, O'Connor K, Smith G et al (2006) Continuation electroconvulsive therapy *versus* pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 63: 1337–1344
17 Prudic J, Sackeim HA, Devanand DP (1990) Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Res* 31: 287–296
18 Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Roose SP, Sackeim HA (2001) ECT in bipolar and unipolar depression: differences in speed of response. *Bipolar Disord* 3: 95–104
19 Sackeim HA, Prudic J (2005) Length of the ECT course in bipolar and unipolar depression. *JECT* 21: 195–197
20 Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR (1983) Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. *Biol Psychiatry* 18: 1301–1310
21 Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, Spitzer G, Santarelli L, Scharf B, Hen R et al (2007) Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. *J Neurosci* 27: 4894–4901
22 Mulsant BH, Haskett RF, Prudic J, Thase ME, Malone KM, Mann JJ, Pettinati HM, Sackeim HA (1997) Low use of neuroleptic drugs in the treatment of psychotic major depression. *Am J Psychiatry* 154: 559–561
23 Sackeim HA (2003) Electroconvulsive therapy and schizophrenia. In: SR Hirsch, D Weinberger (eds): *Schizophrenia, Second Edition.* Blackwell, Oxford
24 Berman RM, Prudic J, Brakemeier EL, Olfson M, Sackeim HA (2008) Subjective evaluation of the therapeutic and cognitive effects of electroconvulsive therapy. *Brain Stim* 1: 16–26

25 Burt T, Prudic J, Peyser S, Clark J, Sackeim HA (2000) Learning and memory in bipolar and unipolar major depression: effects of aging. *Neuropsychiatry Neuropsychol Behav Neurol* 13: 246–253
26 Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990) The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol* 10: 96–104
27 Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S (1987) Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am J Psychiatry* 144: 1449–1455
28 Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA (2003) Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology* 28: 1852–1865
29 Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA (2001) Magnetic seizure therapy of major depression. *Arch Gen Psychiatry* 58: 303–305
30 Burt T, Lisanby SH, Sackeim HA (2002) Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol* 5: 73–103
31 O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, Mcdonald WM, Avery D, Fitzgerald PB, Loo C et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 62: 1208–1216
32 Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S et al (2001) Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 25: 713–728
33 Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ et al (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry* 58: 347–354
34 Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J (2007) Durability of antidepressant response to vagus nerve stimulation (VNSTM). *Int J Neuropsychopharmacol* 10: 817–826
35 Hardesty DE, Sackeim HA (2007) Deep brain stimulation in movement and psychiatric disorders. *Biol Psychiatry* 61: 831–835
36 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. *Neuron* 45: 651–660
37 Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA (2006) Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 31: 2384–2393

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Potential novel treatments for bipolar depression

Carlos A. Zarate Jr and Husseini K. Manji

Laboratory of Molecular Pathophysiology & Experimental Therapeutics, Mood and Anxiety Disorders Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Existing pharmacological treatments for bipolar disorder (BPD), a severe recurrent mood disorder, is in general insufficient for many patients. Despite adequate doses and treatment duration, many individuals afflicted with this disease continue to experience mood episode relapses, residual symptoms, and functional impairment. In contrast to the manic phase of the illness where a fairly large variety of effective treatments are available, in bipolar depression effective therapeutics are scarce. This is especially troubling because the long-term course of BPD is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes. Novel therapeutics – that is, drugs that do not include the existing antipsychotic, antiepileptic, and antidepressant medications – currently being studied to determine their efficacy and safety in bipolar depression include modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, AMPA potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Further study of these drugs will investigate their clinical utility in bipolar depression, and further our understanding of relevant drug targets.

Introduction

Previous chapters of this volume explored the epidemiology, definition, classification, outcome, and currently used pharmacological treatments for bipolar depression. However, it is becoming increasingly clear that current pharmacotherapies are insufficient for many patients with bipolar depression. For instance, a large-scale study funded by the National Institute of Mental Health (NIMH) failed to find any benefit to antidepressant use for patients with Bipolar I and II depression over the course of 26 weeks [1]. In contrast to the manic phase of the illness, where a fairly large variety of effective treatments are available – most notably antipsychotic and antiepileptic agents – in bipolar depression efficacious therapeutics are scarce. This is especially worrisome because the long-term course of bipolar disorder (BPD) is dominated by recurrent depressive episodes and lingering depressive symptoms rather than hypomanic/manic episodes [2].

This chapter will review the efficacy and safety of several novel therapies for bipolar depression. Promising drug targets and agents for bipolar depression involve several systems, including the melatonin and serotonergic

(5-HT2C receptor) systems, the dopaminergic system, the glutamatergic system, and the hypothalamic-pituitary adrenal (HPA) axis. In addition, the GSK intracellular signaling cascade, the arachidonic acid cascade, and the oxidative stress system appear to be worthy of further study. This chapter will review several specific agents, including modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, memantine, ketamine, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. Table 1 summarizes the use and profile of these drugs, all of which meet the category of clinical evidence rating (see Ch. 9) of B, C, or D. The chapter does not review studies in which the treatment of bipolar depression was not the primary issue. Omega-3 fatty acids will also not be reviewed here as they have been extensively reviewed elsewhere (see [3]) and because a large, randomized, controlled study failed to find significant benefits for their use in bipolar depression [4]. Finally, we will not review non-pharmacological somatic treatments (see Ch. 11 for a thorough review of this topic).

Drugs that affect multiple systems

Modafinil

Modafinil is currently approved by the U.S. Food and Drug Administration (FDA) as a wakefulness-promoting agent for the treatment of excessive daytime sleepiness in narcoleptic patients [5]. The presumptive mode of action of this drug is currently unknown, but is hypothesized to be multisystemic in origin. Modafinil has been reported to affect the following neurotransmitter systems: glutamate, GABA, hypocretin, and to a lesser extent, the dopaminergic and noradrenergic systems [6].

Clinically, modafinil appears to benefit patients with mood disorders, particularly in cases where sedation is clinically troublesome. In a 6-week, randomized, double-blind, placebo-controlled evaluation of modafinil (mean daily dose 177 mg) in subjects with bipolar I or II depression who did not adequately respond to mood stabilization with or without adjunctive antidepressant therapy (n = 87), there was both greater baseline to endpoint change and change in week 2 onwards in patients treated with modafinil than with placebo [7]. No manic switches were reported. In another study, Frye and colleagues (unpublished, reported in [8]) compared the add-on modafinil (100 or 200 mg in the morning for 3 weeks) to placebo in the treatment of patients with BPD who also had residual fatigue, depressive symptoms, or both. The study drug was significantly more effective than placebo on a variety of scales, including baseline to endpoint change on the Inventory for Depressive Symptoms (IDS), percentage response rate, remission rate, and Clinical Global Impression (CGI) improvement. In addition, modafinil was not found to be significantly associated with treatment-emergent mania. One published

Table 1. Putative drug targets and agents for the treatment of BPD depression

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Multiple	Modafinil (mean dose 177 mg/day)	87 BPD I or II	DB, PC, add-on	Greater baseline to endpoint change in modafinil *versus* placebo, and from week 2 on between groups; no manic switches	Largely unknown; reported effects on glutamate, GABA, hypocretin, and to a lesser extent, the dopaminergic and noradrenergic systems	No statistically significant side effects. More common side effects included headache, insomnia	[7]
Dopaminergic and Bcl-2	Pramipexole 1–2.5 mg/day	22 BPD I or II	DB, PC, add-on, 6 weeks	Response: Pramipexole: 67%, PBO: 20%; no difference in manic switch; one patient on pramipexole became hypomanic	D2/3 agonist and Bcl-2 enhancer	Nausea more common with pramipexole; other side effects reported include sedation and headache	[12]
Dopaminergic and Bcl-2	Pramipexole 1–3 mg/day	21 BPD II	DB, PC, add-on, 6 weeks	Response: Pramipexole: 60%, PBO: 9%; no difference in manic switch	D2/3 agonist and Bcl-2 enhancer	No statistically significant difference in side effects between the groups; more common side effects with pramipexole: insomnia, tremor, gastrointestinal complaints, and somnolence	[11]
Oxidative stress (Glutathione)	N-Acetyl cysteine (NAC) (1 g twice daily)	75 BPD	DB, PC, add-on, 24 weeks	NAC significantly improved MADRS scores by endpoint	Enhances brain glutathione levels restoring oxidative imbalances	No statistically significant differences in side effects; more common side effects included headaches (18% NAC, 8% placebo), heartburn(16% NAC, 8% placebo), and increased pain in joints (16% NAC, 8% placebo).	[17]

(Continued on next page)

Table 1. (Continued)

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Cholinergic	Scopolamine hydrobromide infusion 1–2–4.0 μg/kg	10 UP, 9 BPD	DB, PC	Significant reductions in MADRS scores comparing endpoint with baseline; no manic switches	Antimuscarinic	Side effects numerically more common with scopolamine: dry mouth, blurred vision, lightheadedness, dizziness, and hypotension; euphoria was reported to be no different than placebo	[29]
Melatonin and Seratonergic (5-HT2C)	Agomelatine 25 mg/day	21 BPD I	Open-label, add-on, 6 weeks acute, 46 weeks extension	Response: acute phase: 81%; no significant side effects in acute phase or manic switches	Agonist of melatonin MT1 and MT2 receptors and 5-HT2C antagonist	No significant adverse events during the acute phase; during the extension phase three of 19 experienced hypomanic/manic episodes, one of which was treatment related	[45]
Glutamate release and AMPA receptor	Riluzole 100–200 mg/day	14 BPD	Open-label, 8 weeks, add-on	Significant reductions in MADRS scores comparing endpoint with baseline; no manic switches	Inhibitor of glutamate release, enhancer of AMPA trafficking and expression of glutamate reuptake transporters	Most common side effects were fatigue, decreased salivation, reduced sleep, nausea, weight loss, and blurred vision	[56]
NMDA antagonist (use dependent)	Memantine 10–20 mg/day	2 BPD, 4 weeks and 2nd case not specified	Case series, add-on	Improvement in cognition and mood symptoms	Use dependent NMDA antagonist	Not specified	[61]
Glucocorticoid synthesis	Metyrapone 2,000–4,000 mg/day	3 BPD, 6 UP	Open-label, 2 weeks	5/9 responded. Reduction in MADRS was correlated to decrease in 11-deoxycortisol metabolites	Inhibitor of GC synthesis	Not specified	[70]

(Continued on next page)

Table 1. (Continued)

Drug target	Drug/dose	Population	Study design	Results	Presumptive mechanism	Side effects	Ref
Glucocorticoid synthesis	Ketoconazole 400–800 mg/day	8 UP, 2 BPD, 7 completers	Open-label, 6 weeks	7/7 completers had gradual improvement in mood	Inhibitor of GC synthesis	Three subjects dropped out because of side effects	[71]
Glucocorticoid synthesis	Ketoconazole up to 800 mg/day	6 BPD I or II	Open-label, add-on, 4 weeks	All three completers responded on HAM-D	Inhibitor of GC synthesis	Mild nausea and constipation	[69]
GR II	Mifepristone 600 mg/PBO	20 BPD, add-on	DB PC CO, 1 week	Statistically significant improvement in MADRS and cognition	GR II antagonist	No dropouts due to side effects and no manic switches	[72]
DHEA	DHEA max 90 mg/day	20 UP, 2 BPD	DB PC, 6 weeks monotherapy/ add-on	Response: 5/11 on DHEA and one (0/11) on PBD	DHEA	Well tolerated; no subjects dropped out because of side effects	[86]
Arachidonic acid metabolism	Celecoxib 400 mg/day	28 BPD depressed or mixed episode	DB, PC, add-on, 6 weeks	Celecoxib was more effective than placebo only at week 1 but not at study endpoint	COX-2 inhibitor	Well tolerated; two patients dropped out because of rash	[81]
Bioenergetics	Creatine 3–5 g/day	8 UP, 2 BPD	Open-label, add-on, 4 weeks	Significant improvement in depressive symptoms for MDD patients. Both BPD patients developed hypomania/mania	Brain energy homeostasis	Mild adverse events; two complained of transient nausea and one of constipation. Both BPD patients developed hypomania/mania	[83]
Bioenergetics	Uridine RG2417; dose unknown	84 BPD, 6 weeks	DB, PC, monotherapy	Significant improvement in MADRS scores compared to placebo	Nucleoside uridine	Not specified	*

Abbreviations: BPD: bipolar disorder, CO: crossover, DB: double blind, DHEA: dehydroepiandrosterone, GC: glucocorticoid, GR: glucocorticoid receptor, HAM-D: Hamilton Depression Rating Scale, MADRS: Montgomery-Asberg depression rating scale, PBO: placebo, PC: placebo controlled, UP: unipolar depression.

* http://www.medicalnewstoday.com/articles/88213.php

case report described a manic switch in a patient with treatment-resistant bipolar depression who was treated with modafinil [9], and two cases of modafinil-induced irritability and aggression in two BPD patients have also been described [10].

The dopaminergic system and Bcl-2

Pramipexole

Pramipexole, a synthetic aminothiazole derivative, is a dopamine D2/D3 receptor agonist that is currently approved by the FDA for the treatment of Parkinson's disease. An abundance of data indicate that it has D3 preferring effects (see [11]). Two small, randomized, placebo-controlled trials have examined the effectiveness of pramipexole in the treatment of bipolar depression. Goldberg and colleagues randomized 22 patients with bipolar depression to receive either pramipexole (1.0 to 2.5 mg/day) plus a mood stabilizer, or placebo plus a mood stabilizer [12]. Pramipexole was well-tolerated, and more patients in the pramipexole group achieved a ≥50% reduction from their baseline Hamilton Depression Rating Scale (HAM-D) scores as well as a greater mean change in their HAM-D scores over the 6-week study duration. Additionally, the switch rates into mania and hypomania were not higher than in the placebo group. Side effects were mild.

Zarate and colleagues randomized 21 BPD II patients to receive either pramipexole (1.0–3.0 mg/day) plus a mood stabilizer, or placebo plus a mood stabilizer [11]. They found that 60% of the participants in the pramipexole group had a therapeutic response (as defined by a 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores) compared to 9% in the placebo group. Pramipexole appeared to be well-tolerated. These encouraging results need confirmation by a Category A study.

Notably, pramipexole upregulates the anti-apototic protein Bcl-2 in several brain areas [13, 14]; it is quite possible that lithium's antidepressant potentiating effects may be due to its ability to similarly and robustly upregulate Bcl-2 [14], which has traditionally been viewed as a 'long-term neuroprotective protein'. Future studies would have to investigate whether selective Bcl-2 enhancers without dopaminergic effects also have antidepressant effects in bipolar depression.

Oxidative stress

N-acetyl cysteine (NAC)

There is increasing evidence that mood disorders are associated with oxidative stress. Glutathione is the main antioxidant substrate in all tissue, and its pro-

duction is rate-limited by its precursor, cysteine; notably, glutathione alterations have been reported in BPD [15, 16]. NAC would thus increase glutathione levels, leading to postulated benefits in BPD because of its antioxidant properties. A recent study by Berk and colleagues reported that NAC was indeed effective in the treatment of BPD [17], and the authors hypothesized that NAC's efficacy might be due to its effects on oxidative stress. In this randomized, double-blind, multicenter, placebo-controlled study, 75 patients with BPD were treated with NAC (1 g twice daily) during the maintenance phase; NAC was added on to treatment as usual over 24 months followed by a 4-week washout phase. The investigators found that NAC significantly improved MADRS and most secondary scale scores by endpoint. Improvement was seen in the Global Assessment of Functioning (GAF) Scale and the Social and Occupational Functioning Assessment Scale (SOFAS) at 8 weeks, and the MADRS at 20 weeks. The benefits obtained were lost shortly after discontinuing the study medication. There were no significant differences in side effects compared to placebo; side effects numerically greater than placebo were headaches (18% NAC, 8% placebo), heartburn (16% NAC, 8% placebo), and increased joint pain (16% NAC, 8% placebo).

The cholinergic system

Scopolamine

Over three decades ago, Janowsky introduced the 'cholinergic-adrenergic imbalance hypothesis' of BPD [18]. He postulated that an imbalance of the regulatory processes of the cholinergic-adrenergic interface might be linked to the pathophysiology of mood disorders, and indeed there is a lengthy history of anticholinergic drug studies in mood disorders research. On a genetic level, there is still little evidence that a dysregulation of the cholinergic system is involved in BPD. One study found an association between 19 cholinergic genes and BPD [19]. In animal models, it has been reported that rats bred for an increased sensitivity of muscarinic receptors showed a behavioral phenotype similar to patients with depression; these animals presented with lethargy, lack of pleasure, and behavioral despair [20]. In humans, cholinergic hyperactivity results in a worsening of depressive symptoms in patients with major depressive disorder (MDD) [18]. Experiments add further support to this theory, as neuroendocrine and pupillary responses to cholinergic activity were found to be supersensitive in depressed subjects [21] and attenuated in manic subjects [22]; improvement of manic symptoms with lithium and valproate leads to normalization of pupillary responses [22].

Cannon and colleagues performed a positron emission tomography (PET) imaging study in patients with BPD and found reduced muscarinic type 2 receptor binding in the anterior cingulate cortex [23]. Additional evidence for an imbalance of the cholinergic system in BPD comes from small controlled

trials with physostigmine (a short-acting cholinesterase inhibitor), which found a rapid but only transitory reduction in manic symptoms following single or multiple intravenous injections [24, 25]. Additional studies with the cholinesterase inhibitor donepezil obtained mixed results in mania [26, 27].

As mentioned above, there is a lengthy history of anticholinergic drug studies in mood disorder research. Initially, the tricyclic antidepressants were believed to be largely effective due to their anticholinergic properties. Early studies found that the anticholinergic drug biperiden had antidepressant properties in 10 severely depressed inpatients [28]. However, this neurotransmitter system remained largely untapped for several decades, perhaps because anticholinergic side effects were a fairly common complaint and reason for discontinuing tricyclic antidepressants in depressed patients. More recently, Furey and Drevets (2006) found that the antimuscarinic drug scopolamine had significant antidepressant effects in subjects with either unipolar or bipolar depression; these effects were reportedly of rapid onset (usually within 1 week) [29]. In the first of two studies, four testing sessions were performed in random order under double-blind conditions, during which subjects received a 15-min intravenous infusion of a saline placebo followed by three doses of scopolamine hydrobromide (2.0, 3.0, and 4.0 μg/kg). In the second study, subjects received a 15-min intravenous infusion of a placebo saline solution or a single dose of scopolamine hydrobromide, 4.0 μg/kg. Patients receiving scopolamine had no significant increase in manic symptoms, and only one patient developed euphoria suggesting that the benefits of scopolamine were not simply due to euphoria. Despite these promising results, the potential side effect of inducing cognitive deficits will need to be addressed when developing scopolamine or similar agents for use in the treatment of BPD.

The melatonin and serotonergic (5-HT2C) systems

Agomelatine

The pineal hormone melatonin produces most of its biological effects via G protein-coupled melatonin receptors (MT1 and MT2) that are mostly expressed in brain. Some studies have reported that patients with BPD, the non-affected offspring of probands with BPD, and monozygotic twins discordant for BPD have an enhanced sensitivity of the melatonin suppressing effects of light [30–32]. However, other investigators did not finding melatonin suppression by light in euthymic BPD patients [33]. Initial reports of a significant association between the Δ502–505 polymorphism in GPR50 (also known as H9, melatonin-related receptor or ML1X, located on Xq28) and susceptibility to BPD [34] have not been replicated [35]. The mood stabilizers lithium and valproate were found to reduce melatonin light sensitivity in healthy volunteers [36, 37]. However, case reports and series indicate mixed results with

melatonin in patients with BPD [38, 39]. No controlled studies of melatonin have been published in BPD.

Agomelatine is a potent agonist of melatonin MT1 and MT2 receptors, and 5-HT2C antagonists have been reported to have antidepressant properties. *In vivo* studies indicate that agomelatine increases both norepinephrine and dopamine in frontal cortex. Chronic agomelatine treatment also increases cell proliferation and neurogenesis in the ventral dentate gyrus, as well as increased survival of these newly formed cells [40]. Agomelatine has antidepressant-like properties in animal models [41, 42] and in anxiety (as assessed by the social interaction test and the Vogel conflict test) [43]; notably, anxiety symptoms commonly co-occur in patients with mood disorders and have significant negative prognostic implications.

Several large, multicenter, multinational, placebo-controlled, short-term studies in MDD have found that agomelatine is a clinically effective and well-tolerated antidepressant [44]. With regards to bipolar depression, 21 patients with BPD I who were experiencing a major depressive episode and had a HAM-D score of ≥18 were treated openly with agomelatine. All patients received 25 mg/day of agomelatine for 6 weeks with a possible extension of up to 46 weeks in combination with either lithium (n = 14) or valpromide (n = 7). Using intent-to-treat data, 81% of patients met criteria for marked improvement at study endpoint, and 47% responded as early as the first week of treatment. Afterwards, 19 patients entered the 1-year extension phase of the study, and, 11 completed it. There were no dropouts due to adverse events during the acute phase of treatment (6 weeks), although six patients experienced serious adverse events during the 1-year period. Three lithium-treated patients experienced manic or hypomanic episodes during the optional extension period, one of which was treatment-related [45].

The glutamatergic system

Contemporary theories of the etiopathogenesis of BPD and recurrent MDD posit that they result from alterations in cellular resilience and neuroplasticity, and the glutamatergic system is being recognized as a likely contributor to the impairments in brain neuroplasticity and cellular resilience observed in patients with BPD. The preclinical evidence supporting the role of the glutamate in the pathophysiology of depression or mechanism of action has been summarized elsewhere [46]. Glutamate is the major excitatory synaptic neurotransmitter in the brain. Its crucial functions include mediating neurotransmission across excitatory synapses, and modulating various physiological functions in the mammalian central nervous system (CNS) such as synaptic plasticity, learning, and memory [47–50]. Excessive concentrations of glutamate are hypothesized to be involved in the etiopathophysiology of several neurodegenerative illnesses. Consequently, several drugs have been created in an attempt to modulate these abnormal concentrations. Evidence that these com-

pounds are neuroprotective in humans with ischemic/traumatic or neurodegenerative disease is still pending.

Several of the glutamatergic compounds being studied as neuroprotective agents have either been or are now undergoing testing in 'proof-of-concept' studies in patients with severe mood disorders [14]. The glutamatergic modulators that are being developed target either the glutamate receptors (N-methyl-D-aspartate (NMDA), AMPA, metabotropic) directly or glutamate before it is released into the extracellular space.

Emerging data indicate that glutamate has an important role in both acute and long-term processes involved in the mode of action of antidepressants and/or mood stabilizers. Synaptic potentiation (i.e., AMPA trafficking) by enhancing AMPA throughput is thought to be involved in acute antidepressant response, while the positive neurotrophic changes resulting from glutamatergic modulators are perhaps more relevant to reducing the recurrence of mood episodes and minimizing the deleterious effects of chronic aberrant neurobiology.

Riluzole

Riluzole is a blood-brain-penetrant glutamatergic modulator with neuroprotective and anticonvulsant properties, and the only drug approved by the FDA for the treatment of the degenerative motor-neuron disease amyotrophic lateral sclerosis (ALS). It acts on the glutamatergic system in diverse ways, including inhibiting glutamate release, enhancing AMPA trafficking by increasing membrane insertion of AMPA subunits GluR1 and GluR2 [51], and enhancing the activity of glutamate reuptake transporters (GLAST, GLT1, and EAAC1) [52]. Riluzole is also known to stimulate the synthesis of growth factors, including brain derived neurotrophic factor (BDNF) in cultured mouse astrocytes [53]; BDNF is implicated in the mechanism of antidepressant action and was recently shown to have antidepressant-like properties in animal models (Gerard Sanacora, personal communication).

Several clinical studies have found that riluzole has antidepressant effects in patients with unipolar depression [54, 55]. Overall, riluzole was well-tolerated in these trials. In bipolar depression, riluzole was studied in combination with lithium [56]. In this study, significant reductions in MADRS scores comparing endpoint with baseline were found for 14 bipolar depressed patients who received riluzole (100–200 mg per day for 6 weeks). These preliminary results need to be confirmed in controlled studies. In mice, pretreatment with riluzole 10 mg/kg, but not 3 mg/kg, moderately decreased amphetamine-induced, but not MK-801-induced, hyperlocomotion [57]. This characteristic suggests that riluzole might have 'antimanic-like' properties, although additional studies are needed to confirm this.

Memantine

Memantine is approved for the treatment of Alzheimer's disease. Its principal mechanism of action lies in the fact that it is a noncompetitive NMDA antagonist in a 'use dependent' manner (it enters and blocks the channel only when there is an excess of extracellular glutamate concentrations). At doses of 5–20 mg/day, it is a fairly selective NMDA receptor antagonist with negligible affinity for other receptors that have been implicated in antidepressant action.

Memantine has antidepressant-like effects [58, 59] in animal studies; in human studies however, a double-blind, placebo-controlled trial of individuals with MDD found that memantine had no antidepressant effects [60]. There is only one report of memantine use in bipolar depression. In this case series involving two patients, memantine at doses of 10–20 mg/day improved depressive symptoms and cognitive performance in patients with BPD when added to ongoing mood stabilizer therapy [61]. Further studies are necessary to address its potential role in bipolar depression.

Ketamine

Contrary to the evidence presented above suggesting that memantine does not possess antidepressant effects in patients with MDD, there is increasing proof that the higher affinity NMDA receptor antagonist, ketamine, has antidepressant effects. Two controlled studies found that ketamine resulted in rapid antidepressant effects in patients with treatment-resistant MDD [62, 63]. The effects noted in the study by Zarate and colleagues were rapid (within 2 h), robust, and relatively sustained (lasting approximately 1 week). Because of the inherent propensity of the compound to produce cognitive deficits and psychotomimetic effects, its use at this time remains limited to the research setting. Studies with more selective subtype NMDA antagonists are underway, in order to determine whether these have antidepressant effects that can occur safely without causing ketamine's undesirable side effects. Emerging data suggest that ketamine's antidepressant properties occur in part by enhancing AMPA throughput [64]. Although no studies of ketamine's effects in bipolar depression have been conducted, the results obtained in patients with treatment-resistant MDD are worth mentioning here. A trial evaluating the use of ketamine in bipolar depression is currently underway at the NIMH.

AMPA potentiators

AMPA receptors are ionotropic receptors that play a major role in learning and memory. These types of glutamatergic receptors mediate the fast component of excitatory neurotransmission. Numerous classes of compounds modulate

AMPA receptors by binding to their allosteric sites and are termed AMPA receptor positive modulators or AMPA Receptor Potentiators (ARPs). ARPs regulate AMPA receptors indirectly by slowing the receptor desensitization rate and/or deactivation in the presence of an agonist (e.g., AMPA and glutamate (see [65] for a review)). These compounds are under active investigation as treatments for cognition, depression, anxiety, stroke, and Parkinson's disease [66]. Chronic treatment with traditional antidepressants increases the expression of AMPA receptors in hippocampal membranes and the phosphorylation of AMPA receptor subunits [46].

The effects of standard treatments for BPD (i.e., lithium, valproate, and lamotrigine) on AMPA receptors suggest that those agents with a predominantly antidepressant profile – namely lamotrigine and riluzole – significantly enhance the surface expression of GluR1 and GluR2 in a time- and dose-dependent manner in cultured hippocampal neurons [51]. In contrast, the predominantly antimanic agents lithium and valproate significantly reduce surface expression of GluR1 and GluR2 [67]. These findings imply that regulation of GluR1/2 surface levels and function may be involved in the different clinical profile of anticonvulsants, and suggests that drugs that mimic these biochemical effects might have a similar therapeutic role.

The glucocorticoid system

Dysfunction of the hypothalamic-pituitary adrenal (HPA) axis has been well-described in bipolar depression. For instance, hypercortisolemia may be central to the etiopathogenesis of both depressive symptoms and the neurocognitive deficits observed in BPD. Attempts to better normalize the effects of cortisol, which may potentially restore HPA axis integrity, have been the focus of recent research. The antiglucocorticoid agents studied in the treatment of mood disorders include cortisol synthesis inhibitors (aminoglutethimide, ketoconazole, and metyrapone) and corticosteroid receptor antagonists (mifepristone and ketoconazole), as well as hydrocortisone, dexamethasone, and dehydroepiandrosterone (DHEA) (reviewed in [68]). Only a few of these compounds have been tested in bipolar depression [69–72]. With regards to the glucocorticoid synthesis inhibitors, fewer than 20 patients with bipolar depression have received this class of drugs; the largest study was an open-label add-on, 4-week study of ketoconazole (up to 800 mg/day) in six patients [69]. Three patients who received a dose of at least 400 mg/day had substantial reductions in depressive symptoms and no development of manic symptoms; cortisol levels were not lowered in any of the subjects. The significant toxicity risk and drug interactions associated with ketoconazole preclude its use on a chronic basis for mood disorders.

Only one placebo-controlled study of an antiglucocorticoid for bipolar depression has been performed [72]. Mifepristone (RU-486) is a non-selective antagonist of the glucocorticoid receptor that has been reported to have anti-

depressant and antipsychotic properties in patients with psychotic depression (reviewed in [68]). Although a recent letter to the editor indicates that two large Phase III studies failed to find significant antipsychotic or antidepressant effects for mifepristone [73], a controlled study suggests that it may possess antidepressant and cognitive enhancing properties in bipolar depression. In this double-blind, placebo-controlled, crossover study, Young and colleagues (2004) compared mifepristone (600 mg) to placebo in 20 subjects with bipolar depression and found that, over the course of the 6-week study, neurocognitive and mood symptoms improved [72]. If mifepristone is found to have beneficial effects in bipolar depression, its use will most likely be limited to acute depressive episodes; longer treatment could result in significant complications including adrenal insufficiency and hepatic injury [74]. A large controlled study with mifepristone in bipolar depression is currently underway (NCT0035912 by Alan Young at the University of British Columbia).

Glycogen synthase kinase-3 (GSK-3)

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase constitutively active in cells, and is deactivated by signals originating from numerous signaling pathways (e.g., the Wnt pathway, the PI-3' kinase (PI3K) pathway, protein kinase A (PKA), and protein kinase C (PKC)) [75]. Preclinical evidence implicates GSK-3 in either the direct or downstream mechanism of action of many other mood stabilizers and antidepressants currently in use (see [76]). In addition, GSK-3 modulates apoptosis and synaptic plasticity and may also modulate the circadian cycle by modulating gene expression of proteins involved in these processes. Recent animal behavioral data (from pharmacologic and genetic models) have shown that manipulation of the GSK-3 signaling cascade produces both antimanic and antidepressant effects in animal models of depression and mania [76–78]. In attempting to achieve selectivity for GSK-3 inhibition, it is critical to avoid the side effects that may occur with GSK inhibitors, which have been putatively linked with cardiac hypertrophy and cancer (due to upregulation of the Wnt pathway, which is common in human cancers) [76].

No GSK inhibitors are included in Table 1 because none are currently available for clinical use.

Arachidonic acid metabolism

Celecoxib

There is increasing evidence for the involvement of the arachidonic signaling pathway in BPD. Administration of the nonselective COX inhibitors indomethacin and piroxicam in rats prevented amphetamine-stimulated loco-

motor activity, and blocked cocaine sensitization (both are rodent models of mania). Moreover, inhibition of COX-2 with NS-398 attenuated restraint stress-induced oxidative changes (a model of depression). In olfactory bulbectomized rats, the COX-2 inhibitor celecoxib showed antidepressant-like properties [79]. In a 6-week, double-blind, placebo-controlled trial in humans, celecoxib showed some antidepressant properties. Muller and colleagues (2006) found that celecoxib (400 mg/day), when added to reboxetine in patients with MDD, produced significant antidepressant effects compared to placebo [80]. Recently, a 6-week, double-blind, placebo-controlled trial found that celecoxib (400 mg/day) was effective in patients with Bipolar I or II depression when added to ongoing mood stabilizer treatment; however, add-on celecoxib was more effective than placebo only at week 1, not at study endpoint [81].

Notably, the extent of celecoxib's ability to penetrate the blood brain barrier remains unclear. In addition, it is also presently unclear whether directly targeting COX-2 is worthwhile, because selective COX-2 inhibitors may be associated with an increased risk of adverse cardiovascular outcomes [82].

Bioenergetics

Creatine

Creatine plays an important role in brain energy homeostasis and altered brain energy metabolism, and has been implicated in BPD. An open-label study consisting of 10 treatment-resistant depressed patients (two of whom had BPD) found that 3–5 mg/day of creatine monohydrate added to ongoing treatment led to a significant improvement in depressive symptoms in patients with MDD [83]. However, the two patients with BPD developed transient hypomanic/manic symptoms. Further studies are warranted to clarify the role of creatine in BPD.

Uridine RG2417

Uridine RG2417 (Repligen corporation) – a biological compound essential for the synthesis of DNA and RNA – is currently in development for the treatment of neuropsychiatric disorders and neurodegenerative diseases. An earlier study suggested that RG2133, the prodrug of RG2417, had antidepressant-like effects in an animal model. RG2417 was recently found to be effective in a Phase IIa multi-site study of bipolar depression. In this multicenter study, 84 patients received either RG2417 or a placebo twice a day (unpublished findings). Over the 6-week treatment period, patients receiving RG2417 experienced a statistically significant improvement in depressive symptoms compared to those patients receiving placebo as assessed by the MADRS ($p = 0.03$), and a strong trend towards improvement on the CGI-BP-C

($p = 0.06$). This study was conducted under a development agreement with the Stanley Medical Research Institute (study ID # NCT00322764; study details are available at: http://www.medicalnewstoday.com/articles/88213.php).

Conclusion

As this chapter has described, a number of targets/compounds could result in putative treatments for bipolar depression. These include the melatonin and serotonergic (5-HT2C receptor) systems, the dopaminergic system, the glutamatergic system, and the HPA axis. In addition, the GSK intracellular signaling cascade, the arachidonic acid cascade, and the oxidative stress system all merit further study. As detailed above, a number of drugs not in routine clinical use are being used and studied in the treatment of bipolar depression. These treatments are currently available (with the exception of uridine RG2417) but are not anticonvulsants, antipsychotics, or conventional antidepressants. The drugs reviewed here include modafinil, pramipexole, N-acetyl cysteine, scopolamine, agomelatine, riluzole, memantine, ketamine, AMPA potentiators, ketoconazole, mifepristone, celecoxib, creatine, and uridine RG2417. It is important to emphasize that none of these drugs are FDA-approved for the treatment of MDD or bipolar depression. In addition, most of the evidence presented here comes from case reports, case series, or proof-of-concept studies, some with very small sample sizes. Thus, generalizability of such preliminary findings to current clinical practice patterns would be premature. We believe, however, that it is of considerable interest to understand where drug development for BPD may be heading. Some other examples of candidate drugs for BPD in early development are reviewed elsewhere [84].

A better understanding of the neurobiological underpinnings of BPD, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly, and are better tolerated than currently available treatments. Of the pharmacological agents reviewed here, modafinil, pramipexole, NAC, scopolamine, and mifepristone have been tested and found to have antidepressant properties in controlled studies. Larger controlled studies should be considered for these compounds. This chapter does not review some important drug targets for BPD – for instance, PKC – because this target has been implicated more in the treatment of bipolar mania than bipolar depression. The reader is referred elsewhere for more information on PKC [85].

Finally, future drug development will also need to focus on identifying molecular targets. Following this path for drug development will result in a better understanding of the cellular and molecular underpinnings of severe mood disorders, and the manner in which they are associated with regional impairments of structural plasticity and cellular resiliency [14]. Ultimately, such ‘plasticity enhancing’ strategies may prove to be very useful in the treatment of mood disorders.

Acknowledgements
We would like to acknowledge the support of the Intramural Research Program of the National Institute of Mental Heath, the Stanley Medical Research Institute and NARSAD. Drs Zarate and Manji are listed among the inventors on a patent application submitted for the use of ketamine in depression. They have assigned their rights on the patent to the US government.

References

1 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 356: 1711–1722
2 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59: 530–537
3 Montgomery P, Richardson AJ (2008) Omega-3 fatty acids for bi-polar disorder. *Cochrane Database Syst Rev* 16: CDD005169
4 Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS et al (2006) Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 60: 1020–1022
5 Littner M, Johnson SF, McCall VW, Anderson WM, Davila D, Hartse SK, Kushida CA, Wise MS, Hirshkowitz M, Woodson BT et al (2001) Practice parameters for the treatment of narcolepsy: an update for 2000. *Sleep* 24: 451–466
6 Ballon JS, Feifel D (2006) A systematic review of modafinil: Potential clinical uses and mechanisms of action. *J Clin Psychiatry* 67: 554–566
7 Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, Leverich GS, Altshuler LL, Nakelsky S, Hwang S et al (2007) A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 164: 1242–1249
8 Post RM, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, Leverich GS, Kupka R, Nolen WA, Grunze H (2006) New findings from the Bipolar Collaborative Network: clinical implications for therapeutics. *Curr Psychiatry Rep* 8: 489–497
9 Wolf J, Fiedler U, Anghelescu I, Schwertfeger N (2006) Manic switch in a patient with treatment-resistant bipolar depression treated with modafinil. *J Clin Psychiatry* 67: 1817
10 Ranjan S, Chandra PS (2005) Modafinil-induced irritability and aggression? A report of 2 bipolar patients. *J Clin Psychopharmacol* 25: 628–629
11 Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, Charney DS, Manji HK (2004) Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry* 56: 54–60
12 Goldberg JF, Burdick KE, Endick CJ (2004) Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 161: 564–566
13 Takata K, Kitamura Y, Kakimura J, Kohno Y, Taniguchi T (2000) Increase of bcl-2 protein in neuronal dendritic processes of cerebral cortex and hippocampus by the antiparkinsonian drugs, talipexole and pramipexole. *Brain Res* 872: 326–341
14 Zarate CA Jr, Singh J, Manji HK (2006) Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. *Biol Psychiatry* 59: 1006–1020
15 Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Cereser KM, Santin A, Gottfried C et al (2007) Serum S100B and antioxidant enzymes in bipolar patients. *J Psychiatr Res* 41: 523–529
16 Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkiline N (2002) Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. *Cell Biochem Funct* 20: 171–175
17 Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008) N-Acetyl Cysteine for depressive symptoms in bipolar disorder-a double-blind randomized placebo-controlled trial. *Biol Psychiatry* 64: 468–475
18 Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ (1972) A cholinergic-adrenergic hypothesis

of mania and depression. *Lancet* 2: 632–635
19 Shi J, Hattori E, Zou H, Badner JA, Christian SL, Gershon ES, Liu C (2007) No evidence for association between 19 cholinergic genes and bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 144: 715–723
20 Overstreet DH (1993) The Flinders sensitive line rats: a genetic animal model of depression. *Neurosci Biobehav Rev* 17: 51–68
21 Dilsaver SC (1986) Pathophysiology of "cholinoceptor supersensitivity" in affective disorders. *Biol Psychiatry* 21: 813–829
22 Sokolski KN, DeMet EM (2000) Cholinergic sensitivity predicts severity of mania. *Psychiatry Res* 95: 195–200
23 Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, Rollis D, Drevets M, Gandhi S, Solorio G et al (2006) Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. *Arch Gen Psychiatry* 63: 741–747
24 Davis KL, Berger PA, Hollister LE, Defraites E (1978) Physostigmine in mania. *Arch Gen Psychiatry* 35: 119–122
25 Khouzam HR, Kissmeyer PM (1996) Physostigmine temporarily and dramatically reversing acute mania. *Gen Hosp Psychiatry* 18: 203–204
26 Burt T, Sachs GS, Demopoulos C (1999) Donepezil in treatment-resistant bipolar disorder. *Biol Psychiatry* 45: 959–964
27 Eden Evins A, Demopulos C, Nierenberg A, Culhane MA, Eisner L, Sachs GS (2006) A double-blind, placebo-controlled trial of adjunctive donepezil in treatment-resistant mania. *Bipolar Disord* 8: 75–80
28 Kasper S, Moises HW, Beckmann H (1981) The anticholinergic biperiden in depressive disorders. *Pharmacopsychiatria* 14: 195–198
29 Furey ML, Drevets WC (2006) Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63: 1121–1129
30 Hallam KT, Olver JS, Norman TR (2005) Melatonin sensitivity to light in monozygotic twins discordant for bipolar I disorder. *Aust N Z J Psychiatry* 39: 947
31 Lewy AJ, Nurnberger JI Jr, Wehr TA, Pack D, Becker LE, Powell RL, Newsome DA (1985) Supersensitivity to light: possible trait marker for manic-depressive illness. *Am J Psychiatry* 142: 725–727
32 Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Rosenthal NE (1981) Manic-depressive patients may be supersensitive to light. *Lancet* 8216: 383–384
33 Nurnberger JI Jr, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy AJ, Miller A, Bowman ES, Miller MJ, Rau L et al (2000) Melatonin suppression by light in euthymic bipolar and unipolar patients. *Arch Gen Psychiatry* 57: 572–579
34 Thomson PA, Wray NR, Thomson AM, Dunbar DR, Grassie MA, Condie A, Walker MT, Smith DJ, Pulford DJ, Muir W et al (2005) Sex-specific association between bipolar affective disorder in women and GPR50, an X-linked orphan G protein-coupled receptor. *Mol Psychiatry* 10: 470–478
35 Alaerts M, Venken T, Lenaerts AS, De Zutter S, Norrback KF, Adolfsson R, Del-Favero J (2006) Lack of association of an insertion/deletion polymorphism in the G protein-coupled receptor 50 with bipolar disorder in a Northern Swedish population. *Psychiatr Genet* 16: 235–236
36 Hallam KT, Olver JS, Horgan JE, McGrath C, Norman TR (2005) Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. *Int J Neuropsychopharmacol* 8: 255–259
37 Hallam KT, Olver JS, Norman TR (2005) Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. *Neuropsychopharmacology* 30: 1400–1404
38 Bersani G, Garavani A (2000) Melatonin add-on in manic patients with treatment resistant insomnia. *Biol Psychiatry* 24: 185–191
39 Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE (1997) Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. *J Clin Psychiatry* 58: 383–388
40 Banasr M, Soumier A, Hery M, Mocaer E, Daszuta A (2006) Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. *Biol Psychiatry* 59: 1087–1096
41 Bertaina-Anglade V, laRochelle CD, Boyer PA, Mocaer E (2006) Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. *Behav Pharmacol* 17: 703–713
42 Papp M, Gruca P, Boyer PA, Mocaer E (2003) Effect of agomelatine in the chronic mild stress

model of depression in the rat. *Neuropsychopharmacology* 28: 694–703
43 Millan MJ, Brocco M, Gobert A, Dekeyne A (2005) Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. *Psychopharmacology (Berl)* 177: 448–458
44 Montgomery SA, Kasper S (2007) Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *Int Clin Psychopharmacol* 22: 283–291
45 Calabrese JR, Guelfi JD, Perdrizet-Chevalier C (2007) Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar Disord* 9: 628–635
46 Sanacora G, Zarate CA Jr, Krystal JH, Manji HK (2008) Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 7: 426–437
47 Bannerman DM, Good MA, Butcher SP, Ramsay M, Morris RG (1995) Distinct components of spatial learning revealed by prior training and NMDA receptor blockade. *Nature* 378: 182–186
48 Collingridge GL (1994) Long-term potentiation. A question of reliability. *Nature* 371: 652–653
49 Collingridge GL, Bliss TV (1995) Memories of NMDA receptors and LTP. *Trends Neurosci* 18: 54–56
50 Watkins J, Collingridge G (1994) Phenylglycine derivatives as antagonists of metabotropic glutamate receptors. *Trends Pharmacol Sci* 15: 333–342
51 Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, Falke C, Zarate CA Jr, Manji HK (2007) The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. *Neuropsychopharmacology* 32: 793–802
52 Fumagalli E, Funicello M, Rauen T, Gobbi M, Mennini T (2008) Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. *Eur J Pharmacol* 578: 171–176
53 Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S (2001) Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. *Neurosci Lett* 310: 117–120
54 Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, Krystal JH (2007) Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry* 61: 822–825
55 Zarate CA Jr, Payne JL, Quiroz JA, Sporn J, Denicoff KD, Luckenbaugh DA, Chandra PS, Charney DS, Manji HK (2004) An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 161: 171–174
56 Zarate CA Jr, Quiroz JA, Singh J, Denicoff KD, De Jesus G, Luckenbaugh DA, Charney DS, Manji HK (2005) An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry* 57: 430–432
57 Lourenco Da Silva A, Hoffmann A, Dietrich MO, Dall'Igna OP, Souza DO, Lara DR (2003) Effect of riluzole on MK-801 and amphetamine-induced hyperlocomotion. *Neuropsychobiology* 48: 27–30
58 Moryl E, Danysz W, Quack G (1993) Potential antidepressive properties of amantadine, memantine and bifemelane. *Pharmacol Toxicol* 72: 394–397
59 Rogoz Z, Skuza G, Maj J, Danysz W (2002) Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. *Neuropharmacology* 42: 1024–1030
60 Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KD, Luckenbaugh DA, Manji HK, Charney DS (2006) A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry* 163: 153–155
61 Teng CT, Demetrio FN (2006) Memantine may acutely improve cognition and have a mood stabilizing effect in treatment-resistant bipolar disorder. *Rev Bras Psiquiatr* 28: 252–254
62 Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47: 351–354
63 Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63: 856–864
64 Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, Manji HK (2008) Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* 63: 349–352
65 Black MD (2005) Therapeutic potential of positive AMPA modulators and their relationship to AMPA receptor subunits. A review of preclinical data. *Psychopharmacology (Berl)* 179: 154–163
66 Du J, Quiroz JA, Yuan P, Zarate CA Jr, Manji HK (2004) Bipolar disorder: involvement of sig-

naling cascades and AMPA receptor trafficking at synapses. *Neuron Glia Biol* 1: 231–243
67 Du J, Gray NA, Falke C, Chen W, Yuan P, Szabo ST, Einat H, Manji HK (2004) Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. *J Neurosci* 24: 6578–6589
68 Quiroz JA, Singh J, Gould TD, Denicoff KD, Zarate CA Jr, Manji HK (2004) Emerging experimental therapeutics for bipolar disorder: clues from the molecular pathophysiology. *Mol Psychiatry* 9: 756–776
69 Brown ES, Bobadilla L, Rush AJ (2001) Ketoconazole in bipolar patients with depressive symptoms: a case series and literature review. *Bipolar Disord* 3: 23–29
70 Raven PW, O'Dwyer AM, Taylor NF, Checkley SA (1996) The relationship between the effects of metyrapone treatment on depressed mood and urinary steroid profiles. *Psychoneuroendocrinology* 21: 277–286
71 Wolkowitz OM, Reus VI, Manfredi F, Ingbar J, Brizendine L, Weingartner H (1993) Ketoconazole administration in hypercortisolemic depression. *Am J Psychiatry* 150: 810–812
72 Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN (2004) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 29: 1538–1545
73 Carroll BJ, Rubin RT (2008) Mifepristone in psychotic depression? *Biol Psychiatry* 63: E1
74 Rothschild AJ (2003) Challenges in the treatment of depression with psychotic features. *Biol Psychiatry* 53: 680–690
75 Gould TD, Manji HK (2004) The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. *J Clin Psychiatry* 65: 598–604
76 Gould TD, Manji HK (2005) Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology* 30: 1223–1237
77 Gould TD, Einat H, Bhat R, Manji HK (2004) AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test. *Int J Neuropsychopharmacol* 7: 387–390
78 Gould TD, Zarate CA Jr, Manji HK (2004) Glycogen synthase kinase-3: a target for novel bipolar disorder treatments. *J Clin Psychiatry* 65: 10–21
79 Myint AM, Steinbusch HW, Goeghegan L, Luchtman D, Kim YK, Leonard BE (2007) Effect of the COX-2 inhibitor celecoxib on behavioural and immune changes in an olfactory bulbectomised rat model of depression. *Neuroimmunomodulation* 14: 65–71
80 Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, Spellman I, Hetzel G, Maino K, Kleindienst N et al (2006) The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* 11: 680–684
81 Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, Bowden CL, Soares JC (2008) Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol* 23: 87–94
82 Velentgas P, West W, Cannuscio CC, Watson DJ, Walker AM (2006) Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. *Pharmacoepidemiol Drug Saf* 15: 641–652
83 Roitman S, Green T, Osher Y, Karni N, Levine J (2007) Creatine monohydrate in resistant depression: a preliminary study. *Bipolar Disord* 9: 754–758
84 Zarate CA Jr, Manji HK (2008) Bipolar disorder: candidate drug targets. *Mt Sinai J Med* 75: 226–247
85 Zarate CA Jr, Singh J, Carlson PJ, Quiroz JA, Jolkovsky L, Luckenbaugh DA, Manji HK (2007) Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord* 9: 561–570
86 Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E (1999) Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 156: 646–649

Section D:
Treatment of bipolar disorder in special populations

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Late-onset bipolar disorder

John L. Beyer and K. Ranga R. Krishnan

Duke University Medical Center, Durham, NC 27710, USA

Abstract

Much is still unknown about late-life bipolar disorder (BPD), especially late-onset BPD. Late-onset BPD may be etiologically different from early-onset BPD, and may be related to the medical and neurological problems that can occur with aging; alternately, it may be an underlying progression of neurological illness associated with certain cases of BPD early in life.

Treatment of late-life BPD requires knowledge of 'best treatment' practices and an understanding of the effect aging has on psychopharmacotherapy. This chapter discusses the various treatment options available to this population. These include the mood stabilizers (e.g., lithium) and anticonvulsants (e.g., valproate, lamotrigine) most often used to treat BPD, as well as alternative treatments such as atypical antipsychotics and ECT. However, adequate clinical trials that would provide good evidence-based treatment recommendations for late-life BPD are not currently available. Therefore, extrapolation from trials in mixed-age populations and adaptation to the older patient is necessary to establish treatment recommendations.

Introduction

The diagnosis of bipolar disorder (BPD) is based on a phenomenological presentation of symptoms rather than etiological criteria [1]. Therefore, there is a large heterogeneity of presentations in patients that may affect course, prognosis, and response to treatment of the disorder. Several divisions have been proposed that provide guidance in treatment decisions. For example, the current phase of illness or the severity of symptoms at presentation for treatment has been recognized by the American Psychiatric Association [1] and multiple other expert consensus treatment guidelines [2–5] as being meaningful in clinical decision-making. Medication selection may vary if patients present in a manic, depressive, or mixed state, or have psychotic symptoms.

Other groupings within the bipolar spectrum may also have heuristic meaning for understanding the etiology of BPD or in modifying clinical decision-making. For example, efforts are currently underway to determine if structural or functional neuroimaging findings, genetic variability, or other biological markers may inform treatment decisions.

Similarly, clinical factors may also serve as markers for modifying clinical treatment. One clinical characteristic proposed as a modifying risk factor is the effect of age and age-of-onset in patients with BPD. This chapter will focus on the impact of older age and aging in late-life BPD, and explore late-life relat-

ed issues. For instance, do patients with BPD early in life 'burn out' with age? Is there a difference in BPD symptoms throughout the life cycle? Are there etiological and phenomenological differences if the disease begins early in life *versus* later in life? Does aging affect treatment?

This chapter is divided into two parts. The first discusses the current literature on aging in BPD with an emphasis on late-life and late-onset disease, and the second part discusses treatment of late-life BPD.

BPD in late life

Prevalence

Although BPD has been a recognized mental illness since the mid 1800s and codified in the first publication of the *Diagnostic and Statistical Manual of Mental Disorders* [6], the prevalence of BPD in the geriatric population remains unclear. From various inpatient program reports, it appears that hospitalization for BPD in patients over the age of 60 is not uncommon. Depp and colleagues [7] reviewed 11 published surveys of geriatric psychiatric admissions and found that 8.7% (mean prevalence) of admissions were for the treatment of BPD. The authors argued that this prevalence rate actually underestimated bipolar admissions because many of the studies focused only on mania (excluding admissions for bipolar depression), or on patients whose BPD began after the age of 60. The mean prevalence rate of geriatric bipolar admissions, however, was similar to findings in a study of Medicare patients admitted for a primary psychiatric diagnosis in the 1990–1991 calendar year [8]. That study of 240,000 geriatric psychiatry admissions found that 6.7% of admissions were for BPD (compared with an admission rate of 28.1% for unipolar depression and 5.7% for schizophrenia).

In the general community, the prevalence of BPD in the elderly has been less clear. Despite the reports of significant numbers of elderly admitted to hospitals for treatment of BPD, the Epidemiologic Catchment Area (ECA) study failed to capture any active manic elderly subjects in their survey of psychiatric disorders in the United States [9]. Using a statistical weighted analysis, the authors reported the 1-year prevalence range of elderly with BPD between 0.0–0.5% (with a cross-site mean of 0.1%). This was markedly lower than the prevalence of BPD reported among young (18–44 years; 1.4%) and middle aged (45–64 years; 0.4%) adults. This range, however, was consistent with three other community-based studies that included assessments of the prevalence of BPD in the elderly. Unutzer and colleagues [10] reviewed a large HMO database and found a prevalence rate of 0.25%. Klap and colleagues [11], reporting on a telephone survey of 9,585 households, found a prevalence rate of 0.08%. Finally, Hirschfeld and colleagues [12] reported results for 85,258 subjects who responded to a screening questionnaire. They found the screen rate for adults 65 and older was 0.5%.

Interestingly, each of these surveys suggested that the prevalence of BPD declines with age or in aging cohorts. This has led some researchers to suggest that bipolar episodes decrease with age [13]. Winokur [14] was the first to propose the concept that manic patients may 'burn out' after a finite number of episodes. In the Iowa 500 study, Winokur and colleagues followed 109 patients admitted for mania up to 20 years. The authors observed that bipolar episodes occurred in 'bursts', and then became quiescent. However in a prospective study, Angst and Preisig [15] followed 209 bipolar patients over a period of 40 years (median age 68). They found that manic episodes did not decrease with age and that many patients continued to have episodes into their seventh decade.

Overall, the decline in the prevalence of BPD with age noted by the community surveys is similar to that seen in prevalence rates of other mental illnesses (such as depression and schizophrenia), and may actually represent a cohort effect or an increased mortality rate.

Modifiers

Presentation

In general, the development of BPD in late life can be divided into four patterns: 1) those who had an early-onset of BPD and have reached old age; 2) those who were previously diagnosed with unipolar depression but had a switch to mania in late life; 3) those whose bipolar symptoms have never been recognized or were misdiagnosed; and 4) those who have never had an affective illness but develop mania in late life (possibly due to a specific medical or neurologic event, or for reasons unknown).

It is not known how common each presentation may be, though the most frequent experience is a patient who developed BPD earlier in life and is now seeking treatment [16]. However, based on findings by Hirschfeld and colleagues [12], it is not uncommon for the diagnosis of BPD to have been missed previously.

Gender

In epidemiologic studies of mixed aged populations, BPD was equally prevalent among men and women [1]. Depp and colleagues [7] reviewed 17 studies reporting various sample populations of patients with late-life BPD. They found a higher prevalence of BPD among older women than men (mean 69%; range 45–89%). However, this percentage is similar to the gender ratio among older adults in the general population.

Age of onset

Though BPD is a life-long illness, the literature tends to focus on the disease in younger individuals. Although the mean age of onset is around age 20 [9], some researchers have found heuristic evidence in dividing BPD into early-

and late-onset subtypes. Most surveys have found that the prevalence of BPD tends to be unimodal with a declining incidence in first-onset mania after the age of 40. A few studies, however, have noted two peaks: the first in the early/mid 20s, and a second peak (much smaller) closer to middle age [17–19]. This bimodal distribution is more prominent in women, with the second peak occurring around the time of menopause [17, 18, 20, 21]. A few studies have identified a second peak occurring in males in the eighth [22] or ninth [20] decade. Sajatovic and colleagues [16], assessed age of onset among 16,330 bipolar patients seen in the VA system during the 2001 fiscal year who were age 60 or older. While the majority of patients (13,477; 82.5%) had an earlier episode, 1,000 individuals (6.1%) had new-onset BPD. The authors analyzed clinical characteristics and suggested that age of onset did appear to create two different and meaningful subgroups of older adults with BPD.

What then is late-onset BPD and why is it important? There actually are no clear definitions of late-onset. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) [1] does not make a distinction, and various studies have used ages as young as 30 or as old as 50 to mark late-onset BPD [23–28]. However, identifying age of onset may suggest a marker for different etiologies of BPD, or even response to treatment.

For example, several studies [26–33] found that patients with early-onset illness have more family members with affective disorders compared to those with a later onset of illness. Researchers have postulated that early-onset patients have a higher genetic loading than those who develop the disease later in life. Countering this argument are several other studies that found no differences in family mental illness between the two groups [34–39], although this could be obscured by the consistent finding that all patients (but especially the younger groups) had high numbers of affectively ill relatives (as many as 4–22% in the late-onset groups) [26, 27, 29, 31, 32].

While family inheritance data are especially suggestive in the younger onset groups, the relationship of late-onset illness to neurological abnormalities is much more consistent across the studies. Though the definition of neurological illness varied, of the five studies assessing this, three [36, 40, 41] showed significantly higher rates in late-onset patients, while the other two [35, 37] showed trends toward increased levels. Snowdon [33], reviewing the admission data of 75 elderly bipolar subjects, found that the 13 patients with a known neurological disease had their first-episode of mania after the age of 50. Cook and colleagues [42] reported that 39 patients with neurological disease preceding the onset of mania had significantly later ages of onset, less family history of mood disorders, fewer depressive episodes, and more irritability and assaultive behavior during the manic episode. These data suggest that a neurological insult may induce BPD, especially late-onset BPD. Alternatively, it is possible that neurological developmental abnormalities that eventually cause neurological illness may also be associated with late-onset illness.

Age of onset has been less consistent in differentiating clinical course and associated factors. Carlson and colleagues [39] noted that age of onset as an

independent variable did not predict either the course or prognosis of BPD. These findings were echoed by Depp and colleagues [34], who found that later age of onset had few significant clinical differences from earlier onset, except that later onset of BPD predicted a lower intensity of psychiatric pathology. Carlson and colleagues [43] also noted that patients with early-onset BPD (first episode before <21 years) were less likely to experience complete episode remission during the following 24 months than later-onset (first episode after 30 years) patients. However, they also found that early-onset subjects were more likely male, had childhood behavior disorders, had substance abuse co-morbidity, and exhibited more paranoia in their psychotic features than late-onset subjects.

Differential diagnosis and co-morbidity

As noted previously, the incidence of new onset mania in late life is relatively uncommon; therefore, all patients presenting with mania should be evaluated for potential medical illnesses that cause manic symptoms. This evaluation would include a thorough neurological examination. Also, because geriatric patients are usually taking multiple medications, these must be reviewed for a temporal association with illness presentation. Laboratory tests should include basic health panels (complete blood count and blood chemistries) as well as a thyroid panel. Consideration should also be given to conducting a neuroimaging test such as an MRI or CT scan. This would be especially important if the new presentation includes psychosis.

Due to the higher association of secondary causes of mania in late-life BPD, several studies have assessed the presence of co-morbid medical problems, the most common being neurological illnesses. Depp and colleagues [7] reviewed eight studies that reported the co-morbid neurological illnesses in the populations, and noted that despite a wide variety in reporting strategies, the sample-weighted prevalence was 23.1%. Shulman and colleagues [44] compared 50 geriatric patients hospitalized for mania to 50 age-matched patients hospitalized for unipolar depression. They found that the rates of neurological illness in manic patients were significantly higher (36% *versus* 8%) suggesting that a risk factor for the development of mania in late life was neurological disease. However, there has been no clear consensus on what neurological diseases or damage location may induce BPD.

Starkstein and Robinson [45] demonstrated that strokes that occur in the right hemisphere (especially the limbic region) are more likely to be associated with manic symptoms than left hemispheric strokes (see also [46–48]). A review of the literature reveals multiple case reports and case series that generally support a tentative association between mania and vascular risk factors, and also between mania and cerebrovascular disease [49–51]. This association has been termed ‘vascular mania’ [52]. Proposed diagnostic criteria have defined a late-age at onset (50+ years) sub-type of mania, with associat-

ed neuroimaging and neuropsychological changes that are not specific to this age group.

Other medical co-morbid disorders are also common in BPD and especially late-life BPD. These include cardiovascular disorders, obesity, diabetes mellitus, respiratory infections, and infectious diseases [53–56]. A clustering of traditional and emerging (e.g., immuno-inflammatory activation) risk factors presage somatic health issues in this population. Iatrogenic factors and insufficient access to primary, preventive, and integrated healthcare systems are also contributory [55].

In addition to medical co-morbidities, psychiatric co-morbidities are frequently seen in patients with BPD, though there is very little information about their prevalence in late-life BPD. There are a few reports of substance abuse, PTSD, and personality disorders in late-life BPD, but no published reports on co-morbid eating disorders, anxiety disorders, or attention disorders – conditions frequently reported to be present in younger bipolar populations. The National Co-morbidity Study (NCS) found that 61% of adults with BPD also had a substance use disorder at some point [57]. However, this nationwide survey did not include anyone over the age of 55. Cassidy and colleagues [58] reviewed rates of substance abuse in 392 patients hospitalized at a state psychiatric facility for BPD. Nearly 60% reported some history of substance abuse (a finding consistent with the NCS), but in the 51 patients over the age of 60 only 29% reported a history of substance abuse. This unexpectedly low prevalence of substance abuse in older patients with BPD was also found in two small inpatient studies [59, 60], a review of elderly patients with BPD in an outpatient mental health system [61], and a large review of the Veterans Health Administration database [62]. The reason for a lower prevalence of substance abuse in older patients with BPD compared with younger is unclear. It may be due in part to poor insight or recall of significant substance use history, or it may represent a better earlier life adaptation that decreased risk for substance abuse.

Molinari and Marmion [63] found an unusually high rate of personality disorders (70%) co-morbid to BPD in a sample of 27 geriatric outpatients and inpatients. The authors suggested that this high rate could be due in part to the difficult and chronic patterns of affective disorders. Sajatovic and colleagues [62] conducted a review of the national Veterans Health Administration database to examine the prevalence of dementia, substance abuse, PTSD, and other anxiety disorders in older patients with BPD. 4,668 subjects with BPD were identified (mean age 70). Of these, 4.5% had co-morbid dementia, 5.4% were found to have PTSD, and 9.4% had an anxiety disorder. The prevalence of anxiety disorders and PTSD is much less than that seen in younger BPD cohorts; however, the prevalence of dementia was higher than expected for this age group, making this a special concern. Four inpatient samples found that co-morbid dementia was highly variable, ranging from 3–25% [37, 60, 64, 65], often depending on the population being assessed. Several researchers have raised the concern that BPD, especially late-life BPD, may be associated with

a higher risk for the development of dementia. Co-morbidity does not necessarily imply an association.

Mortality

Dhingra and Rabins [66] reported that the mortality rate among 25 elderly patients with BPD who had been hospitalized 5–7 years previously was higher than expected compared with the general population. While it is known that individuals with mental illness at all ages have a higher mortality rate than the general population [67], Shulman and colleagues [44] found that the mortality rate of elderly hospitalized patients with BPD was significantly higher than that of elderly hospitalized unipolar depressed patients over a 10–15 year follow-up (50% *versus* 20%). They suggested that late-life mania was a more severe form of affective illness than unipolar depression and had a poorer prognosis. Alternatively, the increased medical and neurological co-morbidities seen in late-life BPD may be a causative factor in the higher mortality rate.

Course

As noted previously, there are different paths to the diagnosis of BPD in late life. Shulman and Post [68] reviewed the course of illness in 67 elderly patients with BPD whose first manic episode occurred around age 60, and described a subset of patients who experienced depression early in life with a long latency (mean = 15 years) before the onset of mania. They hypothesized that cerebral changes that occur with age (or possibly developmental disease) transformed the affective illness to mania. Other investigators have described a similar latency period of 10–20 years in a subgroup of patients between their first depressed episode and the onset of mania [33, 37, 44, 64]. Interestingly, Post [32] and Spar and colleagues [69] found that when mania presents in late life, patients are more likely to exhibit a mixed symptom pattern rather than the classic manic presentation. The literature also has numerous case reports [70–73] of a rapid cycling pattern in older patients, though it is unclear if this is more or less common than among younger patients.

Finally, it should be noted that several reports suggest that late-life BPD is either more difficult to treat or responds more slowly to treatment. Sajatovic and colleagues [59] found that older patients with BPD were hospitalized at the same rate as older patients with schizophrenia. Young and Falk [74] found that older patients with mania who needed hospitalization tended to have a slower resolution of symptoms, and a longer duration of hospitalization, than younger adult patients. Bartels and colleagues [75] found that older adults with BPD used outpatient services at four times the rate of a similarly aged group of unipolar depressed patients. Overall, BPD was associated with substantial disability, comparable to schizophrenia, and incomplete improvement in functioning even among those classified as remitters [76].

Treatment

Pharmacological interventions

Treatment of BPD at any age is a challenge. It is a complex disease with varying intensities of mood and behavioral alterations set in a variable cycle of frequent relapses and residual symptoms. Further, as noted above, the disorder has a high number of medical and psychiatric co-morbidities that demand an individualistic treatment focused on the whole person. Finally, the high incidence of poor insight and resulting poor adherence to medications (or poorly tolerated medications) has made the disease especially challenging to control. In the last few years, there have been several publications of structured guidelines or algorithms for treatment of acute BPD based on systematic reviews of the literature or expert opinions [2–5, 77]. These guidelines have been constructed to assist clinicians in navigating the complexity of pharmacotherapy in BPD; however, recent studies have found that clinical practice frequently differs from guideline recommendations [78–80].

Patients with late life BPD have several additional complications. First, the aging body may affect pharmacologic tolerance or sensitivity. Thus, multiple pharmacological considerations, such as changes in the absorption, distribution, and elimination of medications, must be understood when prescribing medications in this population [81]. While we will reference specific examples below, a fuller review can be found in Catterson and colleagues [82].

Secondly, aging is associated with an increasing number of medical problems [60] and associated medication use. A recent review of BPD treatment in geriatric patients found that the average number of total medications prescribed to a patient was 8.0 ± 4.6 (range 1–24) [83]. The presence of medical problems may also limit treatment options, or cause problems secondary to the treatment. Further, with the increased number of medications used, there is an increased risk of problematic medication interactions. The higher number of associated medical problems may be associated with the higher mortality rate found in BPD patients compared with similar aged non-psychiatrically ill and unipolar depressed groups [44, 66].

Thirdly, older adults frequently have age-related psychosocial problems that potentially complicate treatment (such as loss of ability to drive or limited social support) [84, 85]. Finally, an additional challenge for optimal treatment of the late-life patient with BPD is the limited data available about treatment response of older adults to medications for BPD, even common, currently FDA-approved treatments [86]. While mixed-aged studies have included some geriatric subjects, there have been no controlled prospective studies of acute or long-term management of mania in the geriatric patient population. Of the mixed-aged studies that did include older subjects, only a few have examined the effects of age within their study population [86, 87], thus making informed, evidence-based treatment even more difficult.

Treatment efficacy

Lithium

Multiple studies have validated the role of lithium over the past four decades as the 'gold standard' for treatment of BPD. Until the turn of the century, lithium was the most commonly prescribed medication for BPD, as well as the primary choice in late-life BPD [88–90]. However, there have been no placebo-controlled, double-blind, clinical trials in geriatric patients establishing its efficacy and tolerability. The studies that are available for review have primarily been either naturalistic or retrospective in design.

Young and colleagues [86] reviewed studies that reported on the use of lithium in more than 10 elderly patients with BPD [65, 91–93]. They found that 66% of elderly manic patients improved overall. However, certain groups of late-life patients did better than others. Patients with dementia and drug abuse were found to be especially resistant to treatment, in part due to their increased difficulty in tolerating lithium. This may have contributed to the observation that in the various studies, lithium concentrations varied widely (0.3–2.0 mEq/L). Thus, the recommended lithium level for acute mania in geriatric patients is unclear. Case series [94, 95] have suggested that elderly patients may respond to lower lithium levels (0.5–0.8 mEq/L) than those recommended for younger adults, while other reports have found no difference [96, 97]. Chen and colleagues [93] noted that patients who were able to achieve a serum lithium concentration ≥0.08 were much more improved at discharge than those who did not obtain or could not tolerate this level. Complicating dosing recommendations is the fact that the use of lithium in older patients, especially those over the age of 70, is frequently associated with adverse effects that may occur even at 'therapeutic' levels [98, 99]. Commonly reported adverse effects of lithium in the elderly include cognitive impairment, ataxia, urinary frequency, weight gain, edema, tremor, worsening of psoriasis, or arthritis. Thus, lithium dosing (and 'adequate' serum levels) in the elderly are primarily determined by the patient's medical status and frailty [86, 100].

Guidelines for the use of lithium in the elderly recommend starting at half the dosage normally recommended for younger patients because aging causes significant effects on lithium pharmacokinetics. Although absorption is generally unchanged, the renal clearance of lithium and the volume of distribution are decreased, while the elimination half-life is increased [101–103]. Furthermore, medications commonly prescribed to the elderly may affect lithium levels. Thiazide diuretics, nonsteroidal anti-inflammatory agents, and angiotensin-converting enzyme inhibitors can increase lithium concentrations while other medications, such as theophylline, can decrease lithium concentrations. Finally, the use of lithium itself may be associated with a decline in renal clearance or hypothyroidism. Therefore, lithium should be used with caution in patients with kidney problems or thyroid disorders. Because of these

Table 1. Studies of acute treatment of mania in late-life bipolar patients

Study	Design	N	Age	Diagnosis	Study drug	Dose mg/day	Level mcg/ml	Results
Van der Velde, 1970	Retrospective	12	67 (60–74)	Mania	Lithium	NA (900 mg–2,100 mg)	NA (0.60–2.00)	4/12 (33%) improved acutely; 1/12 maintained stability after 3 years. Younger patients appeared more responsive to lithium
Himmelhoch et al., 1980	Retrospective	81	63.3 ± 6.9 (55–88)	Bipolar I – 74 Bipolar II – 7	Lithium	NA	NA	56/91 (69%) responded to lithium. 23/25 (92%) non-responders had neurological illnesses
Schaffer and Garvey, 1984	Prospective	14	69 (65–77)	Mania	Lithium	NA	NA (0.50–0.90)	11/14 (71%) responded
Puryear et al., 1995	Retrospective	13	70 (63–77)	Mania or mixed mania – 7 Other – 6	Valproate	1,000	57 (34–82) (100–1,750)	12/13 (92%) responded with decrease in BPRS
Kando et al., 1996	Retrospective	35	71.3 (63–85)	Mania – 24 Other – 11	Valproate	743 (250–2,000)	52.9 (11–102)	18/29 (62%) responded
Noaguil et al., 1998	Retrospective	21	71 (60–85)	Mania	Valproate	1,405 (500–3,000)	72 (31–106)	19/21 (90%) responded. 20/21 (95%) were on antipsychotics
Nedermier and Nasrallah, 1998	Retrospective	39	67 (60–82)	Mania – 16 Dementi – 7	Valproate	1,029 (500–2.250)	72 (36–111)	14/16 (88%) responded. Response was best in females, bipolar, younger age

(Continued on next page)

Table 1. (Continued)

Study	Design	N	Age	Diagnosis	Study drug	Dose mg/day	Level mcg/ml	Results
Chen et al., 1999	Retrospective	29	70 (55+)	Mania	30 – Lithium 29 – Valproate	NA	Valproate (25–116) Lithium (0.30–1.3)	20/30 (68%) improved on lithium; 11/29 (38%) improved on valproate; Patients taking lithium with serum levels ≥0.8 mmol/L were more improved at discharge. Patients taking valproate with serum levels between 65–90 microg/mL were more improved at discharge. When response rates among only patients with these 'therapeutic' levels were assessed, they were similar for lithium (82%) and valproate (75%). The difference in efficacy between drugs was maintained in classic mania, but the two drug groups were similar when only mixed mania was analyzed (lithium 63% *versus* valproate 67% improved)
Beyer et al., 2001	Subanalysis, Prospective study	94	57 (50–75)	Mania	47 – olanzapine 31 – valproate 14 – placebo	Valproate – 1,354 (500–2,500) Olanzapine – 15.8 (5–20)	NR	Both olanzapine and valproate groups improved significantly compared to placebo
Sajatovic et al., 2004	Subanalysis, Prospective study	59	62.9 ± 5.7	Mania	59 – quetiapine 31 – placebo	NR	NR	Older and younger subjects had significant improvement compared with placebo. Older adults particularly had a rapid and sustained reduction in symptoms

challenges, approximately one-fifth of geriatric patients have experienced lithium toxicity [102].

Prior to starting lithium, a preliminary medical work-up should include laboratory assessment of renal function, electrolytes, thyroid function tests, fasting blood glucose, and ECG [99]. These should also be rechecked every few months. McDonald [99] has also suggested that slow-release forms of lithium may be better tolerated by elderly patients.

Anticonvulsants

Valproate

Approved by the FDA for the treatment of bipolar mania in 1993 (and originally approved for use as an anticonvulsant), valproate is the most frequently prescribed medication for the treatment of BPD among the elderly [83, 90]. This appears to be due to the poorer tolerance of lithium by older adults, and the reported efficacy of anticonvulsants in non-classic mania [99, 104]. This increased use is even more remarkable considering that, similar to lithium, there are no prospective trials comparing valproate with placebo or lithium in the elderly; only retrospective and open-label studies in the geriatric population have been published.

Young and colleagues reviewed the five published studies of valproate that included more than 10 elderly manic subjects [93, 105–108]. They found that 59% of the combined sample met the various improvement criteria, though again the dose concentrations varied widely (25–120 mcg/ml). In the general population, recommended blood levels for valproate are 50–120 mcg/ml [109], though Chen and colleagues [93] noted that higher concentrations were associated with more improvement in elderly manic patients than lower concentrations (65–90 mcg/ml). Chen and colleagues [93] also noted that valproate was as effective as lithium when atypical mania, rather than classic mania, was the predominant symptoms.

It should be noted that the blood level measurement should be used only as a guide in treatment. As patients age, the elimination half-life of valproate may be prolonged and the free fraction of plasma valproate increased. Thus, the total valproate level (which is the most common laboratory test for valproate concentration) may underreport the amount of valproate clinically available. The clinical significance of this is unknown [86,100]. In addition, common medications may also influence the level of valproate. Aspirin can increase the valproate free fraction while phenytoin and carbamazepine may decrease it. Valproate itself may influence the pharmacokinetics of other medications. It inhibits the metabolism of lamotrigine (thus requiring lower doses) and may also increase the unbound fraction of warfarin (thus requiring careful monitoring of coagulation times) [110].

Prior to initiation of valproate therapy, a medical work-up should include liver enzymes, complete blood count (with platelets), and an ECG [84].

Starting doses for elderly patients are 125–250 mg per day with a gradual titration every 2–5 days of 125–250 mg depending on the medical condition/frailty of the patient. Extended release preparations of valproate are now available. These appear to be well tolerated by the elderly, but it should be noted that correctly drawn trough blood levels may need to be collected 24–36 h after the last dose [111].

In general, valproate is fairly well tolerated in elderly patients. The most common side effects are nausea, somnolence, and weight gain, while less common side effects of special concern in older adults are the possibility of hair thinning, thrombocytopenia, hepatotoxicity, and pancreatitis (though the latter two are less likely to occur with age) [112, 113]. It also should be noted that valproate is available in a sprinkle and liquid formulations for patients who may have difficulty swallowing. In addition, Regenold and Prasad [109] have reported on the intravenous use of valproate in three geriatric patients with good success.

Table 2. Side effects of concern in patients with late-life BPD

Lithium:	cognitive impairment, ataxia, urinary frequency, weight gain, edema, tremor, worsening of psoriasis/arthritis, diabetes insipidus, hypothyroidism
Valproate:	nausea, somnolence, weight gain, hair thinning, gait disturbances, thrombocytopenia, hepatotoxicity, pancreatitis
Carbamazepine:	sedation, ataxia, nystagmus/blurred vision, leucopenia, hyponatremia, agranulocytosis
Lamotrigine:	headache, nausea, Stevens-Johnson Syndrome
Atypical Antipsychotics:	sedation, akathisia, weight gain, diabetes, dyslipidemia, stroke

Carbamazepine

Carbamazepine has been approved for the treatment of bipolar mania since 1996, while the extended release form was approved in 2005. Despite this, there is very limited information on the use of either carbamazepine preparation in elderly patients with BPD. The literature is currently limited only to case reports and the inclusion of some elderly patients in larger studies. Okuma and colleagues [114] noted that seven elderly manic patients were included in a larger sample of 50 treated with carbamazepine in a double-blind study that showed good efficacy. Some researchers have suggested that in contrast to lithium, carbamazepine may best be used as a preferred agent in secondary mania [84, 104].

Possible adverse effects associated with carbamazepine include sedation, ataxia, nystagmus/blurred vision, leukopenia, hyponatremia (secondary to SIADH), and agranulocytosis. Severe and sometimes life threatening skin reactions have been noted to be a rare side effect. These include toxic epider-

mal necrolysis and Stevens-Johnson syndrome. The FDA [115] recently recommended that patients of Asian ancestry have a genetic blood test to identify an inherited variant of the gene HLA = B*1502 (found almost exclusively in people of Asian ancestry) before starting therapy. Those patients testing positive should not be treated with carbamazepine.

Prior to beginning carbamazepine, medical work-up should include assessment of liver enzymes, electrolytes, and complete blood count, and ECG. In the elderly, carbamazepine doses should be initiated at 100 mg either once or twice daily, and gradually increased every 3–5 days to 400–800 mg/day [99]. As in the younger population, targeted serum levels are between 6–12 mcg/l. Because carbamazepine can induce its own metabolism, dose increases may need to be adjusted in the first 1–2 months.

Carbamazepine is metabolized in the liver by cytochrome P450 enzyme 3A4/5. Studies in patients with epilepsy have found that carbamazepine clearance was decreased in an age-dependent manner, presumably due to a reduction in CYP 3A4/5 metabolism [116]. The implication is that elderly patients may require lower doses to achieve similar levels of drug as younger patients. Carbamazepine can also alter the pharmacokinetics of other medications, including oral hormones, calcium channel blockers, cimetidine, terfenadine, and erythromycin [84].

Lamotrigine

Lamotrigine is another anticonvulsant recently found to be effective in the treatment of BPD. Though lamotrigine has not demonstrated efficacy in the treatment of acute mania or depression in BPD, it was approved by the FDA in 2003 for use in the maintenance phase. As with the other pharmacologic treatments for BPD, lamotrigine has not been well-studied in geriatric patients. However, Sajatovic and colleagues [117] conducted a secondary analysis of two placebo-controlled, double-blind, clinical trials for maintenance therapy that included 98 subjects over the age of 55. Focusing on this ‘older’ group, they found that older patients taking lamotrigine who had been stabilized from either an acute episode of mania or depression, demonstrated a significant delay in the recurrence of another mood episode. Response was consistent with that seen in younger patients. When the results were further evaluated, the authors found that lamotrigine was significantly more effective than lithium or placebo in increasing the time-to-intervention for depressive recurrences; however, lithium was more effective in increasing the time-to-intervention for manic recurrences. The mean daily dose of lamotrigine in this older group was 243 mg/day, and the mean daily dose of lithium was 736 mg/day. Overall, the authors found that lamotrigine was well-tolerated (compared with lithium) by older patients with BPD and no increased incidence of rash was noted [117, 118].

Lamotrigine has also been noted to be helpful as an augmentation treatment for bipolar depression in elderly patients. In a case report of five female geriatric bipolar patients with depressive episodes [119], three of the five reported

a remission of depressive symptoms after 6 weeks of augmentation treatment to either lithium or valproate.

Lamotrigine is metabolized in the liver and eliminated through the hepatic glucuronide conjugation. Aging may cause some decrease in hepatic glucuronidation but the effect does not appear to significantly change lamotrigine dosing [120, 121]. The dose of lamotrigine should be halved when administered with valproate because valproate inhibits the metabolism of lamotrigine [122]. Its most common adverse effects are headache and nausea, though serious skin rashes (Stevens-Johnson Syndrome) have also been reported. Because of studies suggesting that lamotrigine may be better tolerated than lithium [117] or carbamazepine [123] in elderly patients, some researchers have suggested that lamotrigine will play an increasingly important role in the treatment of late-life BPD.

Other anticonvulsant agents of interest

Because of the success of valproate, carbamazepine, and lamotrigine for the treatment of various phases of BPD, several other anticonvulsant agents have been evaluated for use as well. Early open-label clinical trials showed gabapentin, oxcarbazepine, topiramate, tiagabine, and zonisamide to be promising treatments for BPD. However, controlled clinical trials have not supported the efficacy of gabapentin as monotherapy or combined therapy [124–126] in acute BPD. Further, at the time of this writing, there is only one published double-blind, placebo-controlled, clinical trial of oxcarbazepine monotherapy [127], and no double-blind, placebo-controlled trials of the other medications supporting their use in BPD. There are even less data about the use of these medications in the elderly [100, 128–131]. It should be noted that the oxcarbazepine study was conducted in adolescents with acute bipolar mania, and the authors did not find any improvement over placebo [127]. The metabolite of oxcarbazepine, licarbazepine, and other related compounds, such as eslicarbazepine, are currently being studied for use in BPD [132].

Antipsychotic agents

Antipsychotic medications have been used empirically for the treatment of acute bipolar mania for many years, either as monotherapy or adjunctive treatment. However, use of conventional antipsychotics has always been problematic in the elderly because of the anticholinergic effects, higher risks of extrapyramidal symptoms, and tardive dyskinesia [100]. In the past decade, five ‘atypical’ antipsychotic agents have been approved by the FDA for the treatment of acute mania (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole); two are FDA-approved for the treatment of acute depression (olanzapine/fluoxetine, quetiapine); and two are approved for the treatment of

the maintenance phase (olanzapine, aripiprazole). These have largely supplanted the use of conventional antipsychotics as first-line antipsychotic treatment in geriatric patients [133]. However, in the treatment for late-life BPD, published controlled clinical trials of atypical antipsychotics are lacking. Most of the current practice recommendations are based on the extrapolated data from mixed population trials, or studies conducted in elderly populations of patients with schizophrenia or dementia.

Information is especially crucial because a black box warning was added [134] to each of the atypical antipsychotic agents indicating that clinical trials of atypical antipsychotics for the treatment of elderly patients with dementia-related psychosis had an increased risk of death compared to placebo. Presumably, the fatalities were related to an increase of cerebrovascular or cardiovascular incidents. The risk of strokes in late-life BPD is unknown.

The other major concern with use of atypical antipsychotics is an increased risk of metabolic abnormalities, such as obesity, diabetes, and dyslipidemia [135]. While the elderly may have less weight gain associated with atypical antipsychotics use [136], each of these medical conditions is frequently observed in elderly patients with BPD (see discussion above concerning medical co-morbidities). Clozapine and olanzapine appear to have a higher risk, while aripiprazole and ziprasidone appear less likely to cause these changes. When using these medications, it is recommended that clinicians monitor weight, waist measurement, blood pressure, and serum glucose and lipid levels at time of initiation and periodically throughout treatment [135].

In general, a lower dose strategy in the elderly has been recommended for most atypical antipsychotics [137], though this may be less of a concern in the acute state.

Olanzapine

Olanzapine is FDA-approved for the treatment of bipolar mania and maintenance phases. The combination pill of olanzapine and fluoxetine was approved for the acute treatment of bipolar depression. There are limited data on its use in late-life BPD. Two subanalyses have been conducted evaluating the efficacy and tolerability of olanzapine in older adults who were included in mixed-age, double-blind, placebo-controlled trials of olanzapine in acute mania. Street and colleagues [138] found that in a subset of eight older manic patients (ages 61–67), those treated with olanzapine improved while those treated with placebo worsened. Beyer and colleagues [139] conducted a pooled subanalysis of subjects over the age of 50 in three double-blind, placebo-controlled acute bipolar mania clinical trials with olanzapine and valproate. Of the 94 older adults (mean age 57), the 78 treated with either olanzapine or valproate demonstrated a significant improvement compared to those on placebo. Olanzapine and valproate were noted to be equally effective for the treatment of acute mania. The mean daily dose of olanzapine was 15.8 mg (range 5–20 mg) and the mean daily dose of valproate was 1,354 mg (range 500–2,500 mg). The side effects experienced by the older group were compa-

rable to those seen in younger patients; the most common were dry mouth, somnolence, asthenia, and headache.

Quetiapine

Quetiapine has been FDA-approved for the treatment of acute mania and depression in BPD. However, again, there are limited data concerning treatment response in elderly patients. Madhusoodanan and colleagues [140] and Tariot and colleagues [141] reported on a series of elderly patients with psychosis, some of who had BPD, who were treated successfully with quetiapine. Sajatovic and colleagues [142] reported on a subanalysis of 59 older adults (mean age 63) from two 12-week double-blind, placebo-controlled studies of quetiapine in bipolar mania. They noted that both older and younger subjects responded compared to placebo, but that the older subjects had a particularly rapid and sustained reduction of symptoms apparent by Day Four. The most common adverse effects were dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness. Few side effects or EPS was noted. The dosing recommendation for quetiapine in bipolar depression is between 300–600 mg, while in mania it is up to 800 mg. Due to the occurrence of common side effects such as sedation, dizziness, and postural hypotension, geriatric patients may start with lower doses, to be titrated as tolerated.

Risperidone

Risperidone is approved by the FDA for the treatment of acute bipolar mania, though again, there are very limited data in late-life bipolar use. Madhusoodanan and colleagues [143, 144] reported on retrospective case reviews noting efficacy in elderly patients with BPD. Significant adverse events included postural hypotension and dose-dependent EPS. It is recommended that for elderly or debilitated patients, risperidone be initiated in doses of 0.5 mg once or twice a day [100] and titrated carefully.

Other atypical antipsychotics

Ziprasidone and aripiprazole have both been FDA-approved for the treatment of bipolar mania. Aripiprazole is also approved for the maintenance phase of BPD. Both medications may be advantageous for use in the elderly due to their less common propensity for dyslipidemias and orthostasis. However, there are currently no published reports about use of these medications in elderly patients with BPD.

Clozapine is not FDA-approved for use in BPD; however, it has been reported to be helpful in the treatment of bipolar mania, rapid cycling, and treatment-resistant disease. There are some limited case reports of its successful use in geriatric patients with BPD [124, 145]. However, the adverse effects of particular concern in the elderly include sedation, postural hypotension, anticholinergic effects, and risk for seizures. In addition, the potential for agranulocytosis has effectively limited its use to refractory conditions.

Antidepressants

In BPD, depressive phases are much more prevalent than manic ones [146, 147]. For many bipolar patients, the depressive phase is also the most problematic, highly associated with morbidity and prompting them to seek treatment [148]. Because of this, antidepressants have been widely used to treat bipolar depression [83]. However, the use of antidepressants in BPD is also controversial among psychiatrists [149]. There are three primary causes of concern: an ambiguity in the literature as to the efficacy of antidepressants in bipolar depression, the potential for antidepressants to induce a manic episode, and the potential of antidepressants to induce rapid cycling. Thase and Denko (2008) reviewed the literature, focusing especially on two recently completed large clinical trials that attempted to clarify the benefits and risks of antidepressant use in bipolar depression [150]. The results did not produce clear guidelines regarding the optimal treatment for bipolar depression. Antidepressant augmentation of mood stabilizers did not distinguish itself as effective compared with placebo, or with the use of a second mood stabilizer. However, based on the data, the authors could not conclude that antidepressants should be avoided or used only in severe cases [151]. Given these limitations, the APA [77] has maintained its recommendations that primary treatment of the depressed phases of BPD should be initiated with a mood stabilizer, and that antidepressant augmentation of the mood stabilizer may be considered if there is limited or no response.

Given the general ambiguity of antidepressant use in bipolar depression, it should not be surprising that there are no specific studies examining the use of antidepressants in geriatric populations. It should be noted that Young and colleagues [152] conducted a retrospective study of elderly inpatients with antidepressant-induced mania. They found that tricyclic antidepressants were more likely than others to induce manias in late life, suggesting that SSRIs may be used preferentially in the elderly.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) has been demonstrated to be very effective in the treatment of mania and mixed affective states [153, 154]. However, there are very limited data on the use of ECT in elderly patients with BPD, especially when compared with the literature on unipolar depression [155]. McDonald and Thompson [156] reported on a case series of three elderly manic patients who also had some dementia and who were resistant to pharmacotherapy, but did respond to ECT treatment. Little and colleagues [157] reported on a case series of five elderly bipolar depressed patients treated with bifrontal ECT. They found this method could be effective, although a third of the patients experienced cognitive side effects. Tsao and colleagues [158] reported on the case of a man with refractory mania who responded to acute

and maintenance ECT. Frequent side effects noted in the elderly include confusion, memory impairment, and hypertension [159].

Current treatment patterns

Evident in the above discussion is that there are very limited data available to guide an evidence-based approach to the treatment of BPD in late-life. Furthermore, the data that are available focus almost exclusively on just one phase of the disorder: the treatment of mania. Therefore, treatment of the depressed phases, hypomanic phases, and maintenance phases must be extrapolated from studies in younger populations. In addition, it is unclear whether certain clinical factors (such as late- *versus* early-onset) or biological and genetic markers may modify treatment response.

There are some data available that describe the current state of treatment in late life. Beyer and colleagues [83] reviewed the treatment of 138 late-life patients with BPD experiencing an affective episode. Mood stabilizers accounted for the highest proportion of medications used (68% of patients), though atypical antipsychotics were frequently used as well (54% of patients). The latter appeared to be used more frequently than is traditional in younger populations. The researchers also noted that despite there being no data on combination treatment in late life, polypharmacy was almost twice as common as monotherapy. This involved the use of some combination of lithium, mood stabilizers, antipsychotics, or antidepressants. Finally, despite using 'good clinical practice', by the end of the treatment period (mean 342 days), 67% of the subjects met criteria for treatment response, but only 35% of the patients progressed to remission.

Recommendations

1. In general, the history of treatment response and tolerability to specific medications will provide the best data for guiding current treatment selection and dosing. It is therefore essential that a good history of illness be obtained, including adverse events and related doses/concentrations [86].
2. Elderly patients (especially those with a new onset of illness) should have a thorough physical and neurological exam. Laboratory evaluations should include basic metabolic panels, complete blood counts, thyroid studies, and liver function tests. Consideration should be given to vitamin B12 and folate levels. Vital signs, including an orthostatic blood pressure and pulse, weight, and waist measurement should be taken.
3. Elimination of unnecessary psychotropic agents along with conservative management may be an effective intervention by itself.
4. In the treatment of mania, monotherapy with a mood-stabilizer is a reasonable first approach. The minimal duration for a medication effectiveness trial is 3–4 weeks [86].

5. Lithium and valproate are the primary first choice options for the treatment of late-life mania. Classic manic symptoms may be more responsive to lithium, while atypical or rapid-cycling mania may be more responsive to valproate. Clinicians should initially target moderate concentration ranges (lithium 0.4–0.8; valproate 50–100); however higher concentration ranges may be more effective acutely (lithium 0.8–1.0, valproate 65–100). Carbamazepine may be used as a second-line agent. Valproate or carbamazepine may be preferred treatments when neurological disease is present. Atypical antipsychotic medications (particularly olanzapine and quetiapine) have shown efficacy as monotherapy treatments and are increasingly being used. Special caution may be required if using these agents in elderly patients with dementia.
6. If monotherapy is only partially effective, consideration should be given to the addition of an atypical antipsychotic or another mood stabilizer.
7. In the treatment of acute bipolar depression, monotherapy with a mood stabilizer is preferred. Lamotrigine may be especially useful for bipolar depression. Antidepressants may be used to augment the mood stabilizer or atypical antipsychotic, but should not be used as monotherapy or in rapid cycling BPD.
8. ECT should be considered in patients in an acute affective illness when they have been shown to be treatment resistant, or are suicidal and require critical intervention.
9. Effective acute treatment should continue for 6–12 months. Ongoing treatment with a mood stabilizer is essential. If remission is sustained, a slow discontinuation of the augmenting agents may be considered. In cases of late-onset mania without previous episodes, the optimal duration of treatment is unknown [86].
10. In the absence of specific treatment recommendations for elderly patients, general guideline recommendations should be followed with the proviso ‘start low and go slow’.

Conclusions

Much is still unknown about late-life BPD, especially late-onset BPD [160]. Generally speaking, late-life BPD is a fairly common presentation to psychiatric practitioners and treatment facilities, despite the prevalence being fairly low in the community. This suggests that the disease may be difficult to manage and recurrences are not uncommon. Late-onset illness may be etiologically different than early-onset, and related to the medical and neurological problems that can occur with aging or to an underlying progression of neurological illness associated with some cases of BPD early in life. The concept of ‘vascular mania’ may be of both heuristic and treatment value in the future.

Treatment of late-life BPD requires knowledge of ‘best treatment’ practices and an understanding of the effect aging has on psychopharmacotherapy.

Adequate clinical trials are not currently available that would provide good evidence-based treatment recommendations for late-life BPD, requiring extrapolation from trials in mixed-age populations and adaptation to the older patient.

References

1 American Psychiatric Association (2000) *Diagnostic and statistical manual of mental disorders*, Fourth Edition: Text Revision (DSM-IV-TR). American Psychiatric Association, Washington, DC
2 Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, Crismon ML, Ketter TA, Sachs GS, Swann AC; Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder (2005) The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* 66(7): 870–886
3 Goodwin GM, for the Consensus Group of the British Association for Psychopharmacology (2003) Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 17: 149–173
4 Goodwin GM, Nolen WA (2001) Treatment of bipolar depressive mood disorders: algorithms for pharmacotherapy. *Int J Psychiatr Clin Practice* 1: 9–12
5 Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP (2000) The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med* Spec No: 1–104
6 American Psychiatric Association Committee on Nomenclature and Statistics (1952) *Mental disorders: diagnostic and statistical manual.* The Association, Washington, D.C
7 Depp CA, Jeste DV (2004) Bipolar disorder in older adults: a critical review. *Bipol Disord* 6: 343–367
8 Ettner S, Hermann R (1998) Inpatient psychiatric treatment of elderly Medicare beneficiaries. *Psychiatr Serv* 49: 1173–1179
9 Weissman MM, Leaf PJ, Tischler GL, Blazer DG, Karno M, Bruce ML, Florio LP (1988) Affective disorders in five United States communities. *Psychol Med* 18(1): 141–153
10 Unutzer J, Simon G, Pabiniak C, Bond K, Katon W (1998) The treated prevalence of bipolar disorder in a large staff-model HMO. *Psychiatr Serv* 49(8): 1072–1078
11 Klap R, Unroe KT, Unutzer J (2003) Caring for mental illness in the United States: a focus on older adults. *Am J Geriatr Psychiatry* 11(5): 517–524
12 Hirschfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 64(2): 161–174
13 Angst J, Baastrup P, Grof P, Hippius H, Poldinger W, Weis P (1973) The course of monopolar depression and bipolar psychoses. *Psychiat Neurol Neurochir* 76: 489–500
14 Winokur G (1975) The Iowa 500: Heterogeneity and course in manic-depressive illness (Bipolar). *Comp Psychiatry* 16(2): 125–131
15 Angst J, Preisig M. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients. (1995) Results of a prospective study from 1959 to 1985. *Schweiz Arch Neurol Psychiatr* 146(1): 5–16
16 Sajatovic M, Blow FC, Ignacio RV, Kales HC (2005) New-onset bipolar disorder in later life. *Am J Geriatr Psychiatry* 13(4): 282–289
17 Petterson U (1977) Manic-depressive illness: A clinical, social and genetic study. *Acta Psychiatrica Scandinavica* 269: 1–93
18 Angst J (1978) The course of affective disorders. II. Typology of bipolar manic-depressive illness. *Arch Psychaitr Nervenkr* 226: 65–73
19 Goodwin FK, Jamison KR (1984) The natural course of manic depressive illness. In: RM Post, JC Ballenger (eds): *Neurobiology of mood disorders*. Williams & Wilkens, Baltimore, 20–37
20 Sibisi CDT (1990) Sex differences in the age of onset of bipolar affective illness. *Br J Psychiatry* 156: 842–845
21 Zis AP, Grof P, Goodwin FK (1979) The natural course of affective disorders: Implications for lithium prophylaxis. In: TB Cooper, S Gershon, NS Kline, M Shou (eds): *Lithium: controversies and unsolved issues*. Exerpta Medica, Amsterdam, 381–398

22 Spicer CC, Hare EH, Slater E (1973) Neurotic and psychotic forms of depressive illness: Evidence from age-incidence in a national sample. *Br J Psychiatry* 123: 535–541
23 Loranger A, Levine PM (1978) Age at onset of bipolar affective illness. *Arch Gen Psychiatry* 35: 1345–1348
24 Eagles JM, Whalley LJ (1985) Ageing and affective disorders: The age at first onset of affective disorders in Scotland, 1969–1978. *Br J Psychiatry* 147: 180–187
25 Ghadirian AM, Lalinec-Michaud M, Engelsmann F (1986) Early and late onset affective disorders: Clinical and family characteristics. *Ann R I C P* 19: 53–57
26 James NM (1977) Early and late onset bipolar affective disorder: A genetic study. *Arch Gen Psychiatry* 34: 715–717
27 Taylor MA, Abrams R (1973) Manic states: A genetic study of early and late onset affective disorders. *Arch Gen Psychiatry* 28: 656–658
28 Hopkinson G (1964) A genetic study of affective illness in patients over 50. *Br J Psychiatry* 110: 244–254
29 Mendlewicz J, Fieve RR, Rainer JD, Fleiss JL (1972) Manic-depressive illness: A comparative study of patients with and without a family history. *Br J Psychiatry* 120: 523–530
30 Baron M, Mendlewicz J, Klotz J (1981) Age-of-onset and genetic transmission in affective disorders. *Acta Psychiatr Scand* 64(5): 373–380
31 Stenstedt A (1952) *A study in manic-depressive psychosis*. Stockholm
32 Post F (1968) The factor of ageing in affective illness. In: A Coppen, A Walk (eds): *Recent developments in affective disorders, special publication 2*. Royal Medico-Psychological Association, London, 105–116
33 Snowdon J (1991) A retrospective case-note study of bipolar disorder in old age. *Br J Psychiatry* 158: 485–490
34 Depp CA, Jin H, Mohamed S, Kaskow J, Moore DJ, Jeste DV (2004) Bipolar disorder I middle-aged and elderly adults: is age of onset important? *J Nerv Ment Dis* 192(11): 796–799
35 Hays JC, Krishnan KR, George LK, Blazer DG (1998) Age of first onset of bipolar disorder: demographic, family history, and psychosocial correlates. *Depress Anxiety* 7(2): 76–82
36 Tohen M, Shulman KI, Satlin A (1994) First-episode mania in late life. *Am J Psychiatry* 151(1): 130–132
37 Broadhead J, Jacoby R (1990) Mania in old age: A first prospective study. *Int J Geriatr Psychiatry* 5: 215–222
38 Glasser M, Rabins P (1984) Mania in the elderly. *Age and Ageing* 13: 210–213
39 Carlson GA, Davenport YB, Jamison K (1977) A comparison of outcome in adolescent- and later-onset bipolar manic depressive illness. *Am J Psychiatry* 134(8): 919–922
40 Wylie ME, Mulsant BH, Pollock BG, Sweet RA, Zubenko GS, Begley AE, Gregor M, Frank E, Reynolds CF 3rd, Kupfer DJ (1999) Age at onset in geriatric bipolar disorder. *Am J Geriatr Psychiatry* 7: 77–83
41 Almeida OP, Fenner S (2002) Bipolar disorder: similarities and differences between patients with illness onset before and after 65 years of age. *Int Psychogeriatr* 14(3): 311–322
42 Cook BL, Shukla S, Hoff AL, Aronson TA (1987) Mania with associated organic factors. *Acta Psychiatr Scand* 76: 674–677
43 Carlson GA, Bromet EJ, Sievers S (2000) Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry* 157(2): 213–219
44 Shulman KI, Tohen M, Satlin A, Mallya G, Kalunian D (1992) Mania compared with unipolar depression in old age. *Am J Psychiatry* 149: 341–345
45 Starkstein SE, Robinson RG (1989) Affective disorders and cerebral vascular disease. *Br J Psychiatry* 154: 170–182
46 Starkstein SE, Robinson RG, Price TR (1987) Comparison of cortical and subcortical lesions in the production of post-stroke mood disorders. *Brain* 110: 1045–1059
47 Starkstein SE, Mayberg HS, Berthier ML, Fedoroff P, Price TR, Dannals RF, Wagner HN, Leiguarda R, Robinson RG (1990) Mania after brain injury: neuroradiological and metabolic findings. *Ann Neurol* 27(6): 652–659
48 Starkstein SE, Fedoroff P, Berthier ML, Robinson RG (1991) Manic-depressive and pure manic states after brain lesions. *Biol Psychiatry* 29(2): 149–158
49 Cassidy F, Carroll BJ (2002) Vascular risk factors in late onset mania. *Psychol Med* 32(2): 359–362
50 Subramaniam H, Dennis MS, Byrne EJ (2007) The role of vascular risk factors in late onset bipolar disorder. *Int J Geriatr Psychiatry* 22(8): 733–737

51 Wijeratne C, Malhi GS (2007) Vascular mania: an old concept in danger of sclerosing? A clinical overview. *Acta Psychiatr Scand Suppl* (434): 35–40
52 Steffens DC, Krishnan KR (1998) Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. *Biol Psychiatry* 43(10): 705–712
53 Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavaluru PV (2002) Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. *J Affect Disord* 70: 19–26
54 Cassidy F, Ahearn E, Carroll BJ (1999) Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry* 156(9): 1417–1420
55 McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, Konarski JZ, Kennedy SH (2007) Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. *Curr Opin Psychiatry* 20(4): 406–416
56 Beyer JL, Kuchibhatla M, Gersing K, Krishnan KRR (2005) Medical comorbidity in an outpatient bipolar clinical population. *Neuropsychopharmacology* 30(2): 401–404
57 Kessler RC, Rubinow DR, Holmes C, Abelson J, Zhao S (1997) The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med* 27: 1079–1089
58 Cassidy F, Ahearn P, Carroll B (2001) Substance abuse in bipolar disorder. *Bipolar Disord* 3: 181–188
59 Sajatovic M, Popli A, Semple W (1996) Health resource utilization over a ten-year period by geriatric veterans with schizophrenia and bipolar disorder. *J Geriatr Psychiatry Neurol* 15: 128–133
60 Ponce H, Kunik M, Molinari V, Orengo C, Workman R, Reich L (1999) Divalproex sodium treatment in elderly male bipolar patients. *J Geriatr Drug Therapy* 12: 55–63
61 Depp CA, Lindamer LA, Folsom DP, Gilmer T, Hough RL, Garcia P, Jeste DV (2005) Differences in clinical features and mental health service use in bipolar disorder across the lifespan. *Am J Geriatr Psychiatry* 13(4): 290–298
62 Sajatovic M, Blow FC, Ignacio RV (2006) Psychiatric comorbidity in older adults with bipolar disorder. *Int J Geriatr Psychiatry* 21(6): 582–587
63 Molinari V, Marmion J (1995) Relationship between affective disorders and axis II diagnoses in geropsychiatric patients. *J Geriatr Psychiatry Neurol* 8: 61–64
64 Stone K (1989) Mania in the elderly. *Br J Psychiatry* 155: 220–224
65 Himmelhoch J, Neil J, May S, Fuchs C, Licata S (1980) Age, dementia, dyskinesias, and lithium response. *Am J Psychiatry* 137: 941–945
66 Dhingra U, Rabins PV (1991) Mania in the elderly: A 5–7 year follow-up. *J Am Geriatr Soc* 39(6): 581–583
67 Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB (2007) Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 68(6): 899–907
68 Shulman K, Post F (1980) Bipolar affective disorder in old age. *Br J Psychiatry* 36: 26–32
69 Spar JE, Ford CV, Liston EH (1979) Bipolar affective disorder in aged patients. *J Clinical Psychiatry* 40: 504–507
70 Camus V, de Mendonca Lima CA, Antonioli D, Wertheimer J (1997) Rapid-cycling affective disorder in the elderly: clinical subtype or specific course of manic-depressive illness? *J Geriatr Psychiatry Neurol* 10(3): 105–110
71 Conlon P (1997) Rapid cycling mood disorder in the elderly. *J Geriatr Psychiatry* 10: 105–110
72 Gnam W, Flint AJ (1993) New onset rapid cycling bipolar disorder in an 87 year old woman. *Can J Psychiatry* 38(5): 324–326
73 King DJ, Salem SA, Meimary NS (1979) A 48-hour periodic manic-depressive illness presenting in late life. *Br J Psychiatry* 135: 190–191
74 Young RC, Falk JR (1989) Age, manic psychopathology and treatment response. *Int J Geriatr Psychiatry* 4: 73–78
75 Bartels S, Forester B, Miles K, Joyce T (2000) Mental health service use by elderly patients with bipolar disorder and unipolar major depression. *Am J Geriatr Psychiatry* 8: 160–166
76 Depp CA, Davis CE, Mittal D, Patterson TL, Jeste DV (2006) Health-related quality of life and functioning of middle-aged and elderly adults with bipolar disorder. *J Clin Psychiatry* 67(2): 215–221
77 American Psychiatric Association (2002) Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159(4 Suppl): 1–50

78 Lim PZ, Tunis SL, Edell WS, Jensik SE, Tohen M (2001) Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines. *Bipolar Disord* 3(4): 165–173
79 Perlis RH (2005) The role of pharmacologic treatment guidelines for bipolar disorder. *J Clin Psychiatry* 66(Suppl 3): 37–47
80 Sachs GS (2003) Unmet clinical needs in bipolar disorder. *J Clin Psychopharmacol* 23(suppl 1): S2–S8
81 Van Gerpen MW, Johnson JE, Winstead DK (1999) Mania in the geriatric patient population: a review of the literature. *Am J Geriatr Psychiatry* 7(3): 188–202
82 Catterson ML, Preskorn SH, Martin RL (1997) Pharmacodynamic and pharmacokinetic considerations in geriatric psychopharmacology. *Psychiatr Clin North Am* 20(1): 205–218
83 Beyer JL, Burchitt B, Gersing K, Krishnan KR (2008) Patterns of pharmacotherapy and treatment response in elderly adults with bipolar disorder. *Psychopharmacol Bull* 41(1): 102–114
84 Sajatovic M (2002) Treatment of bipolar disorder in older adults. *Int J Geriatr Psychiatry* 17(9): 865–873
85 Beyer JL, Kuchibhatla M, Cassidy F, Looney C, Krishnan KRR (2003) Social support in elderly patients with bipolar disorder. *Bipol Disord* 5: 22–27
86 Young RC, Gyulai L, Mulsant BH, Flint A, Beyer JL, Shulman KI, Reynolds CF 3rd (2004) Pharmacotherapy of bipolar disorder in old age: review and recommendations. *Am J Geriatr Psychiatry* 12(4): 342–357
87 Mirchandani IC, Young RC (1993) Management of mania in the elderly: an update. *Ann Clin Psychiatry* 5(1): 67–77
88 Oshima A, Higuchi T (1999) Treatment guidelines for geriatric mood disorders. *Psychiatry Clin Neurosci* 53(Suppl 3): 26S–31S
89 Umapathy C, Mulsant BH, Pollock BG (2000) Bipolar disorder in the elderly. *Psychiatr Ann* 30: 473–480
90 Shulman KI, Rochon P, Sykora K, Anderson G, Mamdani M, Bronskill S, Tran CT (2003) Changing prescription patterns for lithium and valproic acid in old age: shifting practice without evidence. *BMJ* 326(7396): 960–961
91 van der Velde CD (1970) Effectiveness of lithium carbonate in the treatment of manic-depressive illness. *Am J Psychiatry* 123: 345–351
92 Schaffer CB, Garvey MJ (1984) Use of lithium in acutely manic elderly patients. *Clin Gerontol* 3: 58–60
93 Chen ST, Altshuler LL, Melnyk KA, Erhart SM, Miller E, Mintz J (1999) Efficacy of lithium *versus* valproate in the treatment of mania in the elderly: a retrospective study. *J Clin Psychiatry* 60: 181–185
94 Roose SP, Bone S, Haidorfer C, Dunner DL, Fieve RR (1979) Lithium treatment in older patients. *Am J Psychiatry* 136: 843–844
95 Prien RF, Caffey EM, Klett CJ (1972) Relationship between serum lithium level and clinical response in acute mania treated with lithium. *Br J Psychiatry* 120: 409–414
96 Young RC, Kalayam B, Tsuboyama G, Stokes P, Mattis S, Alexopoulos GS (1992) Mania: response to lithium across the age spectrum (abstract). *Soc for Neuroscience* 18: 669
97 DeBattista C, Schatzberg AF (1999) Current psychotropic dosing and monitoring guidelines. *Primary Psychiatry* 65–66
98 Tueth MJ, Murphy TK, Evans DL (1998) Special considerations: use of lithium in children, adolescents, and elderly populations. *J Clin Psychiatry* 59(Suppl 6): 66–73
99 McDonald WM (2000) Epidemiology, etiology, and treatment of geriatric mania. *J Clin Psychiatry* 61(Supp 13): 3–11
100 Sajatovic M, Madhusoodanan S, Coconcea N (2005) Managing bipolar disorder in the elderly: defining the role of the newer agents. *Drugs Aging* 22(1): 39–54
101 Sproule BA, Hardy BG, Shulman KI (2000) Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging* 16(3): 165–177
102 Foster JR (1992) Use of lithium in elderly psychiatric patients: a review of the literature. *Lithium* 3: 77–93
103 Shulman KI, Mackenzie S, Hardy B (1987) The clinical use of lithium carbonate in old age: a review. *Prog Neuropsychopharmacol Biol Psychiatry* 11: 159–164
104 Evans DL, Byerly MJ, Greer RA (1995) Secondary mania: diagnosis and treatment. *J Clin Psychiatry* 56(Suppl 3): 31–37

105 Niedermier JA, Nasrallah HA (1998) Clinical correlates of response to valproate in geriatric inpatients. *Ann Clin Psychiatry* 10: 165–168
106 Noagiul S, Narayan M, Nelson CJ (1998) Divalproex treatment of mania in elderly patients. *Am J Geriatr Psychiatry* 6: 257–262
107 Kando JC, Tohen M, Castillo J, Zarate CA Jr (1996) The use of valproate in an elderly population with affective symptoms. *J Clin Psychiatry* 57: 238–240
108 Puryear LJ, Kunik ME, Workman R (1995) Tolerability of divalproex sodium in elderly psychiatric patients with mixed diagnoses. *J Geriatr Psychiatry Neurol* 8: 234–237
109 Regenold WT, Prasad M (2001) Uses of intravenous valproate in geriatric psychiatry. *Am J Geriatr Psychiatry* 9(3): 306–308
110 Panjehshahin MR, Bowman CJ, Yates MS (1991) Effect of valproic acid, its unsaturated metabolites and same structurally related fatty acids on the binding of warfarin and dansylsacrosine to human albumin. *Biochem Pharmacol* 41: 1227–1233
111 Reed RC, Dutta S (2006) Does it really matter when a blood sample for valproic acid concentration is taken following once-daily administration of divalproex-ER? *Ther Drug Monit* 28(3): 413–418
112 Fenn HH, Sommer BR, Ketter TA, Alldredge B (2006) Safety and tolerability of mood-stabilising anticonvulsants in the elderly. *Expert Opin Drug Saf* 5(3): 401–416
113 Bowden CL, Lawson DM, Cunningham M, Owen JR, Tracy KA (2002) The role of divalproex in the treatment of bipolar disorder. *Psychiatr Ann* 32(12): 742–750
114 Okuma T, Yamashita I, Takahashi R, Itoh H, Otsuki S, Watanabe S, Sarai K, Hazama H, Inanaga K (1990) Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. *Pharmacopsychiatry* 23: 143–150
115 Food and Drug Administration. Carbamazepine Prescribing Information to Include Recommendation of Genetic Test for Patients with Asian Ancestry. *FDA News* 12 December 2007. Accessed 17 February 2008 at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01755.html
116 Battino D, Croci D, Rossini A, Messina S, Mamoli D, Perucca E (2003) Serum carbamazepine concentrations in elderly patients: a case-matched pharmacokinetic evaluation based on therapeutic drug monitoring data. *Epilepsia* 44(7): 923–929
117 Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, Evoniuk G (2005) Maintenance treatment outcomes in older patients with bipolar I disorder. *Am J Geriatr Psychiatry* 13(4): 305–311
118 Sajatovic M, Ramsay E, Nanry K, Thompson T (2007) Lamotrigine therapy in elderly patients with epilepsy, bipolar disorder or dementia. *Int J Geriatr Psychiatry* 22(10): 945–950
119 Robillard M, Conn DK (2002) Lamotrigine use in geriatric patients with bipolar depression. *Can J Psychiatry* 47(8): 767–770
120 Posner J, Holdrich T, Crome P (1991) Comparison of lamotrigine pharmacokinetics in young and elderly healthy volunteers. *J Pharm Med* 1: 121–128
121 Hussein Z, Posner J (1997) Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. *Br J Clin Pharmacol* 43(5): 457–465
122 Calabrese JR, Shelton MD, Rapport DJ, Kimmel SE (2002) Bipolar disorders and the effectiveness of novel anticonvulsants. *J Clin Psychiatry* 63 (Suppl 3): 5–9
123 Aldenkamp AP, De Krom M, Reijs R (2003) Newer antiepileptic drugs and cognitive issues. *Epilepsia* 44 (Suppl 4): 21–29
124 Frye MA, Altshuler LL, Bitran JA (1996) Clozapine in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 16(1): 87–90
125 Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G (2000) Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. *Bipolar Disord* 2(3 Pt 2): 249–255
126 Maidment ID (2001) Gabapentin treatment for bipolar disorders. *Ann Pharmacother* 35(10): 1264–1269
127 Vasudev K, Macritchie K, Geddes J, Watson S, Young A (2006) Topiramate for acute affective episodes in bipolar disorder. *Cochrane Database Syst Rev* (1): CD003384
128 Young AH, Geddes JR, Macritchie K, Rao SN, Vasudev A (2006a) Tiagabine in the maintenance treatment of bipolar disorders. *Cochrane Database Syst Rev* 3: CD005173
129 Young AH, Geddes JR, Macritchie K, Rao SN, Watson S, Vasudev A (2006b) Tiagabine in the treatment of acute affective episodes in bipolar disorder: efficacy and acceptability. *Cochrane*

Database Syst Rev 3: CD004694
130 Aziz R, Lorberg B, Tampi RR (2006) Treatments for late-life bipolar disorder. *Am J Geriatr Pharmacother* 4(4): 347–364
131 Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D et al (2006) A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 163(7): 1179–1186
132 Jeste DV, Rockwell E, Harris MJ, Lohr JB, Lacro J (1999) Conventional *versus* newer antipsychotics in elderly patients. *Am J Geriatr Psychiatry* 7(1): 70–76
133 Popova E, Leighton C, Bernabarre A, Bernardo M, Vieta E (2007) Oxcarbazepine in the treatment of bipolar and schizoaffective disorders. *Expert Rev Neurother* 7(6): 617–626
134 Food and Drug Administration. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients. *FDA News* 11 April 2005. Accessed 3 March 2008 at http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html
135 American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity (2004) Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry* 65(2): 267–272
136 Meyer JM (2002) A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry* 63(5): 425–433
137 Alexopoulos GS, Streim J, Carpenter D, Docherty JP; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients (2004) Using antipsychotic agents in older patients. *J Clin Psychiatry* 65 (Suppl 2): 5–99
138 Street J, Tollefson GD, Tohen M, Sanger TM, Clark WS (2000) Olanzapine for the psychotic conditions in the elderly. *Psychatri Ann* 30(3): 191–196
139 Beyer JL, Siegal A, Kennedy JS, Kaiser C, Tohen K, Berg P, Street J, Baker R, Tohen M, Tollefson G et al (2001) Olanzapine, divalproex, and placebo treatment non-head-to-head comparisons of older adult acute mania. Presented at the International Psychogeriatric Association, Nice, France
140 Madhusoodanan S, Brenner R, Alcantra A (2000) Clinical experience with quetiapine in elderly patients with psychotic disorders. *J Geriatr Psychiatry Neurol* 13(1): 28–32
141 Tariot P, Podgorski C, Blazina L, Leibovici A (1993) Mental disorders in the nursing home: another perspective. *Am J Psychiatry* 150: 1063–1069
142 Sajatovic M, Mullen J, Calabrese JR (2004) Quetiapine for the treatment of bipolar mania in older adults. Presented at the American Association of Geriatric Psychiatry, Baltimore, MD
143 Madhusoodanan S, Brecher M, Brenner R, Kasckow J, Kunik M, Negron AE, Pomara N (1999) Risperidone in the treatment of elderly patients with psychotic disorders. *Am J Geriatr Psychiatry* 7(2): 132–138
144 Madhusoodanan S, Brenner R, Araujo L, Abaza A (1995) Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. *J Clin Psychiatry* 56(11): 514–518
145 Shulman RW, Singh A, Shulman KI (1997) Treatment of elderly institutionalized bipolar patients with clozapine. *Psychopharmacol Bull* 33(1): 113–118
146 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon
147 AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 59(6): 530–537
148 Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon
149 DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 60(3): 261–269
150 Thase ME (2005) Bipolar depression: issues in diagnosis and treatment. *Harv Rev Psychiatry* 13(5): 257–271
151 Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK (2003) Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord* 5(6): 421–433
152 Thase ME, Denko T (2008) Pharmacotherapy of mood disorders. *Ann Rev Clin Psychology* 4: 53–91
153 Thase ME (2007) STEP-BD and bipolar depression: what have we learned. *Curr Psychiatry Rep* 9: 497–503

154 Young RC, Jain H, Kiosses DN, Meyers BS (2003) Antidepressant-associated mania in late life. *Int J Geriatr Psychiatry* 18(5): 421–424
155 Mukherjee S, Sackeim HA, Schnur DB (1994) Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry* 151(2): 169–176
156 Valentí M, Benabarre A, García-Amador M, Molina O, Bernardo M, Vieta E (2008) Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. *Eur Psychiatry* 23(1): 53–56
157 Wilkins KM, Ostroff R, Tampi RR (2008) Efficacy of electroconvulsive therapy in the treatment of nondepressed psychiatric illness in elderly patients: a review of the literature. *J Geriatr Psychiatry Neurol* 21(1): 3–11
158 McDonald WM, Thompson TR (2001) Treatment of mania in dementia with electroconvulsive therapy. *Psychopharmacol Bull* 35(2): 72–82
159 Little JD, Atkins MR, Munday J, Lyall G, Greene D, Chubb G, Orr M (2004) Bifrontal electroconvulsive therapy in the elderly: a 2-year retrospective. *J ECT* 20(3): 139–141
160 Tsao CI, Jain S, Gibson RH, Guedet PJ, Lehrmann JA (2004) Maintenance ECT for recurrent medication-refractory mania. *J ECT* 20(2): 118–119
161 Kujala I, Rosenvinge B, Bekkelund SI (2002) Clinical outcome and adverse effects of electroconvulsive therapy in elderly psychiatric patients. *J Geriatr Psychiatry Neurol* 15(2): 73–76
162 Charney DS, Reynolds CF 3rd, Lewis L, Lebowitz BD, Sunderland T, Alexopoulos GS, Blazer DG, Katz IR, Meyers BS, Arean PA et al (2003) Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. *Arch Gen Psychiatry* 60(7): 664–672

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Treatment of childhood-onset bipolar disorder

Robert L. Findling

Departments of Psychiatry and Pediatrics, University Hospitals Case Medical Center/Case Western Reserve University, Cleveland, Ohio, USA

Abstract

Because pediatric bipolar disorder is a serious condition, there is a substantive need for evidence-based treatments for children and adolescents suffering from this condition. A fundamental intervention used in this patient population is pharmacotherapy. Despite the importance of medication treatment in this patient population, only limited amounts of methodologically stringent data exist pertaining to this form of intervention. The evidence that does exist suggests that some psychotropic medications can provide salutary effects for youths suffering from Bipolar I disorder. Also relevant is the pharmacotherapy of genetically at-risk children suffering from bipolar spectrum disorder, and treatment of psychiatric co-morbidities. Further placebo-controlled trials are needed in order to better characterize the efficacy and safety of psychotropic medication in this population.

Introduction

Pediatric bipolar disorder (PBD) is a chronic and pernicious condition [1]. It is associated with serious psychosocial dysfunction, substantive affective symptomatology, and high rates of psychiatric co-morbidity [2, 3]. For these reasons, evidence-based treatments for this condition and the co-morbid illnesses that accompany it are needed.

Pharmacological therapy is considered to be a fundamental intervention for young people suffering from PBD [2, 4]. In order to provide evidence-based care, clinicians who treat children and adolescents should be familiar with pharmacotherapy studies that have been specifically conducted in pediatric patients, rather than assume that research that has been performed in adults is necessarily applicable to juveniles. The efficacy and safety profiles of psychotropic agents are frequently different in young patients than in adults [5].

Similarly, the manifestations of bipolarity may differ across the life cycle. Kraepelin initially observed that the amount of time patients spend in the depressed phase of bipolar illness increases from adolescence through adulthood [6]. Recent data from pediatric studies have reported that most youths suffering from bipolar disorder do not, in fact, frequently suffer from major depressive episodes, but most commonly experience manic and mixed states [3, 7]. Although ideally this chapter should focus on pediatric bipolar depression,

there is such a paucity of data on this topic for this age group that the chapter will instead predominantly focus on our current knowledge of pharmacotherapy in PBD. The knowledge gleaned from this work may be helpful in eventually designing such studies for pediatric bipolar depression in particular.

Acute monotherapy treatment studies of manic or mixed states

Lithium, anticonvulsants, and omega-3 fatty acids

Open-label data from multiple reports suggest that lithium may have salutary effects in youths suffering from manic or mixed states [8, 9]. There are currently no prospective, double-blind, placebo-controlled studies of adequate statistical power that have specifically tested the role of lithium in the treatment of acute manic states in PBD. However, under the auspices of an NICHD-sponsored contract, such a study is currently planned.

One prospective open-label study has evaluated carbamazepine. Results from that trial suggest possible benefits in the acute treatment of symptomatic youths suffering from PBD [10]. Although some studies have suggested that divalproex sodium may be helpful in the treatment of youths with manic or mixed states [11–13], one placebo-controlled study reported that it was not superior to placebo [14] (see Tab. 1). Conversely, a recent double-blind, placebo-controlled trial comparing divalproex sodium and lithium showed that while divalproex sodium was more efficacious than placebo, lithium was not. However, lithium was associated with a greater response, albeit not statistically significant, when compared to placebo. It is possible that lithium did not demonstrate superiority to placebo owing to the doses employed in the trial and based on the relatively modest sample size [15].

There are data from a placebo-controlled trial to suggest that topiramate might have efficacy in PBD [16]. However, this topiramate study was statistically under-powered because it was stopped prior to its completion, when adult trials failed to demonstrate topiramate's efficacy. Another double-blind and placebo-controlled study of oxcarbazepine showed no superiority for active treatment when compared to placebo [17]. There are no published double-blind or prospective studies that have examined other anticonvulsants in the acute treatment of mixed or manic states in PBD.

One published prospective open-label study examined omega-3 fatty acids in this patient population, and found that omega-3 fatty acids may have modest salutary effects on manic symptomatology [18].

Atypical antipsychotics

The medications that have the best data to support their use in the acute treatment of PBD are the atypical antipsychotics (see Tab. 1). There is evidence

Table 1. Selected, prospective, acute, placebo-controlled, mood stabilizer studies in PBD

Study	Medication	Dose	Patient diagnoses	Sample size (each arm)	Treatment duration	Results
Wagner et al (2007)	divalproex sodium	target serum level 80–125 mcg/mL	BPD-I, manic or mixed	DVPX = 76 placebo = 74	4 weeks	DVPX not superior to placebo; ≥50% YMRS improvement: DVPX = 24%; placebo = 23%
Kowatch et al (2007)	divalproex sodium; lithium	target DVPX serum level 85–110 mcg/mL	BPD-I, manic or mixed	DVPX = 56 Li^+ = 66 placebo = 31	8 weeks	DVPX superior to placebo; CGI-I of 1 or 2: DVPX = 53% Li^+ = 42% placebo = 29%
DelBello et al (2005)	Topiramate	target dose 400 mg/day	BPD-I, manic or mixed	topiramate = 29 placebo = 27	4 weeks	Inconclusive owing to early study termination; however, possible benefit from active treatment was observed
Wagner et al (2006)	oxcarbazepine	mean dose 1515 mg/day	BPD-I, manic or mixed	oxcarbazepine = 59 placebo = 57	7 weeks	No significant difference on change in YMRS from baseline to endpoint
Pandina et al (2007)	Risperidone	0.5–2.5 mg/day 3–6 mg/day	BPD-I, manic or mixed	RIS low = 50 RIS high = 61 placebo = 58	3 weeks	Both doses of RIS superior to placebo; ≥50% YMRS improvement: RIS low = 59% RIS high = 63% Placebo = 26%
Tohen et al (2007)	Olanzapine	2.5–20 mg/day; mean daily dose: 8.9 mg	BPD-I, manic or mixed	olanzapine = 107 placebo = 54	3 weeks	Olanzapine superior to placebo; ≥50% YMRS improvement: olanzapine = 48.6% placebo = 22.2%

(Continued on next page)

Table 1. (Continued)

Study	Medication	Dose	Patient diagnoses	Sample size (each arm)	Treatment duration	Results
DelBello et al (2007)	Quetiapine	400 mg/day 600 mg/day	BPD-I, manic	quetiapine 400 = 93 quetiapine 600 = 95 placebo = 89	3 weeks	Both doses of quetiapine superior to placebo; ≥50% YMRS improvement: quetiapine 400 = 64% quetiapine 600 = 58% placebo = 37%
Chang et al (2007)	Aripiprazole	10 mg or 30 mg	BPD-I, manic or mixed	aripiprazole 10 = 98 aripiprazole 30 = 99 placebo = 99	4 weeks	Both doses of aripiprazole superior to placebo; >50% YMRS improvement: aripiprazole 10 = 44.8% aripiprazole 30 = 63.6% placebo = 26.1%
DelBello et al (2002)	divalproex sodium + quetiapine	DVPX serum level 80–130 mg/dL quetiapine 450 mg/day	BPD-I, manic or mixed	DVPX + quetiapine = 15 DVPX + placebo = 15	6 weeks	DVPX plus quetiapine more effective in manic symptom reduction than DVPX monotherapy; YMRS response rate: DVPX + quetiapine = 87% DVPX + placebo = 53%

BPD-I = bipolar I disorder; DVPX = divalproex sodium; YMRS = Young Mania Rating Scale; CGI-I = Clinical Global Impressions-Improvement Scale; Li^+ = lithium; RIS = risperidone

from double-blind and placebo-controlled studies that risperidone [19], olanzapine [20], quetiapine [21], and aripiprazole [22] are all effective in the treatment of acute manic/mixed states for older children and adolescents (10–17 years).

There are also data from an open-label study to suggest that ziprasidone at doses of 80 or 160 mg/day may be effective in youths ages 10–18 years of age suffering from symptoms of mania [23]. Additionally, data from other open-label studies and case reviews suggest that risperidone [24, 25], olanzapine [24, 26], quetiapine [27], ziprasidone [28], and aripiprazole [29, 30] may all be associated with reductions in affective symptoms and are reasonably well tolerated in the short-term. Open label data suggest that clozapine [31, 32] may be useful in treatment-resistant youths. At present, there do not appear to be published studies pertaining to the use of paliperidone in this patient population.

For those drugs and patient populations for which placebo-controlled data are not available, the question of whether or not these agents truly have acute efficacy remains unanswered. In addition, owing to metabolic and tolerability considerations associated with the atypical antipsychotics, it is not entirely clear whether these drugs' side effect profiles are acceptable over the long-term. These are key empiric questions that deserve further study.

Acute combination pharmacotherapy studies

As indicated above, there are data of varying degrees of methodological stringency to support the assertion that drug monotherapy with certain agents may benefit youths with PBD. However, open-label and double-blind studies consistently report that many youths remain substantively symptomatic despite benefiting from treatment with one drug. As a result, investigators have begun to explore the safety and tolerability of combination thymoleptic drug strategies in the treatment of youths with bipolar disorder.

One study examined combination pharmacotherapy using a prospective, randomized controlled design. In that clinical trial, treatment with divalproex sodium plus quetiapine was reported to be associated with superior symptomatic relief when compared to treatment with divalproex sodium plus placebo [33]. It should be noted that the youths who received both active medications had a higher rate of sedation than those who received divalproex sodium monotherapy. Other combinations that have been studied in open-label prospective studies include lithium plus divalproex sodium [7, 34, 35], lithium plus either a neuroleptic or risperidone [9, 36], and divalproex sodium plus risperidone [36]. These data provide preliminary evidence to support the use of combination thymoleptic treatment strategies in PBD. It is possible that the sedative effects associated with combination therapy may be less well tolerated when used during the depressive phase of the illness; unfortunately no published studies to date have examined this question.

Acute treatment of depressive episodes

As mentioned above, the presentation of major depressive episodes appears to be substantially less common in PBD than manic or mixed episodes. This phenomenon probably partly explains why there is a paucity of data regarding the treatment of the depressed phase of PBD.

One open label study noted that lithium monotherapy was efficacious in the treatment of 27 adolescents with bipolar depression [37]. In addition, another open-label prospective study found that lamotrigine, either as monotherapy or as an adjunctive treatment, was associated with salutary effects in a group of 20 adolescents with bipolar depression [38]. The fact that high placebo-response rates have been observed in youths with major depressive disorder makes the open-label design of these two studies a key methodological consideration. Further, it should be noted that these youths, although suffering from prominent and substantive symptoms of depression, also were experiencing concomitant manic symptomatology at study baseline. In both clinical trials, average pre-treatment Young Mania Rating Scale [39] scores were above 15. Definitive placebo controlled trials in youths with less manic symptomatology are needed in order to develop specifically targeted treatment for youths suffering from the depressed phase of bipolar illness. As noted in the first part of this chapter, a purely depressed phase of illness appears to be uncommon in PBD. This observation will likely be a substantive challenge to conducting such definitive trials in pediatric bipolar depression.

In the absence of more stringent methodological treatment data in youths suffering from the depressed phase of PBD, recommended therapeutic approaches have focused on concerns regarding the potential for mania, mixed states and cycling acceleration associated with antidepressants [40]. It has been suggested that antidepressants should not be prescribed to youths unless the patient is being prescribed a concomitant mood stabilizer [4].

Maintenance therapy: randomized studies

Because PBD is a chronic condition, it is likely that these patients will receive long-term pharmacotherapy. Unfortunately, there are limited data pertaining to maintenance drug treatment in this patient population.

In one discontinuation study, 40 adolescents (ages 12–18 years) who responded to treatment with lithium were randomized to either continued lithium treatment or placebo substitution for 2 weeks [41]. Overall, the authors found that 57.5% of youths experienced a significant clinical exacerbation. Moreover, the rate of exacerbation did not differ between the lithium- and placebo-treated groups.

In another study that employed a discontinuation paradigm, investigators took 60 children and adolescents (ages 5–17 years) who achieved clinical stabilization while being treated with a combination regimen of lithium and dival-

proex sodium and randomized them in equal numbers to receive either drug monotherapy [42]. The investigators found that both agents were equally effective in maintaining clinical stability. However, it is noteworthy that approximately half of the subjects ended study participation within approximately 90 days of randomization.

An additional study randomized, in approximately equal numbers, 296 patients (ages 10–17 years) with pediatric bipolar mania to 4 weeks of acute treatment with aripiprazole 10 mg, aripiprazole 30 mg, or placebo followed by a 26-week continuation phase [43]. Over 30 weeks of treatment (4 weeks acute and 26 weeks continuation), both doses of aripiprazole (10 mg and 30 mg) demonstrated superiority to placebo in the treatment of these youths.

Genetically at-risk populations

A treatment strategy that has received some scientific investigation has been the evaluation of medication therapy early in the course of bipolar illness, before youths develop Bipolar I or Bipolar II disorder. The focus of this research is particularly interesting, because if effective early interventions can be identified for these patients, it is hoped that: 1) the dysfunction and symptomatology that occur during this period of time may be reduced [44], and 2) that diagnostic evolution to more malignant forms of bipolarity can be prevented.

In one study, 30 depressed children, ages 6–12 years who were at risk for developing bipolar disorder were randomized to receive either lithium or placebo for 6 weeks [45]. Symptom amelioration was found both for youths who received placebo and for those who received active medication. Perhaps more importantly, the degree of clinical improvement did not differ between the two treatment groups.

In another study, 24 youths ages 6–18 years who were the offspring of a parent with bipolar disorder and who also suffered from at least mild affective symptomatology were treated with open-label divalproex sodium for up to 12 weeks [46]. In that trial, the authors found that 78% of the study subjects improved. In a randomized, double-blind study, Findling and colleagues treated 56 symptomatic at-risk youths who were between the ages of 5–17 years with either divalproex sodium or placebo [47]. The authors found that treatment with either placebo or divalproex therapy was associated with substantive clinical benefit. In addition, no between-group differences in treatment response were found. The results of this latter study highlight the need to conduct placebo-controlled studies in this patient population.

Finally, in another study, 20 adolescents ages 12–18 years who were both affectively symptomatic and who also had a first degree relative with Bipolar I disorder benefited from 12 weeks of treatment with quetiapine [48]. These findings suggest that further research with quetiapine in this patient population is indicated.

Treatment of psychiatric co-morbidities

As noted above, psychiatric co-morbidity is quite common in PBD. Unfortunately, there are limited double-blind data about the treatment of co-morbid conditions in these youths. At present, clinical trials that have considered interventions in this patient population have been limited to those youths suffering either from concomitant attention-deficit/hyperactivity disorder (ADHD) or substance abuse.

ADHD

ADHD is a common co-morbid condition in PBD. Two recently published studies have examined the safety and efficacy of adjunctive psychostimulants in these youths.

In one randomized, placebo-controlled trial, Scheffer and colleagues treated 40 patients between the ages of 6–17 years suffering from PBD and ADHD with open label divalproex sodium [49]. Using a crossover design, the effects of mixed amphetamine salts (MAS) [32] were compared to placebo. The authors found that treatment with MAS was superior to placebo in the reduction of ADHD symptoms. Moreover, the authors also found that worsening of manic symptoms did not occur with MAS administration.

In another study, 16 euthymic youths who were receiving mood stabilizer treatment received various doses of methylphenidate as well as placebo in a crossover design [50]. The authors found that treatment with methylphenidate was superior to placebo in treating ADHD symptoms. In addition, the authors found that methylphenidate administration was not associated with mood destabilization.

Finally, in their aforementioned maintenance trial, Findling and colleagues noted that adjunctive treatment with psychostimulants was not associated with detrimental effects during drug monotherapy with either lithium or divalproex sodium [42]. When these studies are considered as a group, they provide preliminary evidence to support the use of adjunctive psychostimulants in the treatment of ADHD in youths with ADHD who are already receiving mood stabilizers.

Substance abuse

Geller and colleagues treated a group of 25 teenagers with bipolar disorder and secondary substance abuse with either placebo or lithium for up to 6 weeks [51]. The investigators found that treatment with lithium was associated with greater reductions in substance abuse and superior improvements in overall functioning when compared to placebo.

Conclusions

Until recently, there has only been a modest amount of research pertaining to the pharmacotherapy of PBD. Several recently conducted placebo-controlled trials have failed to show efficacy for some drugs. Other placebo-controlled trials, particularly those that have studied the atypical antipsychotics, have identified drugs that are superior to placebo in the symptomatic amelioration of manic symptoms. However, there is still a substantive need to evaluate the long-term safety and efficacy of psychotropic agents in these vulnerable youths. Besides long-term safety, other areas of research deserving further study include the depressed phase of illness, and the treatment of psychiatric co-morbidity in PBD. Hopefully, even more research will become available in the near future so that clinicians can have adequate information to provide care to their patients based on methodologically-stringent research.

Acknowledgements/disclosures
Dr. Findling receives or has received research support, acted as a consultant, and/or served on a speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Cypress Biosciences, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, Neuropharm, New River, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, and Wyeth.

References

1 Birmaher B, Axelson D (2006) Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol* 18: 1023–1035
2 McClellan J, Kowatch R, Findling RL (2007) Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 46: 107–125
3 Pavuluri MN, Birmaher B, Naylor MW (2005) Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 44: 846–871
4 Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M (2005) Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44: 213–235
5 Wiznitzer M, Findling RL (2003) Why do psychiatric drug research in children? *Lancet* 361: 1147–1148
6 Kraepelin E (1921) *Manic-depressive insanity and paranoia*. E&S Livingstone, Edinburgh
7 Findling RL, McNamara NK, Gracious BL, Youngstrom EA, Stansbrey RJ, Reed MD, Demeter CA, Branicky LA, Fisher KE, Calabrese JR (2003) Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry* 42: 895–901
8 Alessi N, Naylor MW, Ghaziuddin M, Zubieta JK (1994) Update on lithium carbonate therapy in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 33: 291–304
9 Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM (2003) Lithium treatment of acute mania in adolescents: a large open trial. *J Am Acad Child Adolesc Psychiatry* 42: 1038–1045
10 Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ (2000) Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39: 713–720
11 DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, Nelson E, Strakowski SM (2006) A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 45: 305–313
12 Wagner KD, Weller EB, Carlson GA, Sachs G, Biederman J, Frazier JA, Wozniak P, Tracy K, Weller RA, Bowden C (2002) An open-label trial of divalproex in children and adolescents with

bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 41: 1224–1230
13 Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG (2005) Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. *Bipolar Disord* 7: 266–273
14 Wagner KD, Redden L, Kowatch RA, Wilens T, Segal S, Chang K, Wozniak P, Vigna NV, Schmitz PJ, Abi-Saab W et al (2007) Safety and efficacy of divalproex ER in youth with mania. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry:* 23–28 October 2007, Boston, MA
15 Kowatch RA, Findling RL, Scheffer RE, Stanford K (2007) Pediatric Bipolar Collaborative Mood Stabilizer Trial. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry:* 23–28 October 2007, Boston, MA
16 DelBello MP, Findling RL, Kushner S, Wang D, Olson WH, Capece JA, Fazzio L, Rosenthal NR (2005) A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44: 539–547
17 Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D et al (2006) A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry* 163: 1179–1186
18 Wozniak J, Biederman J, Mick E, Waxmonsky J, Hantsoo L, Best C, Cluette-Brown JE, Laposata M (2007) Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. *Eur Neuropsychopharmacol* 17: 440–447
19 Pandina G, DelBello MP, Kushner S, VanHove I, Augustyns I, Kusumaker V, Haas M (2007) Risperidone for the treatment of acute mania in bipolar youth. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry*: 23–28 October 2007, Boston, MA
20 Tohen M, Kryzhanovskaya L, Carlson G, DelBello M, Wozniak J, Kowatch R, Wagner K, Findling R, Lin D, Robertson-Plouch C et al (2007) Olanzapine *versus* placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry* 164: 1547–1556
21 DelBello MP, Findling RL, Earley WR, Acevedo LD, Stankowski J (2007) Efficacy of quetiapine in children and adolescents with bipolar mania: a 3-week, double-blind, randomized, placebo-controlled trial. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry*: 23–28 October 2007, Boston, MA
22 Chang KD, Nyilas M, Aurang C, Johnson B, Jin N, Marcus R, Forbes RA, Carson WH, Kahn A, Findling RL (2007) Efficacy of aripiprazole in children (10–17 years old) with mania. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry*: 23–28 October 2007, Boston, MA
23 DelBello MP, Versavel M, Ice K, Keller D, Miceli J (2006) Ziprasidone dosing study in pediatric patients with bipolar disorder, schizophrenia, or schizoaffective disorder. Presented at: *Association of European Psychiatrists' 14th European Congress of Psychiatry*: 4–8 March 2006, Nice, France
24 Biederman J, Mick E, Hammerness P, Harpold T, Aleardi M, Dougherty M, Wozniak J (2005) Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry* 58: 589–594
25 Biederman J, Mick E, Wozniak J, Aleardi M, Spencer T, Faraone SV (2005) An open-label trial of risperidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 15: 311–317
26 Frazier JA, Biederman J, Tohen M, Feldman PD, Jacobs TG, Toma V, Rater MA, Tarazi RA, Kim GS, Garfield SB et al (2001) A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 11: 239–250
27 Marchand WR, Wirth L, Simon C (2004) Quetiapine adjunctive and monotherapy for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol* 14: 405–411
28 Barnett MS (2004) Ziprasidone monotherapy in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol* 14: 471–477
29 Barzman DH, DelBello MP, Kowatch RA, Gernert B, Fleck DE, Pathak S, Rappaport K, Delgado SV, Campbell P, Strakowski SM (2004) The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 14: 593–600
30 Biederman J, McDonnell MA, Wozniak J, Spencer T, Aleardi M, Falzone R, Mick E (2005) Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectr*

10: 141–148
31 Kowatch RA, Suppes T, Gilfillan SK, Fuentes RM, Grannemann BD, Emslie GJ (1995) Clozapine treatment of children and adolescents with bipolar disorder and schizophrenia: a clinical case series. *J Child Adolesc Psychopharmacol* 5: 241–253
32 Masi G, Mucci M, Millepiedi S (2002) Clozapine in adolescent inpatients with acute mania. *J Child Adolesc Psychopharmacol* 12: 93–99
33 DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM (2002) A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 41: 1216–1223
34 Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA (2003) Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry* 53: 978–984
35 Findling RL, McNamara NK, Stansbrey R, Gracious BL, Whipkey RE, Demeter CA, Reed MD, Youngstrom EA, Calabrese JR (2006) Combination lithium and divalproex sodium in pediatric bipolar symptom re-stabilization. *J Am Acad Child Adolesc Psychiatry* 45: 142–148
36 Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG (2004) Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. *J Affect Disord* 82 Suppl 1: S103–111
37 Patel NC, DelBello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, Strakowski SM (2006) Open-label lithium for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry* 45: 289–297
38 Chang K, Saxena K, Howe M (2006) An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry* 45: 298–304
39 Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133: 429–435
40 Kowatch RA, DelBello MP, Findling RL (2002) Depressive episodes in children and adolescents with bipolar disorders. *Clinical Neurosciences Research* 2: 158–160
41 Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM (2004) Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry* 43: 984–993
42 Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, Calabrese JR (2005) Double-blind 18-month trial of lithium *versus* divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44: 409–417
43 Wagner KD, Nyilas M, Johnson B, Aurang C, Forbes A, Marcus R, Carson WH, Iwamoto T, Carlson GA (2007) Long-term efficacy of aripiprazole in children (10–17 years) with mania. Presented at: *54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry*: 23–28 October 2007, Boston, MA
44 Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Demeter CA, Bedoya D, Kahana SY, Calabrese JR (2005) Early symptoms of mania and the role of parental risk. *Bipolar Disord* 7: 623–634
45 Geller B, Cooper TB, Zimerman B, Frazier J, Williams M, Heath J, Warner K (1998) Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord* 51: 165–175
46 Chang KD, Dienes K, Blasey C, Adleman N, Ketter T, Steiner H (2003) Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J Clin Psychiatry* 64: 936–942
47 Findling RL, Frazier TW, Youngstrom EA, McNamara NK, Stansbrey RJ, Gracious BL, Reed MD, Demeter CA, Calabrese JR (2007) Double-blind, placebo-controlled trial of divalproex monotherapy in the treatment of symptomatic youth at high risk for developing bipolar disorder. *J Clin Psychiatry* 68: 781–788
48 DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM (2007) A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. *J Clin Psychiatry* 68: 789–795
49 Scheffer RE, Kowatch RA, Carmody T, Rush AJ (2005) Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 162: 58–64
50 Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, Whipkey R, Manos MJ, Calabrese JR (2007) Methylphenidate in the treatment of children and adolescents

with bipolar disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 46: 1445–1453

51 Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, Heath J (1998) Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37: 171–178

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Treatment of bipolar disorder during and after pregnancy

Patricia Roy and Jennifer L. Payne

Johns Hopkins School of Medicine, Baltimore, MD 21287, USA

Abstract

The treatment of bipolar disorder (BPD) in women is complicated by reproductive life events such as pregnancy and breastfeeding. This presents a clinical challenge to clinicians and patients who must balance risk of recurrent mood episodes against risks of potential teratogenic and adverse side effects of medications. It is important for the clinician and patient to develop an individualized plan of care during conception, pregnancy, delivery and postpartum to ensure maximum safety and minimal risks. Pregnant women with BPD have the same risk of mood episodes as women who are not pregnant. There is clearly an increased risk for the development of mood episodes in the postpartum period – approximately 22–50% of women with BPD will develop postpartum depression (PPD). Risk factors for PPD in women with BPD include having a family history of PPD and depressive symptoms during pregnancy, but this risk can be significantly reduced with prophylactic medications. The risk for postpartum psychosis (PPP) is also significant, and most cases occur in the first 3 days following delivery. Risk factors include a history of an index manic episode, positive family history, and sleep deprivation during delivery.

Lithium is the first choice for mood stabilization during pregnancy for women with severe illness. The typical antipsychotics also appear to be relatively safe during pregnancy. Venlafaxine, bupropion, mirtazepine, and the tricyclic antidepressants also all appear to be relatively safe in pregnancy. Patients should be monitored carefully during pregnancy. As the pregnancy progresses physiologic changes occur that alter the excretion of drugs and drug levels may change significantly, necessitating dose adjustments. In addition, factors such as vomiting due to morning sickness must be taken into account. Postpartum, women should be closely monitored, in labor and delivery, and at home. Medication changes made during pregnancy may have to be reversed as physiology changes. If women choose to breastfeed, the pediatrician should be part of the clinical team. It is important to use a team approach when treating BPD during pregnancy.

Introduction

Bipolar disorder (BPD) is a serious psychiatric illness that is often chronic and relapsing. The prevalence of Bipolar I Disorder (BPD-I) is similar in both men and women, but treatment can be complicated in women by reproductive life events such as pregnancy, breastfeeding, and perimenopause. Onset of illness typically occurs in teens or twenties, which means that women are at risk of having episodes throughout the bulk of their reproductive years. Pregnancy in women with BPD is a clinical challenge due to potential teratogenic effects of medications, which must be balanced against risks to mother and fetus that

occur during untreated mood episodes. Risks and benefits must be weighed carefully to provide an individualized treatment plan and support system for the patient by a team of healthcare providers working together.

This chapter will review the risks of episode recurrence during pregnancy and postpartum, the implications of taking medications during pregnancy and while breastfeeding, and stress the importance of developing a team approach in order to provide the patient with the maximal support and care for both mother and child. Although ideally this chapter would focus on bipolar depression, there is a paucity of data on this topic in this subgroup. The knowledge gleaned from this work may be helpful in eventually designing studies that investigate bipolar depression, in particular, during pregnancy and the postpartum period.

Why treat BPD during pregnancy and breastfeeding?

While a full review of the reasons to treat BPD during pregnancy and breastfeeding is beyond the scope of this chapter it is important to be clear about the risks associated with no treatment to both the mother and the child. The case for treatment is most obvious when BPD has been severe and there is a history of dangerous behavior that could threaten the health or life of the mother and/or child. Untreated psychiatric illness can result in poor compliance with prenatal and well-baby care, dangerous behavior, substance abuse, and poor infant-mother bonding [1, 2]. Depression during pregnancy and postpartum has been associated with poor outcomes for the child including elevated cortisol levels, behavioral problems, and impaired emotional development, language development, attention, and cognitive skills. Thus, like many chronic medical illnesses, prevention of recurrence during pregnancy and postpartum is important for good outcomes for *both* the mother and child.

Depression and mania during pregnancy

It was previously believed that pregnancy was protective against relapse in mood disorders [3]. Further research has shown that pregnancy is not protective but is rather risk-neutral for the development of mood episodes. Viguera and colleagues (2002) retrospectively compared the risks of recurrence in pregnant and non-pregnant women when tapered off of lithium. They found no difference in the risks of recurrence between pregnant and non-pregnant women over the same time period, with rates of 52% in pregnant women and 58% in non-pregnant women [4]. Viguera and colleagues further reported that in pregnant women who discontinued mood stabilizer there was a recurrence risk of 81–85.5% while women who continued mood stabilizer treatment had a much lower risk of 29–37% [5, 6]. The finding that approximately 80% of women with BPD will relapse when taken off of mood stabilizers suggests that treatment during pregnancy for many patients is necessary in order to prevent recurrence.

Depression and mania postpartum

The literature is clear that there is an increased risk of mood episodes in women with BPD during the postpartum period. Freeman and colleagues (2002) interviewed 50 women with BPD and found that 67% of the women who had given birth experienced a postpartum mood episode after the birth of their first child [7]. In this group of women, having a postpartum mood episode significantly increased the risk of postpartum episodes in subsequent pregnancies. Interestingly, not having a mood episode following delivery was *not* protective for subsequent deliveries. These mood episodes were primarily depressive, and risk factors included having increased depressive symptoms during pregnancy [7] as well as a family history of postpartum depressive episodes [8].

Blehar and colleagues (1998) reported that in a sample of 186 women with BPD, almost half of those who had been pregnant retrospectively reported emotional symptoms in relation to pregnancy. Further, one-third reported that the onset of symptoms occurred during the pregnancy, indicating that having depressive symptoms during pregnancy is a risk factor for postpartum mood episodes. Remaining symptom free during pregnancy is not protective, however, against mood episodes postpartum [9]. Payne and colleagues (2007) found that 22% of 512 women with BPD-I and 22.9% of 89 women with Bipolar II Disorder (BPD-II) retrospectively reported significant postpartum mood symptoms that began after pregnancy and occurred within 4 weeks of delivery [10].

The risk in women who take medication during the postpartum time has been sparsely studied. Cohen and colleagues (1995) followed a group of 27 women with BPD through pregnancy and the postpartum period and found that 1 out of 14 women taking prophylactic treatment during the first 3 months postpartum relapsed; in comparison, 8 out of 13 women who did not take antimanic medications showed evidence of affective instability [11]. Furthermore, Viguera and colleagues (2000) found that the risk of recurrence for a postpartum mood episode was much higher for pregnant women who discontinued lithium treatment (70%) *versus* non-pregnant women who discontinued lithium treatment (24%) [12]. These findings support the need for treatment during pregnancy in an effort to prevent postpartum mood episodes in women with BPD, as well as careful monitoring of medication status during the early postpartum period.

Women with BPD are also at a high relative risk for postpartum psychosis (PPP). PPP is considered a psychiatric emergency and generally resembles a manic episode with agitation, confusion, and psychotic symptoms predominating though the mood may not be clearly elevated as in mania. Postpartum psychosis is estimated to affect 0.1–0.2% of women following childbirth but the risk for women with BPD is at least 25%, and increases to greater than 50% if there is a family history of PPP [13]. The onset of PPP is typically abrupt. For example, Heron and colleagues (2007) retrospectively looked at the onset of clinically significant symptoms in women diagnosed with BPD-

associated PPP and found that onset for over 50% of symptoms occurred in days 1 to 3 postpartum, and that over 22% occurred on day 1 [14]. The clinical implications of this are important, and women with BPD should be monitored closely in the immediate postpartum period. Although it remains unclear if and by how much prophylactic medications reduce the risk of PPP, the abrupt and early onset also supports treating women actively during the third trimester and through labor and delivery (see, for example, Lithium below).

Jones and Craddock (2001) found that women with BPD and PPP were more likely to have a family history of PPP compared to women with BPD without a family history. They concluded that familial factors are implicated in the susceptibility of postpartum episodes in BPD [13]. This same group recently completed a genome-wide linkage analysis of PPP and found significant linkage to chromosome 16p13, which has previously been shown to be associated with an index manic episode in families with BPD [15]. Thus, this is an area where further study is clearly warranted. Robertson-Blackmore and colleagues (2006) found that in BPD-I, the risk of PPP was increased with primiparity and a complicated delivery [16]. Sharma and colleagues (2004) retrospectively found that women (n = 32) hospitalized with PPP were more likely to have had a prolonged labor or nighttime delivery, leading the authors to conclude that loss of sleep may be a risk factor for PPP [17]. Promoting good sleep in the immediate postpartum time in women with BPD may therefore be critically important.

Medications

Few controlled studies examine the efficacy of medications in the treatment of BPD during and after pregnancy. For example, it remains unclear if medications such as lithium should be tapered prior to labor and delivery in order to decrease neonatal complications. It also remains unclear if there are particular medications or regimens that are superior in preventing the onset of postpartum depression (PPD) and/or PPP in the bipolar patient. Until such studies are completed many recommendations regarding medication management for patients with BPD are based on clinical experience and logic. Below we have outlined the common classes of medications used for BPD and the potential risks and clinical management issues associated with particular agents (see Tab. 1).

Mood stabilizers

Lithium

Lithium was once thought to have a high teratogenic risk, particularly of Epstein's Anomaly. This finding was initially based on retrospective reports that suggested a 400-fold increase in risk [18, 19], but more recent research

Table 1. Common psychiatric medications and their use during pregnancy, labor and delivery, and postpartum

Drug and/or class	Management in pregnancy	Management in labor and delivery	Management in the neonate	Management during lactation
Lithium	First trimester: Increased incidence of heart defects although absolute risk is still low. High resolution ultrasound recommended. Renal clearance increases during pregnancy indicating possible need for increased dose	Increased risk for lithium toxicity in mother and infant. Intravenous fluids recommended	Monitor for 'floppy baby' syndrome, rare cases of hypothyroidism and diabetes insipidus	There is decreased renal clearance in infants and a propensity for rapid dehydration febrile illnesses in infants. Lithium is therefore often discouraged but if used, monitor in infant CBC, TSH, and lithium levels
Valproic acid	Known human teratogen and should be avoided. Increased risk of neural tube defects (5–9%) and craniofacial abnormalities. Valproic acid is concentrated in the fetal compartment so there is a higher concentration in fetal blood than maternal blood. There are reports of increased educational needs and autistic spectrum disorders in children exposed to valproic acid *in utero*	None	Risk of neonatal toxicity is associated with heart rate decelerations, withdrawal symptoms, and liver toxicity	No adverse effects reported in infants breastfed by mothers treated solely with valproic acid. Monitor infant CBC, liver enzymes, and drug level
Carbamazepine	Known human teratogen with associations of neural tube defects, microcephaly craniofacial defects, and developmental delay in the exposed child	None	Associated with lower birth weight, fetal vitamin K deficiency	Compatible with breastfeeding. Monitor CBC and drug level
Lamotrigine	Possible association with oral cleft in exposed fetus (rare)	None	Monitor for rash in neonate	No adverse events reported but infant should be monitored for rash

(Continued on next page)

Table 1. (Continued)

Drug and/or class	Management in pregnancy	Management in labor and delivery	Management in the neonate	Management during lactation
Typical anti-psychotics	Use is not associated with increased malformations. Preferred over atypical antipsychotics, valproic acid and carbamazepine	None	Withdrawal syndrome includes irritability and tongue-thrusting with feeding difficulty and tremor. Also has EPS-associated symptoms that generally resolve within days of giving birth. Toxicity reports include neuroleptic malignant syndrome	None
Second generation anti-psychotics	Olanzapine has not been associated with malformation in small studies but is associated with weight gain, insulin resistance, gestational diabetes and pre-eclampsia	None	Possible self-limited withdrawal syndrome with irritability, feeding difficulty, tongue-thrusting, tremor and EPS-associated symptoms	None
Benzo-diazepines	Small association with oral cleft malformations	'Floppy Baby' syndrome possible	Withdrawal syndrome with chronic use	There have been isolated reports of sedation with longer acting benzo-diazepines
SSRIs	Paroxetine has been implicated in congenital malformations and should be reserved for women with severe symptoms who have failed trials of other antidepressants. There has been a report of increased incidence of persistent pulmonary hypertension of the newborn but this is unreplicated	None	Neonatal withdrawal syndrome with jitteriness, mild respiratory distress, transient tachypnea, weak cry, poor tone and increased NICU admissions	Paroxetine and Sertraline should be considered first line for women who are breastfeeding starting an anti-depressant in the postpartum period Fluoxetine and citalopram are associated with a relatively higher risk of adverse effects

(Continued on next page)

Table 1. (Continued)

Drug and/or class	Management in pregnancy	Management in labor and delivery	Management in the neonate	Management during lactation
Bupropion	No increased risk of malformations compared with other antidepressants	None	None	There has been one reported incidence of seizures in an exposed infant
Venlafaxine	Not associated with increased congenital malformations. Associated with poor neonatal adaptation, which is transient	None	Withdrawal syndrome	Low number of case reports suggests no adverse effects. It has been suggested that breast milk exposure could attenuate withdrawal in neonates exposed prenatally
Duloxetine	Little to no data available	No data	No data	Very little information has been reported. It is known that the drug and its metabolites are excreted in the milk of lactating rats but it is unknown if they are excreted in human milk
Tricyclic antidepressants	No significant increase in malformations	None	None	Anecdotal evidence only. Monitor drug levels in infant

suggests that the risk is much lower than originally thought. Cohen and colleagues (1994) conducted a meta-analysis evaluating the published clinical data on lithium in pregnancy and concluded that although there was an increased relative risk of cardiac anomalies associated with first trimester exposure to lithium, the absolute risk was approximately 1 out of 1,000 [20]. This risk can be eliminated by withdrawing lithium during conception and reintroducing it after the first trimester in appropriate patients.

Use of lithium during the third trimester has been associated with more perinatal complications and may result in hypotonicity and cyanosis, better known as 'floppy baby' syndrome [21]. Rare cases of neonatal hypothyroidism and nephrogenic diabetes insipidus have also been described. It has therefore been suggested and, at times has been common practice, to lower the dose and even discontinue lithium close to labor and delivery. However, the absolute risk of neonatal toxicity appears to be rare, and the risks of peripartum relapse to the mother are significant [12]. Further, neurobehavioral sequelae were not evident in a 5-year follow-up of 60 school-aged children exposed to lithium during gestation [22]. Therefore no tapering prior to labor and delivery is currently recommended [23].

Valproic acid

Valproic acid is a known teratogen associated with up to a 7–10% risk of neural tube defects [5, 23]. Valproic acid is also associated with craniofacial anomalies and a higher risk of cognitive and educational difficulties in children exposed *in utero*. It has also been associated with autistic spectrum disorders [24]. It is therefore not recommended for treatment of BPD during pregnancy and should be avoided if at all possible.

Carbamazepine

Similar to valproic acid, carbamazepine has been associated with neural tube defects, though the risk is smaller (1% with first trimester exposure). Craniofacial anomalies as well as microcephaly are also associated with first trimester exposure [5, 23].

Lamotrigine

Lamotrigine is approved for the treatment of BPD and is more commonly used to treat depressive symptoms. There has been no overall risk of major malformations associated with lamotrigine according to the International Lamotrigine Pregnancy Registry, but the North American Antiepileptic Drug Registry has suggested an increased risk for oral clefts.

Choice of mood stabilizer during pregnancy

Given the significant risks associated with valproic acid and carbamazepine during pregnancy their use should be avoided during the first trimester and thereafter if possible. It remains unclear if folate supplementation of 4 mg/day reduces drug-associated neural tube defects but the supplement should be offered, as should prenatal surveillance for congenital anomalies for any fetus exposed to either of these two medications [23]. In comparison, lamotrigine, to date, appears relatively safe during pregnancy. It remains unclear whether lamotrigine is effective as a mood stabilizer during and after pregnancy. For patients with severe illness, lithium has the most evidence for effectiveness but should be used in conjunction with fetal heart echocardiography in women exposed during the first trimester. In women with mild or infrequent illness, slow tapering of medications prior to conception and clinical monitoring during pregnancy may be successful. In women with moderate severity of illness, avoidance of teratogenic agents during the first trimester and reinstitution thereafter may be the best approach [23].

Antipsychotics

Antipsychotics are often used to treat BPD and the atypical antipsychotics are gaining popularity in the maintenance treatment of BPD. Newport and colleagues [25] conducted a prospective observational study of women treated with haloperidol or atypical antipsychotics during pregnancy and compared maternal and fetal drug concentrations after delivery. Placental passage was highest for olanzapine, which was also associated with a higher percentage of low birth weight and increased admissions to neonatal intensive care unit. Quetiapine had the lowest placental passage, followed by risperidone and then haloperidol [25]. McKenna and colleagues [26] reported on a cohort of 151 pregnant women who were treated with atypical antipsychotics including olanzapine, risperidone, quetiapine, and clozapine. There were no statistically significant differences in pregnancy outcomes with the exception of low birth weight in 10% of exposed neonates [26].

Recently, Coppola and colleagues evaluated 713 case reports of pregnant women treated with risperidone and found no increased risk of spontaneous abortions, structural malformations, or fetal teratogenic risks above that of the general population. Extrapyramidal effects were seen in neonates after maternal exposure in the third trimester but were self-limited [27]. Little data beyond the above reports (except for case reports) exists for the other atypical agents, including clozapine, olanzapine, quetiapine, aripiprazole, and ziprasidone.

The typical antipsychotic medications have a longer (greater than 40 years) and larger reproductive safety profile than the atypicals. No significant teratogenic effect has been shown for chlorpromazine, haloperidol, and per-

phenazine [23]. A multi-site prospective study followed 215 pregnancies exposed to haloperidol and penfluridol and found no difference in the treated group compared to controls in congenital anomalies; however, there was a higher rate of elective terminations, a higher rate of preterm births (13.9% *versus* 6.9%), and a lower median birth weight (3,155 g *versus* 3,370 g) in the exposed group. There was also a possible association with limb defects in the treated group, prompting the authors to recommend ultrasound evaluation to women exposed in the first trimester [28]. Fetal and neonatal toxicity reports have included neuroleptic malignant syndrome, dyskinesia, and extrapyramidal side effects.

Choice of antipsychotics during pregnancy

In general, given the long history of successful use of typical agents coupled with the minimal risks associated with them for pregnancy, the first line choice should be a typical antipsychotic such as haloperidol. Further, given the minimal risks associated with them, typical agents may be used in place of mood stabilizing agents such as lithium and valproic acid during pregnancy. The minimal effective dose should be used and neonates should be evaluated for side effects after labor and delivery.

Antidepressants

Untreated depression in pregnancy is associated with increased risk of preterm birth, fetal growth restriction, pre-eclampsia, newborn behavioral effects, and impaired maternal psychosocial functioning [29]. Antidepressant use is becoming more prevalent during pregnancy. For example, a recent multi-site study looking at the use of antidepressants in 118,935 pregnancies from 2001–2005 found an increased use of antidepressants, with nearly 8% of pregnant women in 2004 and 2005 taking antidepressants during pregnancy [30]. The teratogenic effects of antidepressants have been extensively studied and will be summarized here.

The National Birth Defects Prevention Study retrospectively compared rates of maternal Selective Serotonin Reuptake Inhibitors (SSRI) use in over 9,500 infants with birth defects to rates of maternal SSRI use in normal infants. Maternal use of SSRI's in the first trimester was not associated with significantly increased risk of congenital heart defects. Three types of birth defects were associated with maternal SSRI use in the first trimester but the absolute risks were still low. Those birth defects were anencephaly (adjusted odds ratio (AOR) 2.4), craniosynostosis (AOR 2.5), and omphalocele (AOR 2.8). The results were limited by the relatively small number of children with each type of birth defect [31]. In contrast, the Slone Epidemiology Center Birth Defects Study compared first trimester exposure to SSRIs in 9,849

infants with birth defects to 5,860 infants without birth defects and found no significantly increased risks of craniosyntosis, omphalocele, or heart defects associated with SSRI exposure [32]. Interestingly, both studies found a small increased association of right ventricular outflow tract obstruction with maternal use of paroxetine [31, 32]. A meta-analysis reviewing the data on paroxetine use during the first trimester concluded that there were increased risks of cardiac anomalies, although absolute risk remained low [33]. Thus, maternal use of paroxetine during pregnancy should be limited to women who have severe symptoms and for whom other agents have proven ineffective.

Exposure to SSRIs in the third trimester has been associated with transient 'withdrawal' symptoms in neonates, such as jitteriness, mild respiratory distress, transient tachypnea, weak cry, poor tone, and NICU admission [23, 34]. There is an unconfirmed association of SSRI use with persistent pulmonary hypertension of the newborn, which is an extremely rare condition [35].

Einarson and colleagues [36] reported on a multicenter prospective study of pregnant women taking venlafaxine and found that there did not appear to be any increased risk of major malformation in infants exposed to venlafaxine *in utero* [36]. Similarly, Cole and colleagues (2007) reported that there did not seem to be an increased risk of malformations for infants exposed to bupropion *in utero* [37], and one study indicated that it can be helpful for pregnant women who are trying to quit smoking [38]. Finally, Djulus and colleagues conducted a prospective study of 104 pregnant women taking mirtazepine and found no apparent increase in major fetal malformations [39].

Overall, there is a long history tricyclic antidepressant use during pregnancy that indicates that there is little to suggest any teratogenic effect or increased perinatal problems [5, 23, 40]. Thus the use of antidepressants during pregnancy, though controversial, may be advised in specific patients. Older agents should be used if possible as there is more safety data available. The use of paroxetine should probably be avoided except in specific patients. Newborns should be monitored for signs and symptoms of 'withdrawal' and given supportive care.

Benzodiazepines

Early studies reported an increased risk of oral clefts with benzodiazepine use which has subsequently been called into question or been shown to be minimal (increased risk by 0.01%) [23, 40]. Wikner and colleagues reviewed records of over 2,000 infants from the Swedish Medical Birth Registry who were exposed to benzodiazepines *in utero* and found an increased risk of preterm birth and low birth weight in the exposed group. There was also an increased risk of congenital malformations with an adjusted OR 1.24 [41]. Use of benzodiazepines shortly before delivery is associated with 'floppy infant syndrome', characterized by hypothermia, lethargy, poor respiratory effort,

and feeding problems as well as neonatal withdrawal symptoms for as long as 3 months postpartum [23]. Benzodiazepines should be tapered and not stopped abruptly and their use should be avoided if possible late in the third trimester.

General guidelines

Pre-pregnancy planning

Women with BPD are frequently advised by physicians to avoid getting pregnant. Reasons cited include potential fetal exposure to psychotropic medications, many of which are associated with teratogenic risks, and/or risk of recurrence that can be damaging to both the mother and fetus. Despite these obstacles, many decide to pursue pregnancy and should have a comprehensive and unique review of treatment options, ideally pre-pregnancy, in order to understand the risks and benefits associated with various treatment options [4].

In the pre-pregnancy planning phase, it is important to counsel patients on the risks and benefits of medications as well as a possible recurrence of mood episodes. Another consideration is the fact that many medications commonly used in the treatment of BPD can disrupt the menstrual cycle and interfere with fertility. For example, antipsychotic medications, commonly used as mood stabilizers or antimanic agents in BPD, can increase prolactin levels, which subsequently disrupt the menstrual cycle and reduce fertility. Similarly, valproic acid is associated with polycystic ovarian disease that may also disrupt the menstrual cycle and decrease fertility [42].

The clinician should also take into account some of the possible psychosocial complications of BPD. Women with BPD are more likely to be single parents and are more likely to suffer from addictions or substance abuse compared to women without BPD. As a result, patients with BPD are also more likely to have obstetric complications during pregnancy, and are more likely to have placental abnormalities such as placenta previa, antepartum hemorrhages, and other complications due to nicotine, alcohol, and illicit drug use [2]. These factors should be taken into account during pre-pregnancy planning and included as part of the overall treatment plan. For example, women should be advised on how to stop drinking and smoking prior to and during pregnancy, and support systems should be examined and put into place if possible. Psychosocial interventions can range from initiating psychotherapy to meeting with the patient's partner and family in order to provide education and devise a plan for maintaining appropriate sleep patterns during the postpartum time.

Monitoring during pregnancy

Monitoring during pregnancy should continue at a rate that is clinically appropriate. Physicians should be aware that, as pregnancy progresses, extensive

physiological changes occur that may affect the absorption, distribution, metabolism, and excretion of many drugs due to alterations in the activity of metabolic enzymes and alterations in renal and hepatic function [43]. Lithium is excreted by the kidneys and serum levels should be monitored on a regular basis during pregnancy [44]. Similarly, lamotrigine serum levels have been shown to decrease during pregnancy; thus, regular monitoring of serum levels is also indicated [43]. Many antidepressants – including paroxetine, duloxetine, fluoxetine, and citalopram – have also been shown to be metabolized at a higher rate during pregnancy and may need to be increased as pregnancy progresses. Finally, clozapine and olanzapine may have decreased metabolism during pregnancy and thus may need to be reduced to avoid side effects [43]. Factors such as vomiting due to morning sickness may also need to be taken into account when deciding the timing of checking medications such as lithium (i.e., sooner rather than later).

Monitoring postpartum

As noted above, the postpartum time is clearly a risky time period for women with BPD. Women with BPD therefore need to be followed closely during this time – both while in the hospital during labor and delivery, and after returning home. Family members should be educated about the potential signs and symptoms of an emerging PPP as well as PPD. Good and regular sleep habits should also be promoted; as noted above, Sharma and colleagues have shown preliminarily that sleep loss may precipitate PPP [17]. Because sleep loss has been shown to precipitate a mood episode regardless of pregnancy state [45], the risk could be particularly high. Involvement of the patient's partner and family with nighttime care can be helpful. A check-up with the woman (preferably within the first week postpartum) is advisable, even if only by phone, as many women find it difficult to keep doctors' appointments right after childbirth. Furthermore, because new mothers may be more likely to see their child's pediatrician in the first few weeks postpartum than their own doctor, pediatricians should also be on the lookout for postpartum changes. Medication changes that were instituted during pregnancy due to metabolic reasons may need to be reversed over the next few months and, when appropriate, serum levels should be checked.

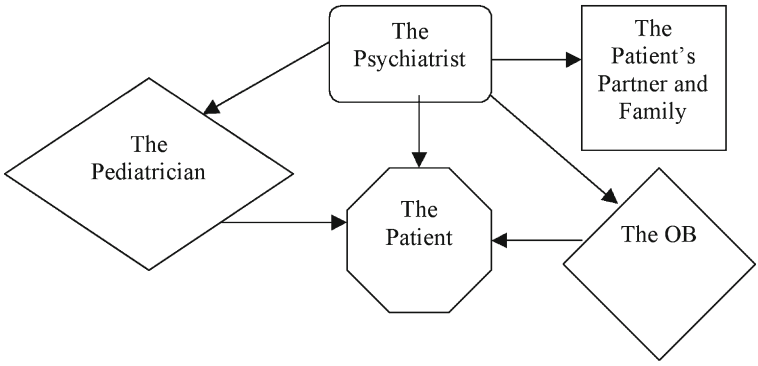
Breastfeeding

Monitoring of the baby exposed to medications *in utero* or via breastfeeding should be done by the pediatrician; thus, communication between the treating psychiatrist and the pediatrician during the postpartum time is advisable. All psychotropic drugs enter breast milk, and limited studies have been conducted on the potential long-term consequences of exposure to medications during

breastfeeding. That being said, exposure during breastfeeding is less than the exposure that occurs during pregnancy for the infant [46]. Drugs enter breast milk by passive excretion and breast milk concentration is directly proportional to maternal serum concentration. Milk concentration is also determined by qualities specific to the drug such as half-life, peak absorption, molecular weight, degree of ionization, lipid solubility, and protein-binding capacity. Recommendations have been made to breastfeed immediately prior to taking a medication in order to minimize infant exposure. Unless clinically necessary, it has also been recommended that patients remain on the same medication while breastfeeding that they took during pregnancy, thereby exposing their infants to one, not two or more different medications. Stowe [46] reviews recommendations for the use of lithium, antiepileptic medications, and atypical and typical antipsychotics. Where appropriate, serum levels and blood work to monitor for potential side effects should be obtained in the infants. For example, if lithium is used during breastfeeding, a lithium level, a complete blood count, blood urea nitrogen/creatinine, and thyroid-stimulating hormone level should be obtained. In contrast to the dangers associated with their use in pregnancy, antiepileptic medications appear to be compatible with breastfeeding [46].

Team approach

It is important to use a team approach when treating pregnant women with BPD (or any other psychiatric disorder) (see Fig. 1). The husband or partner, and when appropriate, other members of the family, should be educated about the potential risks and benefits of treatment as well as the signs and symptoms of emerging illness. The obstetrician and psychiatrist should communicate in detail about the treatment decisions made and the reasons behind them in order to minimize miscommunication and to maximize compliance with treatment.



Figue 1. The team approach

Similarly, the child's pediatrician should be included in the process. A team approach is likely to improve outcomes and provide more consistent support to the mother who must make difficult choices about her own health and the health of her baby.

References

1 Schneid-Kofman N, Sheiner E, Levy A (2008) Psychiatric illness and adverse pregnancy outcome. *Int J Gynaecol Obstet* 101: 53–56
2 Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA (2005) Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *Am J Psychiatry* 162: 79–91
3 Grof P, Robbins W, Alda M, Berghoefer A, Vojtechovsky M, Nilsson A, Robertson C (2000) Protective effect of pregnancy in women with lithium-responsive BP. *J Affect Disord* 61: 31–39
4 Viguera AC, Cohen LS, Bouffard S, Whitfield TH, Baldessarini RJ (2002) Reproductive decisions by women with BP after prepregnancy psychiatric consultation. *Am J Psychiatry* 159: 2102–2104
5 Cohen, Lee S (2007) Treatment of bipolar disorder in pregnancy. *J Clin Psychiatry* 68 (suppl 9): 4–9
6 Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS (2007) Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* 164: 1817–1824
7 Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, Keck PE Jr (2002) The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry* 63: 284–287
8 Payne JL, MacKinnon DF, Mondimore FM, McInnis MG, Schweizer B, McMahon FJ, Nurnberger Jr, JI, Rice JP, Scheftner W, Coryell W et al (2008) Familial aggregation of postpartum mood symptoms in families with bipolar disorder. *J Bipolar Disord* 10: 38–44
9 Blehar MS, DePaulo JR Jr, Gershon ES, Reich T, Simpson SG, Nurnberger JI Jr (1998) Women with BP: findings from the NIMH Genetic Initiative Sample. *Psychopharmacol Bull* 34: 239–243
10 Payne JL, Roy PS, Murphy-Eberenz K, Weissman MM, Swartz KL, McInnis MG, Nwulia E, Mondimore FM, MacKinnon DF, Miller EB et al (2007) Reproductive cycle-associated mood symptoms in women with major depression and bipolar I disorder. *J Affect Disord* 99: 221–229
11 Cohen LS, Sichel DA, Robertson LM, Heckscher E, Rosenbaum JF (1995) Postpartum prophylaxis for women with BP. *Am J Psychiatry* 152: 1641–1645
12 Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ (2000) Risk of Recurrence of BP in pregnant and nonpregnant women after discontinuation of lithium maintenance. *Am J Psychiatry* 157: 179–184
13 Jones I, Craddock N (2001) Familiality of the puerperal trigger in BP: results of a family study. *Am J Psychiatry* 158: 913–917
14 Heron J, Robertson Blackmore E, McGuinness M, Craddock N, Jones I (2007) No 'latent period' in the onset if bipolar affective puerperal psychosis. *Arch Women Mental Health* 10: 79–81
15 Jones I, Hamshere M, Nangle JM, Bennett P, Green E, Heron J, Segurado R, Lambert D, Holmans P, Corvin A et al (2007) Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16. *Am J Psychiatry* 164: 1099–1104
16 Robertson-Balckmore E, Jones I, Doshi M, Haque S, Holder R, Brockington I, Craddock N (2006) Obstetric variables associated with bipolar affective puerperal psychosis. *Br J Psychiatry* 188: 32–36
17 Sharma V, Smith A, Khan M (2004) The relationship between duration of labour, time of delivery and puerperal psychosis. *J Affect Disord* 83: 215–299
18 Nora JJ, Nora AH, Toews WH (1974) Lithium, Ebstein's anomaly, and other congenital heart defects (letter). *Lancet* 2: 594–595
19 Weinstein MR, Goldfield M (1975) Cardiovascular malformations with lithium use during pregnancy. *Am J Psychiatry* 132: 529–531
20 Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML (1994) A reevaluation of risk *in utero* exposure to lithium. *JAMA* 271: 146–150

21 Newport DJ, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN (2005) Lithium passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry* 162: 2162–2170
22 Schou M (1976) What happened later to the lithium babies? A follow-up study of children born without malformations. *Acta Psychiatr Scand* 54: 193–197
23 American College of Obstetrics and Gynecology (ACOG) Practice Bulletin (2007) Use of psychiatric medications during pregnancy and lactation. *Obstetr Gynecol* 87: 1179–1198
24 Duncan S (2007) Teratogenesis of sodium valproate. *Curr Opin Neurol* 20: 175–180
25 Newport DJ, Calamaras MR, DeVane CL, Donavan J, Beach AJ, Winn S, Knight BT, Gibson BB, Viguera AC, Owens MJ et al (2007) Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry* 164: 1214–1220
26 McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citron O, Levinson A, Zipursky RB, Einarson A (2005) Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry* 66: 444–449
27 Coppola D, Russo LJ, Kwarta RF Jr, Varughese R, Schmider J (2007) Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. *Drug Saf* 30: 247–264
28 Diav-Citron O, Shechtman S, Ornoy S, Arnon J, Schaefer C, Gabris H, Clementi M, Ornoy A (2005) Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. *J Clin Psychiatry* 66: 317–322
29 Bonari L, Pinto L, Ahn C, Einarson A, Steiner M, Koren G (2004) Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry* 49: 726–735
30 Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, Rolnick SJ, Roblin D, Smith SH, Willy ME et al (2008) Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol* 198: 194e1–194e5
31 Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM (2007) Use of serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *New Engl J Med* 356: 2684–2692
32 Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA (2007) First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *New Engl J Med* 358: 2675–2683
33 Bar-Oz B, Einarson T, Einarson A, Boskovic R, O'Brien L, Malm H, BErard A, Koren G (2007) Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. *Clin Ther* 29: 918–926
34 Ferreira E, Carceller AM, Agogue C, Martin BZ, St-Andre M, Francoeur D, Berard A (2002) Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 119: 52–59
35 Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA (2006) Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New Engl J Med* 354: 579–587
36 Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, Mastroiacovo P, Addis A, Matsui D, Schuler L et al (2001) Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 158: 1728–1730
37 Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM (2007) Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 15: 474–484
38 Chan B, Einarson A, Koren G (2005) Effectiveness of bupropion for smoking cessation during pregnancy. *J Addict Dis* 19: 19–23
39 Djulus J, Koren G, Einarson TR, Wilton L, Shakir S, Diav-Citron O, Kennedy D, Voyer Lavigne S, DeSantis M, Einarson A (2006) Exposure to mirtazepine during pregnancy: a prospective, comparative study of birth outcomes. *J Clin Psychiatry* 67: 1280–1284
40 Altshulter LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J (1996) Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 153: 592–606
41 Wikner BN, Stiller CO, Bergman U, Asker C, Kallen B (2007) Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf* 16: 1203–1210
42 Joffe H (2007) Reproductive biology and psychotropic treatments in premenopausal women with BP. *J Clin Psychiatry* 68 Suppl 9: 10–15
43 Hodge LS, Tracy TS (2007) Alteration in drug disposition during pregnancy: implications for drug

therapy. *Expert Opin Drug Metab Toxicol* 3: 557–571
44 Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, Manber R, Viguera A, Suppes T, Altshuler L (2004) Management of BP during pregnancy and the postpartum period. *Am J Psychiatry* 161: 608–620
45 Goodwin FK, Jamison KR (eds) (2007) *Manic-depressive illness. Bipolar disorders and recurrent depression*. Oxford University Press, New York
46 Stowe Z (2007) The use of mood stabilizers during breastfeeding. *J Clin Psychiatry* 68 (suppl 9): 22–28

Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Conclusion

Carlos A. Zarate Jr and Husseini K. Manji

Laboratory of Molecular Pathophysiology & Experimental Therapeutics, Mood and Anxiety Disorders Research Program, National Institutes of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

Although our knowledge of mood disorders in general is expanding steadily, comparatively little is known about bipolar depression in particular. The purpose of this book was to bring together clinicians and researchers, in order to offer the most up-to-date information about the diagnosis, treatment, and research surrounding bipolar depression.

Clinically, bipolar disorder continues to be one of the most debilitating medical illnesses. Afflicted patients generally still experience high rates of relapse, a chronic recurrent course, lingering residual symptoms, functional impairment, psychosocial disability, and diminished wellbeing. Furthermore, it is a sad fact that bipolar disorder is frequently unrecognized, misdiagnosed, and mismanaged. In Chapter 1, Dr. Marneros points out that depression and mania are mankind's oldest known mental disorders; they were the first mental disorders conceptualized by Hippocrates as a part of medicine, and mania and depression as two parts of the same disease was first described in the 1st century AD. Yet even today, a diagnosis of bipolar disorder is often missed in patients who report depressive rather than manic symptoms. Bipolar mania is often well-recognized by physicians, but bipolar depression, though more common, is often misdiagnosed and mistreated as unipolar depression. Thus, the depressed phase of bipolar disorder remains an enormous challenge for patients, their families, and clinicians. Furthermore, as Dr. Rihmer so poignantly discusses in Chapter 4, suicidal behavior in patients with bipolar disorder occurs almost exclusively during severe major depressive episodes and the suicide rate of untreated patients with bipolar disorder is 25 times higher than the same rate in the general population.

Undiagnosed patients with bipolar disorder often present for evaluation during a depressed episode. These patients are then most frequently misdiagnosed with unipolar depression and treated with antidepressants. For some patients, such treatment may be ineffective or deleterious for them. Much more research is needed to determine precisely which patients would benefit from short- and/or long-term antidepressant therapy. As Drs Young and Wang note in Chapter 6, there has long been debate about whether bipolar depression is similar to or different from unipolar depression, with the recognition that different

treatment responses and clinical courses suggest a different neurobiology. Drs Parker and Fletcher (Chapter 2) note that 'bipolar depression' is not a specific type of depression, with most episodes phenotypically weighted to melancholic or psychotic depression and that, clearly, the current diagnostic systems employ imprecise criteria to differentiate sub-types of bipolar disorder. Compounding this issue is that the lack of well-established guidelines for the diagnosis and treatment of bipolar disorder makes misdiagnosis even more likely.

As this volume discusses in some detail, mood stabilizing drugs are useful for treating different phases of bipolar disorder including the treatment of mania and depression acutely, and prophylaxis against relapse into either state. There is a general consensus that treating either acute depression or preventing relapses into depression is more challenging than treating mania, and that the drugs we use to treat the disorder are less effective for these symptoms. The thoughtful chapters by Drs Beyer and Krishnan, Findling, and Payne and Roy (13, 14, and 15, respectively), highlight the further difficulties associated with treating the disease in different populations.

Fittingly, the chapters in this volume highlight that the treatment of bipolar depression is another area where dramatic improvements are needed. In Chapter 9, Dr. Sachs points out that acute depression is the condition for which patients with bipolar disorder most often seek treatment; although the foundation of best clinical practice is double-blind, placebo-controlled trials with adequate sample size, in bipolar depression such evidence exists only for lamotrigine, quetiapine, olanzapine monotherapy, and olanzapine plus fluoxetine. Interestingly, the most common treatment for bipolar depression – the adjunctive use of standard antidepressants along with lithium or valproate – has not been shown to be effective in any Category A study. Furthermore, many depressed bipolar patients do not respond adequately to currently available treatments.

Expanding upon this idea, in Chapter 10 Drs Calabrese and Gao note that, so far, only lithium and lamotrigine, and to some extent divalproex, have been investigated in both manic and depressive index episodes. Dr. Sackeim (Chapter 11) gives a thorough overview of the usefulness of electroconvulsive therapy (ECT) in bipolar depression, as well as its essential limitations. His chapter introduces promising new developments in this field including new forms of ECT administration that dramatically reduce the frequency and severity of adverse cognitive effects, including alterations in the administration of ECT, Magnetic Seizure Therapy (MST) and Focal Electrically Administered Seizure Therapy (FEAST), as well as novel interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). Similarly, Chapter 12 reviews some of the novel agents being explored to treat this population, focusing on drugs that do not include the existing antipsychotic, antiepileptic, and antidepressant medications. These include modafinil, pramipexole, N-acetyl cysteine (NAC), scopolamine, agomelatine, riluzole, ketaconazole, mifepristone, celecoxib,

memantine, creatine, and uridine RG2417. Although much of this work is preliminary, many of these agents have proven initially very promising, and further work will continue to explore their clinical utility in bipolar depression.

Despite these difficulties, the information contained in these chapters also highlights how far the field has progressed in recent years. In Chapter 6, Drs Wang and Young describe how many studies have shown altered neurobiology in patients suffering from bipolar disorder, including decreased brain volume and cell number in prefrontal and limbic regions, decreased serotonin metabolite 5-HIAA and serotonin transporter activity in cerebrospinal fluid, brain, or platelets of subjects with bipolar depression, decreased glucose metabolic rate and cerebral blood, and defects in mitochondrial electron transport chain and oxidative damage. In Chapter 8, Drs Savitz and Drevets give a thorough review of some of the pathophysiology of bipolar disorder, noting that reductions in gray matter volume and a concomitant increase in glutamatergic neurotransmission are observed in the pregenual (pgACC) and subgenual anterior cingulate cortex (sgACC), the orbitofrontal, frontal polar and ventrolateral prefrontal cortex (PFC), the posterior cingulate, ventral striatum, and hippocampus of patients with bipolar disorder. In Chapter 5, Drs Schulze and McMahon succinctly review the genetic evidence surrounding bipolar disorder and conclude that, although linkage and candidate gene association studies failed to deliver consistently replicable results, the advent of genome-wide association studies (GWAS) has spurred new hopes for the identification of true susceptibility genes. They note that after close to a century of genetic studies, bipolar disorder is emerging as a complex (non-Mendelian) disorder with a polygenic etiology.

Therefore, a better understanding of the genetics and molecular mechanisms of bipolar disorder, and particularly of bipolar depression, is critical to improving treatment for the disease. As the chapters in this volume attest, there is cause for hope. Research in recent decades has made great advances toward a better understanding of this illness so that better treatments can be developed. A better understanding of the neurobiological underpinnings of this condition, informed by preclinical and clinical research, will be essential for the future development of targeted therapies that are more effective, act more rapidly and are better tolerated than currently available treatments. Importantly, advancements in our understanding of the neurobiology of bipolar disorder continue to be made and do hold promise for future clinical applications.

Despite the devastating impact of bipolar depression on the lives of millions worldwide, there has been a dearth of knowledge concerning its underlying etiology and pathophysiology. This dearth, in turn, has undoubtedly contributed to the lack of development of improved therapeutic strategies for bipolar depression. Collectively, many questions remain unanswered regarding the diagnosis and treatment of patients with bipolar depression. To treat them more effectively, clinicians need additional diagnostic and screening tools, validated in a variety of practice settings; early detection and intervention programs; large-scale controlled clinical trials comparing the effectiveness of

novel interventions and single *versus* combination therapies; clinical studies to determine the most effective treatment regimens for patients with bipolar depression; and, finally, evidence-based standards for medications and psychosocial treatments. Much of that is lacking. However, as the information contained in this book has shown, new strides are being made daily in this field.

Index

The MDT-Series
Milestones in Drug Therapy

The discovery of drugs is still an unpredictable process. Breakthroughs are often the result of a combination of factors, including serendipidity, rational strategies and a few individuals with novel ideas. *Milestones in Drug Therapy* highlights new therapeutic developments that have provided significant steps forward in the fight against disease. Each book deals with an individual drug or drug class that has altered the approach to therapy. Emphasis is placed on the scientific background to the discoveries and the development of the therapy, with an overview of the current state of knowledge provided by experts in the field, revealing also the personal stories behind these milestone developments. The series is aimed at a broad readership, covering biotechnology, biochemistry, pharmacology and clinical therapy.

Forthcoming titles

Erythropoietins and Erythropoiesis, 2nd edition, G. Molineux, M.A. Foote, S.G. Elliott (Editors), 2009
PEGylated Protein Drugs: Basic Science and Clinical Applications, F.M. Veronese, M.J. Bossard (Editors), 2009
Bortezomib in the Treatment of Multiple Myeloma, K.C. Anderson, P.G. Richardson, I. Ghobrial (Editors), 2009
Influenza Virus Sialidase – A Drug Discovery Target, M. von Itzstein (Editor), 2010

Published volumes

Treatment of Psoriasis, J.M. Weinberg (Editor), 2008
Pharmacology of Obesity, J.P.H. Wilding (Editor), 2008
Entry Inhibitors in HIV Therapy, J.D. Reeves, C.A. Derdeyn (Editors), 2007
Drugs affecting Growth of Tumours, H.M. Pinedo, C. Smorenburg (Editors), 2006
TNF-alpha Inhibitors, J.M. Weinberg, R. Buchholz (Editors), 2006
Aromatase Inhibitors, B.J.A. Furr (Editor), 2006
Cannabinoids as Therapeutics, R. Mechoulam (Editor), 2005
St. John`s Wort and its Active Principles in Anxiety and Depression, W.E. Müller (Editor), 2005
Drugs for Relapse Prevention of Alcoholism, R. Spanagel, K. Mann (Editors), 2005
COX-2 Inhibitors, M. Pairet, J. Van Ryn (Editors), 2004

Calcium Channel Blockers, T. Godfraind (Author), 2004
Sildenafil, U. Dunzendorfer (Editor), 2004
Hepatitis Prevention and Treatment, J. Colacino, B.A. Heinz (Editors), 2004
Combination Therapy of AIDS, E. De Clercq, A.M. Vandamme (Editors), 2004
Cognitive Enhancing Drugs, J. Buccafusco (Editor), 2004
Fluoroquinolone Antibiotics, A.R. Ronald, D. Low (Editors), 2003
Erythropoietins and Erythropoiesis, G. Molineux, M. Foote, S. Elliott (Editors), 2003
Macrolide Antibiotics, W. Schönfeld, H. Kirst (Editors), 2002
HMG CoA Reduktase Inhibitors, G. Schmitz, M. Torzewski (Editors), 2002
Antidepressants, B.E. Leonard (Editor), 2001
Recombinant Protein Drugs, P. Buckel (Editor), 2001
Glucocorticoids, N. Goulding, R.J. Flower (Editors), 2001
Modern Immunosuppressives, H.-J. Schuurman (Editor), 2001
ACE Inhibitors, P. D'Orleans-Juste, G. Plante (Editors), 2001
Atypical Antipsychotics, A.R. Cools, B.A. Ellenbroek (Editors), 2000
Methotrexate, B.N. Cronstein, J.R. Bertino (Editors), 2000
Anxiolytics, M. Briley, D. Nutt (Editors), 2000
Proton Pump Inhibitors, L. Olbe (Editor), 1999
Valproate, W. Löscher (Editor), 1999