AM:STARs
Adolescent Medicine: State of the Art Reviews

Current Psychopharmacology for Psychiatric Disorders in Adolescents

Robert L. Hendren, DO
Alya Reeve, MD, MPH
Editors

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Adolescent Medicine: State of the Art Reviews

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CURRENT PSYCHOPHARMACOLOGY FOR PSYCHIATRIC DISORDERS IN ADOLESCENTS

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CURRENT PSYCHOPHARMACOLOGY FOR PSYCHIATRIC DISORDERS IN ADOLESCENTS

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Preface

Adolescent Psychopharmacology Update

The prescription of psychotropic medications for adolescents is growing rapidly. A study of the National Comorbidity Survey (2002-2004) examined the 12-month prevalence of psychotropic medication use among adolescents and found 7.0% of adolescents used at least one psychotropic medication. The medications most commonly used were antidepressants (3.9%), followed by stimulants (2.8%), anxiolytics (0.8%), antipsychotics (0.5%), and mood stabilizers (0.4%).[1] Another database study found that 14.2% of adolescents reported that they had been treated with a psychotropic medication in the past 12 months.[2] Most of these medications are prescribed by primary care practitioners, not child and adolescent psychiatrists.[3]

Increasingly, primary care practitioners are being asked to prescribe psychotropic medications for adolescents by patient's families, HMOs, community service agencies and third party payers. While they may not feel comfortable doing this, practitioners are prescribing because there is inadequate availability of child and adolescent psychiatrists in their region. We believe that competent primary care physicians and non-physician clinicians will benefit from a practical framework about psychopharmacological strategies in adolescents so that, as prescribing practitioners, they can operate within a reasoned evidence-based approach. Dr. Riddle points out in *Pediatric Psychopharmacology in Primary Care: A Conceptual Framework,* of this issue of *Adolescent Medicine: State of the Art Reviews (AM:STARs),* that many primary care pediatricians report that it was their responsibility to identify and possibly manage adolescents with attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and substance abuse, yet many of them do not feel well trained to carry this out.

This issue of AM:STARs focuses on the increasingly important, yet controversial topic of psychopharmacologic treatment of adolescent emotional and behavioral disorders. It begins with 2 related and practical "when and how to medicate" guides for primary care practitioners and then follows with concise, comprehensive reviews of the medications used to treat the major disorders seen in a child and family practice. We have divided adolescent psychopharmacology into related symptoms-and-diagnosis topics. Each author provides a clear description of the treatment target and a vignette; then dosing, side effects, toxicity, laboratories, and FDA indications; and closes with other non-pharmacological treatments.

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The first article is an introduction to the principles of psychopharmacology of psychiatric disorders and brain injury by Alya Reeve, MD, MPH. Mark Riddle, MD and Jane Foy, MD provide a marvelous conceptualization for medicating adolescents with ADHD, depression, and anxiety disorders. A thorough review of agents targeting the inattention found in ADHD with Keith McBurnett, PhD as the lead author follows and includes a discussion of stimulant medications and adrenergic agonists. David Mullen, MD and Jonathan Terry, DO address the use of antidepressants for the treatment of impulsivity/irritability/depression. This is followed by a state-of-the-art review of the treatment of psychosis in adolescents by Murat Pakyurek, MD and Cameron Carter, MD, and a review of the treatment of mood instability and bipolar disorder by Melissa DeFilippis, MD and Karen Wagner, MD, PhD.

We wanted to be certain that we covered all the treatments in which the primary care practitioner might have interest or might encounter, so we have a near final article on biomedical/complementary and alternative treatments by a student, Jenna Cheng, who is just starting medical school with senior author Robert L. Hendren, DO. The closing article by Dan Duhigg, MD considers the complicating factor of substance abuse, which increasingly coexists with mental illness signs and symptoms.

We believe that this review will be very helpful to primary care practitioners who see adolescents in their practice. By determining clear treatment targets and choosing appropriate interventions, the physician or non-physician clinician will be prepared to prescribe psychotropic medications effectively and appropriately.

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Principles of Psychopharmacology for the Adolescent Patient

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INTRODUCTION

This article presents an overview of the general psychopharmacologic approach to adolescent patients with psychiatric disorders and behavioral disturbances. Throughout this issue the term "physician" will be used to identify a broad range of physician practitioners, nurse practitioners, physician assistants, social workers, and other non-physician clinicians. It is my hope that taking the time to formulate an outline of the psychopharmacologic approach will assist physicians in the assessment and treatment of routine and novel psychiatric presentations. Having a framework in mind that can be applied consistently through practice increases the opportunities to make good clinical decisions and to prevent untoward outcomes. Reviewing previous conclusions and constructing new hypotheses for treatment efforts is integral to an iterative model of treatment. This model enhances good outcomes when hypotheses, treatments, conclusions, and analyses are documented consistently in the medical record and shared with the patient and his or her supports (eg, family or team, other specialists, etc.). Treatment, especially when using medications, relies on the active participation of the patient or guardian. The following sections outline general principles of psychopharmacology.

DEVELOP A STRATEGY

Any patient who accepts ingesting medications engages in a great act of risk, exhibiting trust that the person who is providing these new substances has knowledge, experience, and the patient's best interest in mind. As physicians,

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our goal must be the welfare of the child and adolescent, maintaining awareness of their lifelong needs. Most of our patients are minors, for whom the final consent and agreements for treatment are provided by their guardians. Guardians may be parents, other first-degree relatives, or court-appointed representatives. This is the first point of discussion because we must approach the assessment and treatment of symptoms in response to at least 2 points of view or experiences—that of the patient and that of the guardian. Agreement to participate in treatment is made independently by each of these parties and (in most cases, one hopes) in mutual cooperation to a final decision.[1] For this reason, we must be able to address the intended effects of our treatment recommendations, any potential side effects, and all questions that each party might have.

The bio-psycho-social model of human functioning is the proper framework in which to commit the initiation of treatment. This includes understanding the patient's community, values, life experiences, and motivations. Addressing the issues of guardianship and consent, as described earlier, is part of the social context; other aspects include a comprehensive understanding of the scope and depth of involvement in activities such as religious organizations, creative endeavors, sports, hobbies, animals, friends, and family. Having a picture of the network of social connections provides physicians with a better concept of the breadth of social interactions and commitments made by their patient(s). It adds to our ability to assess the developmental progress our individual patient has made, and the extent to which an ongoing or new psychiatric illness or medication/treatment is impeding his or her current developmental tasks. The roles patients have in different contexts help us to understand how they perceive, handle, and overcome various types of challenges or stressful situations. These roles are windows for assessing a patient's psychologic makeup.

An individual's psychologic attributes communicate a great deal about what is meaningful in his or her life, as well as his or her style of communication; reactions to adversity, praise, and pleasure; and tolerance for being out of his or her comfort zone. The more accurately we can understand the psychology of a person, the better we can tailor our treatments to meet his or her strengths and to provide changes that will reduce his or her weaknesses. For example, sedation should be avoided, especially daytime sedation, in a person whose coping mechanism is to maintain control of his or her immediate environment. This person might theoretically benefit from a medication that would decrease his or her attachment to rigid structure, so that options to explore greater flexibility would not create an internal experience of disaster and distress. Conversely, the reason to avoid excess sedation in a patient who sleeps all day to avoid perceived pressures and stressors is to increase the patient's energy and motivation to engage in healthier activities. These considerations cross the diagnostic categories we use in determining presence or absence of mental illness and need for medications. They occur in all people, including those with brain injuries, intellectual disabilities, autism spectrum disorders, histories of traumatic experiences, and spe-

cific mental illnesses. For each patient, we need to discover the particular constellation of experiences, the psychologic development, and the biologic individuality.

The biologic substrate that is contained within each person's genetic material is similar to all other humans and unique to each individual. This contributes to the science and art of effectively prescribing psychotropic medications (Table 1). As a rule, one wants to find the lowest dose possible of a medication that will produce the intended (positive) effects. However, exceptions seem to arise frequently. One way to make the unintended consequences of medication trials useful is to keep a careful log of doses, duration, and effects. It is recommended that the patient/guardian team keep a comprehensive log, because information is often misplaced, misrecalled, or otherwise lost. Depending on the half-life of the medication and the rate of metabolism of the individual, increases in dosage of a given medication should follow a systematic time interval. (A *working* estimate is to stay at a dosage for at least 4 half-lives of the drug, preferably longer; when decreasing, the rate of decrease sometimes needs to be drawn out much slower to prevent withdrawal symptoms.[2,3]) In any person with underlying damage or disease of the brain, the doses will usually be lower; it is recommended to start at one-quarter to one-half the initial recommended dosing and to increase slowly to mitigate the likelihood of side effects and to notice clinical efficacy. In people who have cognitive compromise, anticholinergic, dopaminergic, and some anticonvulsant medications have significant tendencies to interfere with cognitive function and should be avoided or their use minimized.[4] In short,

Table 1.
Principles of Psychopharmacology

1. Start at the lowest dose.
   - You may use one-fourth or one-half of the lowest available dose if the tablet can be broken or if liquid is available.
2. Increase slowly.
   - Follow the recommended rate of increase per unit (rather than the per mg-dose).
   - Adjust as indicated based on physiologic and psychologic responses.
3. Titrate side effects.
   - Increase dosage based on patient's tolerance.
   - Wait as needed for physiologic adaptation to uncomfortable effects.
   - Do not wait when emergency side effects appear.
4. Use monotherapy whenever possible.
5. Treat dysfunction—focus on symptom reduction.
6. Monitor side effects affecting homeostasis.
   - Weight
   - Energy
   - Appetite
   - Sleep
7. Minimize cognitive dysfunction.
   - Monitor for alertness, attention, concentration, and memory.

every person is his or her own best predictor of response to medication, sensitivity to side effects, and need for continuing treatment.

As long as it is possible and prudent, monotherapy, or treatment with one drug, is preferred. This is intended to minimize possible complications, the confounding variables of drug-drug interactions, and to increase the likelihood of patient adherence to the recommended prescription. In real life, problems do not occur singly. Many times, young people have to cope with concurrent medical illness, mental illness, substance abuse, and the demands of a growing and maturing body. Systematic reviews of the necessity for every medication, for overlapping effects, for simpler substitutions, and for possible drug interactions must be made at least by the primary care provider, if not by every physician on that individual's team.[5] The weight gain associated with valproic acid, for example, may be helpful in the slender preteen with both complex partial seizures and impulsive anger. For the same youth a few years later, the weight gain and possible increase in facial acne (or risk for polycystic ovarian disease), may be reason for trying to avoid taking the medicine altogether. It would be prudent to hear the patient's concerns and switch to alternative medications before the patient decides on his or her own to change the therapy by not taking any pills.

All the best intentions do not result in successful treatment outcomes unless we have an effective means of communicating our clinical understanding and concerns with our patients and their guardians. After carefully collecting as much history and contextual information as possible and conducting our clinical examinations, we must be able to describe our assessment of the patient's condition(s) and our treatment recommendations. We must also provide a mechanism for the patient and his or her guardians to provide us feedback on all the effects of treatment (intended and unintended, tolerable and intolerable). It is likely that this takes extra effort on the part of the physician and the patient. Language and cultural attitudes toward illness, physicians, medications, and medical care have great effect on the potential for building a successful alliance in addressing the mental health treatment of adolescents. When there is not a shared (fluent) language between physician and patient, interpreters should be used. Interpretation by other family members may be helpful, but the physician should be wary of the *potential* for editorial changes made by the volunteer translator and by the patient censoring his or her comments (see Case Study).

Case Study

Miranda, a 15-year-old Hispanic girl, was referred by her mother to the school counselor for sessions regarding her mood lability and "talking back" to her parents, her mother in particular. The mother and daughter were interviewed

together at the first interview, then several sessions occurred during school hours with the daughter alone, and finally, a family session was held after hours at the counselor's private office. In the course of the history taking, it was learned that Miranda is the youngest of 8 children, ranging from ages 15 to 39. She had a brother who died 5 years ago at age 24 by probable suicide. The next oldest sibling is a sister, age 18, who lives nearby but out of the house. Three siblings live out of state; the others live in larger cities several hours away. There is a family history of depression in a maternal aunt and alcohol abuse in both parents until 13 years ago. Miranda has a boyfriend, age 17, whom her parents don't like. He is not in school but is "working." They have been sexually active for about 6 months. They deny using heroin, cocaine, or methamphetamine. Miranda admits to intermittent alcohol use, trying marijuana, and occasional cigarettes with her boyfriend.

Miranda admits she has felt very sad since a spontaneous miscarriage 6 weeks before the initial intake. She was looking forward to being pregnant. Her parents did not know that she was pregnant. As soon as she missed her period she made sure not to use any alcohol or smoke. Since the miscarriage, she acknowledges feeling more moody, having greater fatigue, and arguing with her mother a lot. She admits that her grades had slipped from all As to a mixture of As, Bs, and Cs. She wants her mother off her case. Her mood seemed to improve with counseling sessions; she felt more motivated to complete her school work. About 3 months later, she reported having another miscarriage. Again, she felt sad, irritable, and had more fights with her parents, whom she felt were trying to be too controlling.

On a weekend, her mother took her to a different practice in town, where an assessment using biofeedback was performed. Through their diagnostic system they asserted that Miranda had bipolar disorder and was showing initial symptoms of schizophrenia. Her mother agreed for Miranda to start risperidone (3 mg) and trazodone (200 mg) for mood control and sleep problems, respectively. Miranda took the pills as administered by her mother for the first 4 days. She saw the school counselor and reported these events. She did not feel like herself. She was asked if she had spoken of the miscarriages. Miranda replied that no one had asked.

DISCUSSION

This brief synopsis illustrates the potential for questionable practices to influence and affect the care of patients, especially if all relevant information is not obtained. Nowhere in the history or clinical interactions was any psychotic behavior or loss of time or distortion of reality reported or noted. Yet in the setting of incomplete history taking and rushed clinical judgment, a decision to implement an antipsychotic medication was made. It is of more concern given that the risk of long-term involuntary movement disorders is increased when antipsychotic medications are used for nonpsychotic conditions.

The most concerning aspect of this story (based on a real-life situation) is that the patient was not asked about her sexual history or activity, whether in the presence of her mother or alone. A salient aspect of the reasons behind her mood shifts was therefore missed and inappropriate therapy initiated. Her parent was therefore also misled by the professional opinion cemented with an incorrect label and treatment that was unable to redress the underlying problems. Treatment is needed that is directed to communication within the parent–child relationship, sleep disorder, mood problem, and choice of sexual activity. All likely could be addressed effectively by counseling and psychotherapy rather than medication. Additional history regarding parental behavior and attitudes toward their other children are relevant. The fact that one of their children committed suicide in the relatively recent past is a relevant issue to be addressed with at least both parents and Miranda together to see how it affects their current relationship.

The information necessary for a comprehensive history is not usually gathered in a single interview. Although the basic, immediately pertinent information may be elicited during the initial encounter, nuances of symptoms over time, family predilections and family history, and social effect of symptoms generally only evolve as a therapeutic relationship is established between the patient and physician. An important aspect of having an overall strategy is to leave room in the story to learn and incorporate additional relevant information. Each time a hypothesis is generated (see Hypothesis Generation; Repeated Formulation in this article and the appendix), the original data and relevant added factors should be retrievable for review. As the physician and patient/team commit to initiating a specific treatment, the diagnostic and therapeutic plan will be freer for future revision if the data about symptoms and function are maintained independent of interpretation. In doing so, it is relatively easy to invite the patient/team to be active partners in providing relevant information and feedback that contribute to clinical decisions. This also sets up the expectation for the patient that change is likely to occur over time. By having a strategy based on inquiry and repeated assessment, the physician creates a therapeutic environment and interaction that encourages appropriate discussion and questioning. This environment leads to a better informed patient participant who learns how to report his or her experiences and, we hope, to become an effective self-advocate.

AFFECTING BRAIN DEVELOPMENT

From birth into the third decade of life, human brains are dynamic, developing organs. Neurons have to finish migrating to their proper cortical locations; myelination is completed by the end of the second decade. A huge network of dendritic branching occurs while the brain is increasing in size, until around age 7 to 10. Pruning and increased specialization of abilities occur over 10 to 15 years, from early teens into the late twenties. Even at the end of life, autopsies and brain imaging have demonstrated that neurons are sending out new dendritic processes to establish new links to other neurons.[6] This organ is a vital,

developing, and responsive group of cells that responds to experiences by changing intensities of synaptic connections, speed of circuit linkages, and cleanup of excitotoxic materials.

Patterns of use, built on associating different regions with each other, lead to well-developed circuits or networks. During adolescence these patterns are pliable and full of experimentation. The development of the frontal cortex is progressive, estimated to be completed by the end of the third decade (late twenties). In other words, until the frontal cortical connections are well-established, at the cellular level there is little inhibitory modulation on impulsive actions and emotions generated by circuits connected with the amygdala.

All of us have had experience with anxiety, from performance-related worries (eg, public speaking) to fear-based experiences (eg, accidents). It is important not to mask or amplify normal anxiety responses, especially in adolescents who already struggle with appropriate decision-making. Masking can make the adolescent more willing to believe their own invincibility; amplifying anxiety may ingrain avoidant responses that of themselves may create maladaptive outcomes.

HYPOTHESIS GENERATION; REPEATED FORMULATION

Every time a pharmacologic agent is initiated, there should be a reasoned justification for its use. This is especially true in the treatment of minors. Physicians know that many different etiologies manifest through similar clinical symptoms. Therefore, it is essential that symptoms and diagnoses are kept separate. As clinical symptoms become acute, or substantiated, their specific signs and characteristics must be recorded. As groups of symptoms seem to fall into a pattern, a hypothesis should be generated about the goodness of fit of the grouping and/or the etiology contributing to the symptoms. The physician can direct treatment to this hypothesis, noting the responses to any interventions, such as medications, psychotherapy, or alternative therapies. When the desired response is achieved, everyone can be pleased with an uncomplicated response. Often there are intolerable side effects (eg, dizziness), lack of clinical response, or variable attention to adherence to recommended daily dosages. (I do not use the term *non-compliance* because, especially in teens, this behavior is often not directed at the treating provider.) The physician must seek all sources of information contributing to the decision to not take medications as prescribed; often, other psychiatric illness, other medical concerns, or social pressures (economics, social supports, timing, and "being different") are revealed (Table 2). As the information accumulates, a more comprehensive picture of appropriate need for medication (or lack thereof) will become apparent. Physicians can repeatedly return to the listing of symptoms, to which additional characterizations are added, to reformulate a hypothesis of the underlying reasons for symptom presentation.

Table 2.
Searching for Information

Patient:
• May be able to describe symptoms accurately; may need another to mitigate anxiety or compensate/translate for lack of vocabulary for their experiences.
• Nonverbal communication: drawing, body position, agreement with other people reporting information
Immediate family members:
• Note power relationships/dynamics
• Sibling experiences
Friends, peers:
• Do their perceptions match the patient's?
Interactions with clinic staff and examiner:
• Directness of communication; personal accountability vs. deference to accompanying adult
• Is reticence warranted or unwarranted?
Historical documents:
• School records: teacher notes, formal evaluations
• Neuropsychologic testing
• Developmental records
Observations:
• Attitude toward examination
• Physical findings and interview

This iterative process is a critical piece of the art of using medications effectively because it engages the patients and their families as expert reporters and provides a means to initiate a conversation regarding the effectiveness and limitations of any medication approach. Through this process, patients are increasingly engaged in their treatment and develop knowledge of their conditions.

As patients are openly engaged in the assessment of efficacy of medication trials, it helps them to develop more realistic expectations of this form of treatment. With a transparent engagement in a treatment process, there is less likelihood of needless adverse events or legal threats of malpractice.

Generation of hypotheses and revisiting the data at regular intervals are essential to good medical practice. Too often, it seems, physicians depend on patients to voice complaints. The formulation of a diagnosis and of a treatment approach should include the expectation of review and assessment. As physicians, we should be prepared to critique our assumptions, as well as the therapeutic clinical course of our patients. Given the knowledge that our adolescent patients will achieve major biologic changes, along with social and emotional development, we should build into our clinical practice the opportunities and necessity for review of all material. A new formulation should be created if the current one no longer suites the clinical picture.

It is important that original symptoms and the results of ongoing treatment are recorded in a manner that allows the physician to return and review the data.

Over time, symptoms build into characteristic patterns, and a patient shows his or her idiosyncratic responses to various therapeutic interventions. As the physician reviews these patterns with the patient (and family, as appropriate) he or she is helping the patient to become more aware of the patient's specific strengths, weaknesses, needs for support, and general capacity in a holistic sense. From these discussions and perceptions, the patient (and family) can become stronger self-advocates and more effective partners with their clinical team. This process establishes a pattern that will permit the patient to be challenged to be accountable for his or her role in treatment.

DSM: Moving from IV-TR to 5

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is a diagnostic communication tool. A transition is under way for this reference, from the previous edition, the DSM-IV-TR, to the recently published DSM-5.[7,8] Along with the World Health Organization's *International Classification of Diseases* (ICD-10),[9] which classifies psychiatric as well as medical diagnoses, these taxonomies of diagnoses represent major communications about psychiatric disorders. Every time there is a change from one diagnostic system to another, challenges arise about the reliability and validity of the framework, unless it is based on well-constructed clinical trials. The DSM-5 is based on practice, consensus statements, and reports by experts in the field, with a sampling of reliability and validity conducted in the last 2 to 3 years.[10] The intent of the DSM-5 was to be based on neurotransmitter systems, to address stability or change across the life span, and to recognize the most treatable disorders. Given that the DSM-5 was published as this volume was prepared for print, it is premature to definitively address similarities or differences between the 2 editions. It should be noted that in 2013, the National Institute of Mental Health is requesting all investigators to follow research domain criteria (RDoC).[11]

One area of change is in the category of autistic symptoms. The new criteria have recognized the width of the clinical symptom spectrum, as well as its longevity through the life span. Instead of separating types of autistic disorders by intelligence quotients (such as Asperger syndrome), all fall under the general category of autism spectrum disorders. The category of pervasive developmental disorder, not otherwise specified, has also been subsumed into this category.[12] When patients do not have a clear (documented) history of very early normal development with a subsequent falling off from the expected development trajectory, the diagnosis of autistic disorders is more difficult. In addition, intensive interventions can ameliorate social reciprocity deficits by over-learning more appropriate behavior, leading to adults with essentially no apparent deficit. This leads some in the field to question the validity of the diagnosis. It would be more productive and realistic to realize that with intensive behavioral (and pharmacologic) supports, people can recover from some disorders.

DOCUMENTATION

Interacting with patients and families takes skill, practice, and knowledge. Morgan and Engel carefully outlined the ideal behavior of the physician and the need to meet the patient's needs in their seminal book about clinical examination.[13] In our modern day, we often rely on these same skills and tenets, but our methods of documentation have progressed to electronic records, electronic prescriptions, and electronic communication with our patients. Although youth may be most comfortable interacting through electronic and social media, we need to be assiduous about recording our actions and the decision-making behind them. This is particularly true for adolescents as they recover from brain injuries,[14] when integrating clinical examination, neuropharmacology, and rehabilitation will affect the possibilities for long-term good outcomes. As they age, this information will continue to be relevant to future illnesses and accidents and their recoveries from those events. The records we keep should be developed with this in mind—access to a history of drugs used, dose ranges, desired responses, and untoward responses.

As we move to an era of greater openness with our patients, it is likely that they will have direct access to their medical information. This is a reminder that we should write about patients as we would care to read about ourselves. Dispassionate writing is great; pejorative, vindictive, or labeling writing is not justified. Prognoses should be given if known; however, if truly a conjecture, that should be clearly described. It is imperative that patients have reasonable expectations to hope for improvement and to continue to engage in their therapy.

Developing a method of recording all the pertinent information and discussions about decisions with both the patient and any guardians is a necessity. Electronic records can be modified with specific templates of your own design, or existing notes can have sections labeled and updated. Communication through other media needs to be recorded within the electronic or written record if the information is important for understanding treatment decisions. The record should be comprehensible for another physician to read and to be able to understand the clinical decision-making, the range of possible treatments considered, and the systematic reviews conducted. Electronic reminders can be built in (within some systems) to remind the physician to review treatment to date. If not, annual reviews are the minimum expectation to revisit the need for continued psychiatric medications and screen for any untoward side effects.

When it is not evident that the treatment is necessary, or that it is effective, a note should be recorded of clinical findings and the interpretation. Subsequent decisions regarding further treatment should also be noted. Whether the patient and guardian took part in this discussion and, if so, the opinions they expressed should be clearly noted. In other words, all our thinking about the rationale for psychopharmacologic interventions should be documented.

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Appendix
Clinical Examination Primer Notes

A. BACKGROUND
   1. Referral source(s)
      i. Physician, system, insurance, family, self, etc.
   2. Identified primary concern for evaluation
      i. Brief office visit/in-depth assessment
      ii. New problem or exacerbation of chronic condition
      iii. Eligibility for some type of service
   3. Demographics
      i. Age, gender
      ii. Existing conditions and medications

B. OBSERVATIONS
   1. Group
      i. Who are the people present? What are their roles?
      ii. What are the attitudes (active, passive; inclusive, dismissive) toward patient?
      iii. Do they present a coherent picture of information: attitude, level of detailed information, apparent active relationship with patient, etc.?
      iv. What are the dynamics between the individuals; team conflict or competition?
   2. Individual
      i. Assess the patient's movement: gait and mobility, range of motion, responsiveness to others.
      ii. Does the patient communicate his/her preferences verbally or nonverbally?
      iii. Is there concurrence with the reports from others? Is the patient's point of view being passed over or misinterpreted?
      iv. Does the patient initiate activity?
      v. Is the patient responsive to direct comments by strangers? By well-known or familiar people? Only very trusted people?
      vi. Note physical and mental examination findings: tone, range of motion, reflexes, coordination, affect, mood, processing speed, awareness of conversation and room dynamics, mental functioning, etc.
   3. Physiologic
      i. Vital signs
      ii. Laboratory test results

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C. HISTORY
   1. Developmental milestones, treatment and surgeries, chronic conditions
   2. Breadth of experiences, social functioning, educational successes, aspirations for the future, relationship to family members
   3. Family history for medical conditions, psychiatric conditions, relationships, living relatives (and their locations)
   4. Active acute or chronic medical conditions that are a focus of treatment or are of concern (including ongoing health promotion and prevention efforts); allergies
   5. Reports and assessments from other sources

D. ASSESSMENT
   1. Prioritize acuity.
      i. Address urgent concerns first: pain, infection, emergent conditions.
      ii. Prevent longer-term complications.
      iii. Address chronic conditions at a more measured pace, so that improvements or change can be absorbed and become the new platform for future improvements.
   2. Group physiologic symptoms: vegetative symptoms, arousal symptoms, dysregulation/impulsivity, processing patterns, need for communication.
   3. Search for clues about triggering cues: changes in volume in the environment, attitude or speed of responses from others, distance between people, specific looks or situations.
   4. Review ALL medications for drug–drug interactions, duplicate efforts (pharmacologic actions) and side effects, excess sedation or arousal, gastrointestinal upset. Consider new allergies or unpleasant reactions to drug preparations, foods, etc.
   5. In the setting of previously calm behavior, assume changes are caused by underlying medical problems or new noxious stimuli rather than from new-onset psychiatric disorder.

E. HYPOTHESIS GENERATION; REPEATED FORMULATION
   1. Collate observations and assessment information into a reasonable hypothesis.
   2. Develop a strategy for addressing this problem: consider psychopharmacology and complementary therapies.

F. PLAN
   1. Outline a timeframe for beneficial response and what should be done in the event of a negative response.
   2. Involve patient, team members, family or guardian, and colleagues in moving the plan forward and in establishing appropriate expectations for responses.
   3. Articulate what documentation or feedback is needed to assess the efficacy of the articulated plan.

G. RECORD
   1. Keep the symptoms and signs that contribute to assessment and hypothesis in a manner that is accessible and comprehensible to yourself and reviewers. Add to this data as new information becomes available.

2. Send copies of current assessment and plan to colleagues and people who are providing support to the individual (the treatment team).
3. Record uncertainties, relevant differential diagnoses as clues to other ideas under consideration.
4. Make sure the date of recorded data is clear, so that subsequent decisions can build on history with accuracy and reliability.

H. FOLLOW-UP
1. Schedule follow-up at appropriate interval for the level of response expected, not based on convenience or habit.
   i. Do not evaluate sooner than a response can be noted. Do not postpone evaluation past initial response to the point of losing initial positive steps.
   ii. Follow-up may be effectively conducted by phone or other visual media, if HIPAA-compliant and secure.
2. Allow for urgent appointments should the situation change or a new problem emerge.
3. Use appropriate intervals to build relationship with the patient.
   i. This is a critical response for psychosomatic problems, or for people who have difficulty with novel situations—regular intervals allow them to become accustomed to visiting a place and making more effective use of clinical supports.

I. MODIFICATIONS
1. Special circumstances
2. Curbside consults

J. HAND-OFFS
1. Cross-coverage
   i. Notes must contain sufficient information for decisions to be made based on the history available.
   ii. Current medications, anticipated problems, or new information should be specifically listed or called to the covering provider.
2. Ongoing care (transfer of care)
   i. Summary of care and current working assessment should be provided in a note.
   ii. Document reason and circumstance for termination of care, without prejudice.

K. REVIEWS
1. Episodic: review history, sources of information, new information, and treatment course.
   i. Annual
      a. Often required by mandates and is good preventive care.
   ii. Major events
      a. Medical conditions, hospitalizations, accidents, etc.
      b. Unanticipated side effects or responses to the medications provided
   iii. Treatment plateau
      a. When apparent stall of expected treatment response occurs, it makes sense to "go back to the drawing board" and review all available material.

2. Terminal
    i. Morbidity and mortality review
        a. Relevant factors contributing to illness and death
        b. Identification of preventable contributing factors to illness or death; examination of treatment course for earlier clues to unwanted or unanticipated outcomes
    ii. Termination of care by the patient or team
        a. Review approaches and strategies for opportunities to change methodology, to identify contributing factors, and to accurately identify missed opportunities for improved communication.

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Pediatric Psychopharmacology in Primary Care: A Conceptual Framework

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INTRODUCTION

According to a 2004 survey conducted by the American Academy of Pediatrics (AAP), more than 80% of primary care pediatricians reported that it was their responsibility to *identify* children with attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and substance abuse. Most (70%) also believed it was their responsibility to *manage* ADHD; however, only about one-quarter thought it was their responsibility to manage anxiety (29%), depression (25%), or substance abuse (21%).[1] In a policy statement published in July 2009, the AAP recommended that pediatric primary care physicians (PCPs) achieve competence in initiating care not only for children with ADHD, but also for children with anxiety, depression, and substance use/abuse. Because treatment for 3 of these conditions—ADHD, anxiety, and depression—may, under certain conditions, include medication, the primary purpose of this article is to offer guidance to assist PCPs in decision-making about their use of psychotropic medications for these conditions. Secondarily, other medications that may be useful for other disorders will be noted.

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PREREQUISITES FOR PRESCRIBING PSYCHIATRIC MEDICATIONS IN PEDIATRIC PRIMARY CARE

The safe and effective use of psychiatric medications in the primary care setting requires several conditions, outlined in Table 1.

Determining Whether to Prescribe Medication

An accurate diagnosis of medication-responsive disorders (ie, disorders for which, at a minimum, there is sufficient evidence of a clinically meaningful reduction of symptom severity in response to medication) is important in pediatric psychopharmacology because it ensures that those children who may benefit from medication are offered a trial and it prevents needless use of medication in children who will not benefit from such treatment. Even with an accurate diagnosis and evidence-based treatments, there is no completely sensitive and specific way to determine which individual child will respond to medication or any other evidence-based therapy for psychiatric disorders, nor is there a way to predict who will experience treatment side effects or what type of side effect may emerge.

Table 1.
Conditions for safe and effective prescribing of psychiatric medications by primary care physicians

The *disorder* for which medication is prescribed needs to be:
• Sufficiently common to be seen regularly by a PCP
• Efficiently and accurately diagnosable by a PCP
The *medication* needs to:
• Have demonstrated efficacy
• Be relatively safe, as assessed by several parameters
• Have side effects that are reasonably predictable, readily detected, and readily managed
The *dosing and monitoring* of the medication need to:
• Follow guidelines that are reasonably established and easily followed
• Include somatic monitoring that is limited to vital signs and height/weight
The prescribing *physician* needs to have:
• Expertise in diagnosing the relevant disorders
• Knowledge of available psychosocial treatments (eg, PBMT, CBT)
• Knowledge of the medications prescribed
• Procedures for monitoring medication effects and adherence
The *system of care* needs to provide:
• Access to pediatric psychopharmacology expertise for consultation on issues beyond the expertise of the PCP
• Adequate payment for services rendered
• Minimal administrative and regulatory barriers

CBT, cognitive-behavioral therapy; PBMT, parent behavior management training; PCP, primary care physician.

The uncertainty underlying these issues presents considerable clinical challenges for the prescribing physician. A relatively simple approach to assessing whether or not to recommend medication is outlined in Table 2. This approach approximates the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[2] in terms of essential components or criteria and practice guidelines for therapies.

The term *sufficient* (or *sufficiently*) appears in each of the criteria or components in Table 2. Thus, the physician must judge whether symptoms cross a threshold of severity that warrants a recommendation for medication.

All physicians struggle with threshold when deciding on a diagnosis and determining whether to initiate a specific treatment. A familiar example in primary care pediatrics is ADHD; all 18 symptoms of ADHD in the DSM include the term *often,* but there is no specific definition of *often*. Other examples include diagnosis and treatment of pain or insomnia.

Parent reports and self-reports can provide useful information about a child's symptoms and their severity. Among the many available reporting tools, the following generally incorporate current DSM criteria and are not protected by copyright: Vanderbilt Attention-Deficit/Hyperactivity Disorder Rating Scale for parents and teachers[3] or DuPaul Rating Scale[4] for symptoms of ADHD; the Screen for Anxiety Related Disorders (SCARED), parent and child versions, for symptoms of anxiety[5]; and the Center for Epidemiological Studies Depression Scale for Children (CES-DC; available at http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf) for symptoms of depression.

Assessing Common Disorders

It is important to recognize that there is a hierarchy of difficulty in making accurate diagnoses of specific psychiatric disorders. Among the disorders addressed in this chapter, ADHD is generally the easiest and most straightfor-

Table 2.
Assessing whether to prescribe medication

1. Does the child have *sufficient* symptoms to support a syndrome or disorder?
2. Have the symptoms been present for a *sufficient* period?
3. Is the child experiencing *sufficient* impairment and/or distress from the symptoms in ways that negatively affect academic development, family life, interactions with peers, participation in activities, or emotional well-being?
4. Is this disorder *sufficiently* different from normal levels of activity and impulsivity (in contrast with ADHD), worry and concern (in contrast with an anxiety disorder), or demoralization or grief (in contrast with an episode of depression)?
5. Have evidence-based therapies (eg, PBMT for ADHD; CBT for anxiety or depression) been tried, if available?

CBT, cognitive-behavioral therapy; PBMT, parent behavior management training.

ward to diagnose because the symptoms of ADHD are observable by multiple informants (eg, parents, teachers) in multiple settings. Yet, even ADHD can often be confused with comorbid cognitive difficulties, anxiety, and/or the effects of trauma.

Anxiety disorders may be more difficult to diagnose than ADHD but are common among children and adolescents. Although anxiety and depression are both considered internalizing conditions, most symptoms of anxiety can be observed or easily elicited. Physical symptoms (eg, abdominal pain, muscle tension) are common in children with anxiety[6] and are familiar to PCPs. Other symptoms, such as avoiding social situations or phobic stimuli or entering the parents' bedroom or bed at night in response to separation concerns, are either reported by the children to their parents or are readily observed by parents.

Depression may be difficult to diagnose because demoralization and grief, which are not uncommon in children and adolescents, can mimic the symptoms of depression. Consultation with a child and adolescent psychiatrist may be needed to confirm the diagnosis of the child or adolescent who is suspected of being depressed.

Information about assessment (and treatment) of various psychiatric disorders can be found in other articles in this volume. See Article 3: Pharmacotherapy of Inattention and ADHD in Adolescents, and Article 4: Impulsivity, Irritability, Depression: Antidepressants.

Early Determinants of Need for Referral

Youth with attention, anxiety, or mood problems may be experiencing specific environmental stressors. Domestic violence, community violence exposure, bullying, parental mental illness, parental substance abuse, and child abuse are examples of situational factors that may cause significant problems or symptoms that require specific safety planning, psychosocial interventions, and sometimes involvement of specific community agencies (eg, Child Protective Services). It is important to inquire about or screen for these types of significant stressors in the evaluation. If a parent's mental illness is affecting the child's mental health, referral of the parent for his or her own care is indicated.

Youth with undiagnosed learning disabilities may also present with significant mood or behavior problems. These problems may be related to school maladjustment (eg, symptoms occur primarily in a school setting, not at home). Parents may benefit from referral to family advocacy programs or support programs available in the school system that can provide information on obtaining learning disabilities evaluations and advocating for disability services.

Finally, children living with complex psychosocial situations (eg, those whose parents have mental health or substance abuse issues, cognitive impairment, or significantly impaired parenting skills or those who have been maltreated or exposed to significant childhood adversities) may need a more thorough evaluation by a mental health professional because symptoms of ADHD, depression, and anxiety may mimic those of other psychiatric disorders.

Psychosocial Treatments

Effective, evidence-based psychosocial treatments, often described simply as therapy, are available for many pediatric psychiatric disorders. See a review by Ginsburg[7] for a summary of these therapies and the evidence supporting them. Psychosocial treatments are often tried before considering medication and are also used in combination with medication. For very young children, guidelines recommend at least 2 trials of psychosocial treatment before starting medication. Evidence from large studies sponsored by the National Institute for Mental Health (NIMH) demonstrates the advantage of combining psychosocial and medication treatment over medication or therapy alone for ADHD (ages 7–9),[8] common anxiety disorders (separation anxiety disorder, social phobia, generalized anxiety disorder; ages 7–17),[9] and depression (ages 12–17).[10]

It is important to consider when psychosocial interventions are preferred over medication. Many children and adolescents present to PCPs with mild depression or anxiety (ie, they meet diagnostic criteria but symptoms and impairment are minimal) or subthreshold depression or anxiety (ie, they do not meet the diagnostic criteria for the disorder). In general, such a child is likely to benefit from a psychosocial intervention and may not need medication.

Despite the clear effectiveness of psychosocial treatments and the pressing need for them, there are still far too few mental health physicians and therapists with the proper training and experience to provide high-quality evidence-based therapy, and families face many administrative and financial barriers to access. For many PCPs, these factors add pressure to prescribe psychopharmacologic therapy as a single first-line treatment. Pediatricians can join with families and mental health specialists in their community to advocate for evidence-based psychosocial services in both public and private systems of care. Ideally, psychosocial interventions always accompany pharmacologic interventions.

OFF-LABEL PRESCRIBING IN PEDIATRICS

Before the mid-1990s, there were very few psychiatric medications that had been approved by the Food and Drug Administration (FDA) for pediatric indications (ie, approved for use in children younger than 18 years). These included stimulants for ADHD, tricyclic antidepressants for enuresis, a few antipsychotics

for psychosis, and lithium for mania in children with bipolar disorder. Thus, to treat psychiatric disorder in children and adolescents, it was often necessary to prescribe off-label. The number of pediatric indications has increased markedly over the past 20 years. This has occurred in response to federal legislation, including the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Also, the NIMH began funding large, multisite treatment studies in the mid-1990s.

Currently, a number of medications are available with indications for psychiatric disorders in children, including ADHD, depression, obsessive-compulsive disorder (OCD), bipolar disorder, schizophrenia, and for irritability in children with autism. Thus, prescribing off-label, especially for a medication that has no indication for any psychiatric disorder in children and adolescents, should be carefully justified and documented in the medical record. Prescribing off-label is likely to become even more uncommon as more medications obtain FDA-approved pediatric indications.

CONCEPTUAL FRAMEWORK FOR PRESCRIBING PSYCHIATRIC MEDICATIONS

Definition of Level 1 and Level 2 Medications

The evidence base for the treatment of ADHD, common anxiety disorders (ie, generalized, social, and separation), and depression has been demonstrated in several multisite randomized clinical trials conducted since the mid-1990s (eg, The MTA Group,[8] March et al,[10] Walkup et al[9]). With expertise and skill, pediatricians can safely and effectively prescribe medications to treat children and adolescents with these disorders. The medications proposed as appropriate for use in the primary care setting are referred to as level 1 medications (see Table 3). Medications included on this list have a proven evidence of efficacy, a demonstrated record of safety, and a dosing and monitoring profile that is sufficiently simple and straightforward.

In addition to prescribing these level 1 medications, pediatricians may be called on to collaborate with psychiatrists and other mental health specialists in the care of children with more severe or uncommon disorders. They may be asked to take on partial responsibility for monitoring the therapeutic and side effects of a variety of other medications.

These level 2 medications can be monitored in primary care settings but generally are prescribed by child psychiatrists (or other specialists). Because level 2 medications generally have (1) limited efficacy data supporting their use, (2) a more serious safety profile, and/or (3) more complicated monitoring requirements, it is recommended that they be prescribed by specialists.

Table 3.
Pediatric psychopharmacology for primary care: level 1 medications for prescribing[a]

Drug (Mode of Action)	Indication(s)	FDA Approval/ Approved Age	Level of Evidence[b]	Generic
ADHD[c]				
Methylphenidate (stimulant)	ADHD	Yes; ≥6	A	Yes
Amphetamine (stimulant)	ADHD	Yes; ≥6	A	Yes
Guanfacine (α-adrenergic agonist)	ADHD	Yes; ≥6	A	Yes
Clonidine (α-adrenergic agonist)	ADHD	Yes; ≥6	A	Yes
Atomoxetine (NRI)	ADHD	Yes; ≥6	A	Yes
Certain anxiety disorders,[c] MDD[d], OCD[c]				
Fluoxetine (SSRI)	Anx	No	B	Yes
	OCD	Yes; ≥7	A	
	MDD	Yes; ≥8	A	
Sertraline (SSRI)	Anx	No	B	Yes
	OCD	Yes; ≥6	A	
	MDD	No	B	
Escitalopram (SSRI)	MDD	Yes; ≥12	A	Yes

ADHD, attention-deficit/hyperactivity disorder; Anx, anxiety disorders; FDA, Food and Drug Administration; MDD, major depressive disorder; NRI, norepinephrine reuptake inhibitor; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

[a]**Eight Medications for Prescribing:** Level A or B evidence,[b] favorable side effect profile, and management of disorder within primary care competencies; for a detailed discussion on pediatric mental health competencies for primary care, see Committee on Psychosocial Aspects of Child and Family Health and Task Force on Mental Health. The Future of Pediatrics: Mental Health Competencies for Pediatric Primary Care. *Pediatrics.* 2009;124(1):410–421

[b]**Level of evidence:** *A,* proven (2 or more well-designed, randomized clinical trials); *B,* supported (only 1 well-designed, randomized clinical trial); *C,* suggested (only by observational surveys, uncontrolled studies, or case reports).

[c]**Certain anxiety disorders (Anx):** Generalized anxiety disorder, social anxiety disorder, separation anxiety disorder.

[d]For each of these disorders there are also evidence-based psychosocial interventions. See **Evidence-Based Child and Adolescent Psychosocial Interventions** at http://www.aap.org/mentalhealth/docs/CR%20Psychosocial%20Interventions.F.0503.pdf.

Depending on an individual primary physician's skills and experience and (lack of) availability of specialists for referral, some primary care physicians may need to prescribe level 2 medications. Details regarding level 2 medications, which include antipsychotics, mood stabilizers, and other antidepressants and anxiolytics not in level 1, can be found in other articles in this volume. In addition, updated information regarding specific level 2 medications is available at the Johns Hopkins Bloomberg School of Public Health, Center for Mental Health Services in Pediatric Primary Care Web site (http://web.jhu.edu/pedmentalhealth/index.html).

General Rationale for Level 1 Medications

A number of factors led to the selection of medications that PCPs might consider basic to the management of ADHD, anxiety, and depression:

First, medications were selected that meet "A level" *criteria for efficacy*—that is, 2 or more double-blind, placebo-controlled clinical trials that used standard outcome measures to assess efficacy in the pediatric population.

Second, the following *dosing and monitoring criteria* were applied:

- Dosing guidelines can be reasonably established and followed without intensive therapeutic monitoring (ie, plasma drug levels).
- Somatic monitoring is limited to vital signs and height/weight (ie, laboratory tests are not needed beyond the baseline evaluation).
- Side effects are reasonably predictable, readily detected, and easily managed in primary care settings.

Third, 5 *criteria concerning safety* were applied:

1. An FDA-approved pediatric indication (a proxy for a minimal standard of research data supporting short-term safety and efficacy of a medication for a specified indication)
2. At least 10 years on the market (a proxy for sufficient time to discover rare adverse long-term consequences and rare complications with long-term exposure; ie, greater exposure over time increases the chance to detect rare and harmful events that would not otherwise be detected in brief clinical trials)
3. Minimal overdose harm, determined by a review of the available literature
4. Lack of clinically significant boxed warnings (a formal FDA proxy for rare, major adverse events)
5. Lack of known long-term potential harm, determined by a review of available literature

Table 4 applies these safety criteria to the 4 categories of medications that meet A-level efficacy criteria and have reasonable dosing and monitoring standards.

Seven of the 8 medications included in Table 3 have FDA-approved pediatric indications for use in children and adolescents for ADHD, anxiety, or depression. These include 5 medications for ADHD and 2 serotonin selective reuptake inhibitors (SSRIs) for depression. Thus, these medications can be prescribed on-label to treat either ADHD or depression in children and adolescents.

Unfortunately, there are no medications with FDA-approved pediatric indications for an anxiety disorder (except for OCD, an anxiety-related condition).

Table 4.
Safety profile of 4 medication classes in children and adolescents

Safety Criteria	Stimulants	α-Adrenergic Agents	NRIs	SSRIs
FDA Approval	≥6 years	≥6 years	≥6 years	≥8 years
Years on market[a]	>50 years	>20 years	>10 years	>20 years
Overdose harm	Low	Low	Very low	Very low
Boxed warning (Major AEs)[b]	Rare: drug abuse potential	None	Rare: suicidality	Rare: suicidality
Long-Term Risk to Health[c,d]	Rare: growth deceleration	None known	None known	None known

AEs, adverse events; FDA, Food and Drug Administration; NRIs, norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
[a]Years on the market: measure of exposure in large populations; time to observe potentially harmful events.
[b]SSRI and Suicidality: Original FDA meta-analysis: 2% for placebo and 4% active in forced dose titration studies. More recent review[11]: difference of 0.67%, down from 2% difference.
[c]Lack of studies to assess long-term risk to health, with the exception of stimulants.
[d]Stimulants and growth: data are not convincing.

This is, in large part, because of a discrepancy between FDA rules regarding anxiety disorder indications and the efficacy studies that have been conducted in children and adolescents with anxiety. The FDA requires that studies used to support an application for an indication focus on a single anxiety disorder, such as social anxiety disorder (SoAD), separation anxiety disorder (SAD), or generalized anxiety disorder (GAD). In children, symptoms of these anxiety disorders often co-occur and change over time. Thus, several well-designed studies sponsored by the National Institutes of Health (NIH) have examined use of an SSRI, such as fluoxetine,[12] fluvoxamine,[13] or sertraline,[9] to treat children with 1, 2, or 3 of these common childhood anxiety disorders (SoAD, SAD, or GAD). Most commonly, the participants in these studies met criteria for 2 or 3 disorders, not just 1. Therefore, the FDA did not use data from these studies to support an indication.

Thus, sertraline, an SSRI, is included in Table 3 as appropriate for use in the primary care setting because it has (1) adult indications for depression and several anxiety disorders, (2) a child/adolescent indication for OCD, and (3) the best available data for treatment of anxiety in children.[9]

As all physicians who prescribe to children and adolescents well know, many medications must be prescribed off-label. As long as there are good data to support the safety and efficacy of this off-label use, such prescribing is considered within the community standard. This is the case not only for sertraline but also for fluoxetine[12] when used to treat SoAD, SAD, or GAD.

Specific Rationale for Prescribing Level 1 Psychotropic Medications in Primary Care

The level 1 medications that are appropriate for use in the primary care setting belong to 4 different classes of medications. The rationale for using specific medications is presented here.

Stimulants. Despite the numerous products available on the market, there are just 2 distinct stimulant chemical entities: *methylphenidate* and *amphetamine*. The available literature has not shown advantages of different racemic mixtures (*d* vs. *l* vs. *d,l*). Thus, different racemic preparations are considered interchangeable, except for dose. Methylphenidate and amphetamine are available in numerous release preparations that provide a treatment effect ranging from 3 to 12 hours. Physicians should develop familiarity with at least 1 immediate-release and 1 sustained-release preparation for both stimulant entities. Those with longer time on the market and lower cost are preferred, but that is a general suggestion, not a preparation-specific recommendation.

α_2-Adrenergic Agonists. *Guanfacine* is FDA-approved for ADHD in children and adolescents. It is relatively specific to the α_{2A} receptor subtype, which mediates attention and other executive functions.

Clonidine is FDA-approved for ADHD in children and adolescents. It nonspecifically interacts with α_{2A}, α_{2B}, and α_{2C} receptors subtypes. The B and C receptors mediate the sedation and hypotension/bradycardia side effects. Thus, clonidine may have an unfavorable side effect profile compared with guanfacine. There are no direct comparative data regarding this issue.

Norepinephrine Reuptake Inhibitors. *Atomoxetine* is the only norepinephrine reuptake inhibitor (NRI) on the US market. It is FDA-approved for ADHD in children and adolescents.

Selective Serotonin Reuptake Inhibitors. There are 6 SSRIs marketed in the United States: fluoxetine, sertraline, escitalopram, paroxetine, citalopram, and fluvoxamine. Three SSRIs are level 1 medications for the following reasons:

- *Fluoxetine*: FDA indications in children and adolescents for depression and OCD; the first SSRI marketed in the United States; longest half-life, so abrupt discontinuation results in slow, safe fall in plasma and brain levels.
- *Sertraline*: FDA indication in children and adolescents for OCD; second longest SSRI on the market; shorter half-life; best data for anxiety in youth[9]; thus, offers alternative to fluoxetine when shorter half-life may be indicated (eg, for a child taking multiple medications with further changes likely) or when fluoxetine cannot be used because of interactions with metabolic enzymes (eg, inhibition of CYP2D6).

- *Escitalopram*: FDA indication in children and adolescents for depression; "cleanest" of SSRIs because it does not interact with hepatic CYP450 enzymes.

The following 3 SSRIs were *not* included in level 1 for the following reasons:

- *Paroxetine* has nonlinear kinetics in the therapeutic dose range; that is, hepatic enzymes can saturate at therapeutic levels, resulting in steep increases in plasma levels with modest dose increases. Likewise, this can result in rapid and large decreases in plasma levels with dosage decreases. Thus, paroxetine is associated with withdrawal side effects.
- *Citalopram* offers no benefit over escitalopram, which is the therapeutically effective s-enantiomer of the racemic mixture citalopram. Also, citalopram has an FDA warning regarding maximum dose in adults because of the risk of QTc prolongation; relevant dosage maximum is not known in children and adolescents. Thus, the potential need to monitor with electrocardiograms complicates treatment.
- *Fluvoxamine* has no FDA approval for depression or anxiety disorders (except OCD) in adults (in contrast with the other SSRIs) and, because it is infrequently prescribed, is generally unfamiliar to PCPs.

Efficacy. Table 5 summarizes the efficacy data supporting the use of the level 1 medications. As a proxy for the magnitude of effect, the rate of responders on active drug and placebo are listed. It is important to note that a responder is not the same as a remitter. A patient who remits no longer meets diagnostic criteria and has no or very mild residual symptoms, whereas a responder generally meets a severity criterion of "much better" or "very much better" but may still have mild to moderate symptoms. Thus, a remitter is generally more improved than a responder. The last column notes whether or not ratings were done by "independent evaluators" (IEs). An IE is a rater who is not involved in data collection other than to conduct blinded symptom severity ratings at specified times during a study. The use of IEs is thought to reduce bias because the presence or absence of medication side effects (which are not known to the IEs) can help investigators to guess the participant's medication status: active or placebo. Finally, all completed NIH-sponsored studies are included in the tables. However, there may be unpublished industry-sponsored studies that are not listed.

PRESCRIBING LEVEL 1 PSYCHOTROPIC MEDICATIONS IN PEDIATRIC PRIMARY CARE

The rationale for prescribing and monitoring psychiatric medications in primary care pediatrics is described in previous sections. Provided here is a brief introduction to clinical issues associated with prescribing and monitoring psychiatric medications in primary care pediatrics. Details about prescribing and monitoring of level 1 medications are presented in Articles 3 and 4.

Table 5.
Pediatric psychopharmacology for primary care: evidence supporting short-term safety and efficacy of level 1 medications

Drug	Indication	Support	Age	Rate of Responders	IE[a]
Methylphenidate: short acting	ADHD	Spencer et al (1996)[14]: Review	N/A	N/A	N/A
		The MTA Cooperative Group (1999)[8]	7–9.9 yr	Not specified	No
		The PATS Team (2006)[15]	3–5.5 yr	A: 21%, P: 13%	No
Methylphenidate: long acting	ADHD	Greenhill et al (2002)[16]	6–16 yr	A: 64%, P: 27%	No
		McGough et al (2006): *Daytrana Patch*[17]	6–12 yr	A: 71%, P: 16%	No
		Findling et al (2010): *Patch*[18]	13–17 yr	A: 66%, P: 21%	No
Amphetamine: short acting	ADHD	Spencer et al (1996): Review[14]	N/A	N/A	N/A
Amphetamine: long acting	ADHD	McGough et al (2005)[19]: *Adderall XR*	6–12 yr	Not specified	No
		Domnitei, Madaan (2010)[20]: *LDX*	6–12 yr	A: 70%, P: 18%	No
Guanfacine: short acting	ADHD	Scahill et al (2001)[21]	7–15 yr	A: 53%, P: 0%	No
		Arnsten et al (2007)[22]: Review	N/A	N/A	N/A
Guanfacine: long acting	ADHD	Biederman et al (2008)[23]	6–17 yr	A: 50%, P: 26%	No
		Sallee et al (2009)[24]	6–17 yr	A: 56%, P: 30%	No
Atomoxetine	ADHD	Michelson et al (2001)[25]	8–18 yr	Not specified	No
Fluoxetine	ANX	Birmaher et al (2003)[12]	7–17 yr	A: 61%, P: 35%	No
	MDD	Emslie et al (1997)[26]	7–17 yr	A: 56%, P: 33%	No
		Emslie et al (2002)[27]	8–18 yr	A: 65%, P: 53%	No
		TADS Team (2004)[10]	12–17 yr	A: 61%, P: 35%	Yes
	OCD	Riddle et al (1992)[28]	8–15 yr	A: 33%, P: 12%	No
		Geller et al (2001)[29]	7–17 yr	A: 49%, P: 25%	No
		Liebowitz et al (2002)[30]	6–18 yr	A: 57%, P: 27%	Yes
Sertraline	ANX	Walkup et al (2008)[9]	7–17 yr	A: 55%, P: 24%	Yes
	MDD	Wagner et al (2003)[31]	6–17 yr	A: 36%, P: 24%	No
	OCD	March et al (1998)[32]	13–17 yr	A: 42%, P: 26%	No
		POTS Team (2004)[33]	7–17 yr	A: 21%, P: 4%	Yes
Escitalopram	MDD	Wagner et al (2006)[34]	6–17 yr	A: 63%, P: 52%	No
		Emslie et al (2009)[35]	12–17 yr	A: 62%, P: 52%	No

A, active drug recipients; ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety; IE, independent evaluator; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; P, placebo recipients.

[a]Use of independent evaluators to rate symptom severity may help reduce bias because these individuals are blinded to patient side effects that could reveal their treatment assignment.

Adverse Events

Adverse events are usually evaluated based on either severity or frequency. In package inserts required by the FDA, severity is emphasized; that is, "boxed warnings" are more severe than "warnings and precautions," which are more severe than "adverse events." In Table 6, adverse events from level 1 medications are presented based on frequency—common, less common, and rare. In addition, withdrawal symptoms are noted. Except for fluoxetine and atomoxetine, tapering of medication is recommended to minimize withdrawal symptoms. The most severe adverse events are given boxed warnings by the FDA; they are presented in the next section.

FDA Boxed Warnings

It is important to keep in mind that all the adverse events described in the boxed warnings listed here occur infrequently and may never be seen by an individual physician.

SSRIs and Suicidality. The FDA's boxed warning for suicidality for all antidepressants is an obstacle for many primary care pediatricians considering prescribing SSRIs for anxiety and depression. The boxed warning stating that all antidepressants pose significant risk of suicidality (suicidal ideation or suicide attempts; not completed suicides) in children and adolescents was issued in October 2004. The warning recommended close monitoring for increased suicidality. Specific recommendations for monitoring were described in a medication guide provided by the FDA (http://www.fda.gov/drug/antidepressants_MG.pdf). A medication guide is a descriptive handout provided by pharmacists to inform parents or patients of the indications, proper administration, and potential side effects or concerns about a prescribed medication.

The medication guide included specific guidelines for monitoring, as follows: "your child should generally see his or her healthcare provider": weekly for the first 4 weeks; every 2 weeks for the next 4 weeks; at 12 weeks; and at the "healthcare provider's advice" after 12 weeks. This prescriptive monitoring mandate presented a major barrier to the use of SSRIs in the primary care setting because this level of intensive monitoring is not compatible with most primary care practices.

In May 2007, the FDA issued a revised medication guide that no longer included specific mandates for monitoring (http://www.fda.gov/drug/antidepressants/MG_2007[1].pdf). Instead, it focuses on information parents need to know regarding suicidality and antidepressants.

Antidepressant-induced suicidality is rare. The original FDA estimate, based solely on data from more than 4300 research participants in 23 studies, was that

Table 6.
Adverse effects associated with level 1 psychiatric medications

Medication Class	Adverse Effects *Common adverse effects in italics*	Withdrawal Symptoms
Stimulants	*Common: Insomnia, appetite suppression, headache, stomachache*	ADHD symptoms "worsen" at end of day when medication wears off [b]
methylphenidate[a] (Ritalin and others)	Less common: Cognitive dulling, irritability, exacerbation of tics (controversial)	
dextroamphetamine[a] (Dexedrine and others)		
amphetamine salts[a] (Adderall and others)	Rare: Growth retardation, hallucinations (usually visual or tactile, not auditory), cardiac arrhythmia in children with preexisting cardiac disease	
	MONITOR: BP, pulse, BMI	
Norepinephrine reuptake inhibitors	*Common: Dry mouth, insomnia, nausea, decreased appetite*	None
atomoxetine[a] (Strattera)	Less common: Increased heart rate, BP, palpitations, dizziness, sweating, dysuria, weight change	Tapering not necessary
	MONITOR: BMI, BP, HR	
α-Adrenergic agonists	*Common: Somnolence*	Elevated BP, nervousness, headache, confusion[b]
guanfacine[a] (Tenex, Intuniv)	Less common: Dry mouth, headache, nausea, decreased BP	
clonidine[a] (Catapres, Kapvay)	**MONITOR:** BP, pulse	
SSRIs	*Common: "Activation" (restlessness, insomnia, impulsiveness, talkativeness—usually occurs early in treatment) without mood elevation, GI upset, nausea, diarrhea*	Especially for shorter half-life SSRIs, such as sertraline: flulike syndrome; dizziness (most common), nausea or emesis, fatigue, headache, gait instability, insomnia, mood changes, myalgia[b]
fluoxetine[a] (Prozac)		
sertraline[a] (Zoloft)		
escitalopram[a] (Lexapro)	Less common:	
	Autonomic (eg, diaphoresis, mydriasis)	
	Cardiovascular (eg, flushing, sinus tachycardia, hypertension)	
	Sexual (decreased libido, delayed ejaculation)	Tapering not needed for fluoxetine

	Akathisia Rare: Serotonergic syndrome—potentiated by drug interaction with other pro-serotoninergic agents (eg, MAOIs, trazodone, lithium, opioids, amphetamine/stimulants, cocaine, St John's Wort, ginseng): agitation, ataxia, diaphoresis, diarrhea, hyperreflexia, mental status changes, myoclonus, shivering, tremor, hyperthermia NMS (associated with dopamine antagonists) Suicidal thinking or behavior "Switching" (emergence of true mania—usually occurs within 4 weeks of treatment) **MONITOR:** BMI, worsening of depression, emergence of suicidal thinking or behavior (especially with initiation or dose escalation), or unusual changes in behavior, such as sleeplessness, agitation, or withdrawal from normal social situations

ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; BMI, body mass index; FDA, Food and Drug Administration; HR, heart rate; MAOI, monoamine oxidase inhibitor; NMS, neuroleptic malignant syndrome; SSRI, selective serotonin reuptake inhibitor.

[a]FDA-approved for children.

[b]Tapering suggested.

Information is current as of April 1, 2010; check for psychopharmacologic medication updates from a reliable source such as the following: National Library of Medicine or National Institutes of Health, MedlinePlus Drugs, Supplements, and Herbal Information. Patient- and family-friendly language. Available at: http://www.nlm.nih.gov/medlineplus/druginformation.html. Accessed July 16, 2013. US Food and Drug Administration. Available at: http://www.fda.gov. Accessed July 16, 2013. American Academy of Child & Adolescent Psychiatry. Available at: http://www.aacap.org. Accessed July 16, 2013. Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents: The AACAP Practice Parameters describe generally accepted practices. They are designed to assist physicians in providing high-quality assessment and treatment for children and adolescents consistent with best available scientific evidence and clinical consensus. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0890-8567/PIIS0890856709601568.pdf. Accessed July 16, 2013. Medication guides. The physician can download medication guides for many drugs from the US Department of Health and Human Services Food and Drug Administration Web site. These guides, in lay language, provide families with information about the drug's risks and benefits. Physicians can review the guide with the family and document the discussion by obtaining a signature on the guide and retaining a copy. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm. Accessed July 16, 2013.

2% of children and adolescents receiving placebo and 4% receiving an antidepressant developed suicidal thoughts or attempted suicide.[36] Thus, the risk difference was 2%. A subsequent analysis, based on data from 27 randomized controlled trials involving more than 5300 participants, found a risk difference of just 0.7% (95% CI: 0.1%–1.3%).[11] Of note, the most recent estimate, which was based on data from 35 randomized controlled trials involving more than 6000 participants, found a risk difference of 0.9% (95% CI: −0.0005–0.0182), just missing statistical significance.[37]

The most recent, and presumably best, analyses suggest that there may be a very slight increased risk of suicidality with antidepressants in children and adolescents. Clinical prudence indicates the need to educate patients and parents about suicidality and to provide careful monitoring for suicidality and other adverse effects during the initial phase of treatment (when the risk of suicidality is generally greatest from both the depression and the medication) and throughout treatment.

Amphetamines and Cardiac Concerns. The boxed warning for amphetamines states, "Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions."[38] This warning does not say that clinical use is a problem; only "misuse." However, it is important to take a personal and family cardiac history, with emphasis on structural heart defects, syncope, sudden unexplained death, and arrhythmias before prescribing a stimulant for the first time. This screening is similar to that for sports physicals.

Stimulants and Concerns About Abuse and Dependence. The boxed warnings for both amphetamines and methylphenidate state that they have a high potential for abuse and that prolonged administration may lead to dependence. Fortunately, there are no reports of children who were treated with therapeutic doses of stimulants developing dependence. Available data suggest that children with ADHD who are treated with stimulants are not more likely than those who did not receive stimulant treatment to develop substance abuse later in life.[39–43] A related problem is diversion—that is, patients selling their prescription stimulants to be used as drugs of abuse.[44]

Monitoring Level 1 Medications

Table 6 presents guidance for monitoring adverse events when prescribing level 1 medications. Frequency of monitoring may vary depending on a particular patient's health status, but in general it is more frequent during the initial phase of treatment with all level 1 medications. During this time, dosage is changing frequently as it is being titrated up to an effective and safe dose, and side effects often occur before benefit. Poor adherence is common, so monitoring for adherence is important to prevent unwarranted and potentially unsafe dose escalations in the child who is not adherent. Finally, more frequent monitoring may be indicated for patients with certain medical conditions.

For stimulants and atomoxetine, monitoring blood pressure, heart rate, height, and weight are recommended. In addition, patients taking stimulants should be observed for, and parents questioned about, tics. No specific laboratory studies are recommended. The recommendations for guanfacine and clonidine are similar, except that height and weight can be omitted.

Patients taking SSRIs should be monitored for several parameters during the first several weeks of treatment: emergence of suicidal thinking or behavior, worsening of depression, or the activation phenomenon (eg, agitation, insomnia, or increased energy/activity). Over the longer term, height and weight, as well as signs of social or emotional withdrawal or decreased motivation, should be monitored. No specific laboratory tests are recommended.

OTHER ISSUES

Informed Consent

Obtaining informed consent from the parent or guardian and assent from the patient can be more complicated and difficult for psychiatric medications than for other medications. This is because of parental concerns about the potential effect of medications that affect the child's developing brain and the controversy in the media regarding psychiatric medications. The basic steps involved in obtaining informed consent and assent are the same, no matter what psychiatric medication is recommended. A description of areas to cover in the consent process, as well as a simple form to complete for the chart, is available on the Johns Hopkins Bloomberg School of Public Health, Center for Mental Health Services in Pediatric Primary Care Web site (http://web.jhu.edu/pedmentalhealth/index.html). Of note, in addition to the initial consent process, informed consent is usually an ongoing process that unfolds as the patient and parent develop new questions and concerns about the medication over time.

Multiple Medications

Many children treated in the primary care pediatric setting for ADHD, anxiety, or depression will need only 1 psychiatric medication. Some will need 2—for example, the youth with ADHD, anxiety, and depression who requires medication as part of the treatment plan. Fortunately, the medications for ADHD (methylphenidate, amphetamine, guanfacine, clonidine, and atomoxetine) can be used safely in combination with the medications for anxiety or depression (the SSRIs fluoxetine, sertraline, and escitalopram).[45]

If a child requires 3 or more psychiatric medications to effectively manage symptoms, advanced expertise in pediatric psychopharmacology or consultation with a child and adolescent psychiatrist consultation is strongly advised. The primary

care pediatrician can, in either case, play an important role in monitoring the medications and in promoting a healthy lifestyle.

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Pharmacotherapy of Inattention and ADHD in Adolescents

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INTRODUCTION

This article reviews the current use of stimulants in adolescents. The evidence base for treatment of attention-deficit/hyperactivity disorder (ADHD) in adolescents is meager compared with that of ADHD in children, and much recent research of older populations with ADHD has been directed toward adults rather than adolescents. The structure of psychosocial treatment of ADHD differs across developmental ranges. For example, in children, treatment of ADHD uses direct behavior modification via parents and teachers. Treatment approaches then change toward contracting in adolescents (acknowledging the emerging independence common at this age) and toward self-management and coaching in adults. Medication for ADHD, however, does not substantially differ across developmental epochs. In supplementation of data, specifically on adolescence, much of our understanding of treating adolescents comes from upward or downward extension of the child and adult data. Symptomatic treatment (treatment for inattention, hyperactivity, or impulsive behavior) has always been a parallel approach to diagnostic and developmentally specific selection of treatment based on an incomplete literature. In recognition, this article assumes that inference from children or adults to adolescents, in the absence of adolescent-specific data, is commonplace and often confirmed with clinical experience. Such inferences, in the face of literature gaps, in no way obviate the need for continued research focused on adolescence.

PREVALENCE OF DIAGNOSIS AND SYMPTOMS

ADHD has long been considered a chronic developmental disorder, arising in childhood and often persisting into adulthood. Cases are usually referred for

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diagnosis based on associated functional impairment. There is no diagnostic test for ADHD, and response to stimulant medication is no indication of the presence or absence of the disorder. Diagnosis is typically made based on history and clinical interviews (usually with the custodial parent), supplemented with instruments such as behavior rating scales and structured or semistructured diagnostic interviews. Psychological testing is not required, but it is recommended to screen for learning disorders and for low intellectual functioning and to gain understanding into what might be expected of a child in terms of academic performance were ADHD not present. A key focus of the diagnostic process is to determine the presence or absence of 18 symptoms of ADHD. If 6 or more symptoms from among the 9 inattention symptoms are judged by the physician or nonphysician clinician to have been present for at least the past 6 months, the symptom count criterion for inattention is met. Similarly, if 6 or more from among the 9 hyperactivity-impulsivity symptoms are judged to be present, the symptom count criterion is met for hyperactivity-impulsivity. Symptom-count criteria determine which of 3 presentations are assigned (combined presentation if both criteria are satisfied; predominantly inattentive or predominantly hyperactive—impulsive presentation if 1 criterion is met). These presentations of ADHD are new nomenclature in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5).[1] They correspond to the ADHD types in the prior edition of the DSM (DSM-IV), but the term *presentation* was preferred over *type* to avoid implying that the subcategories were temporally stable.[2,3] The characteristics of DSM-5 presentations are not expected to differ from those of DSM-IV types, because the methods used to identify subtypes are similar.

By far, the most common presentations are the combined and predominantly inattentive. Much of the adaptive impairment associated with ADHD is a function of inattention, and because the 2 prevalent types both meet the symptom count criterion for inattention, there are relatively few distinctions between the presentations. Among the differences that have been reported are a stronger association with external comorbidity, higher male-to-female ratio, earlier onset, and greater difficulty with inhibiting behavioral impulses in the combined presentation, and sometimes higher internalizing comorbidity in the predominantly inattentive presentation.[4] On occasion, predominantly inattentive ADHD has been reported to respond optimally to lower doses of stimulants compared with combined ADHD.[5–7] With psychosocial treatment, a similar situation has been reported: The predominantly inattentive type responds well to specialized behavioral treatment that has been modified, in part by reducing components targeting oppositional and conduct problems.[8]

Other criteria must be met in order to justify a diagnosis of ADHD. The age of onset was relaxed from 7 in DSM-IV to 12 in DSM-5. Concerns have been raised that this will increase the prevalence of ADHD, but there is strong evidence that later onset does not identify meaningful differences,[9,10] and thus the change in

this criterion should improve the validity of the diagnosis. Symptoms must be present in at least 2 life settings, and symptoms must be associated with functional impairment. Symptoms must be primary and not better explained by other comorbidities.

Notably, the hyperactive-impulsive symptoms tend to improve across childhood and early adolescence, compared with inattention. In another change from DSM-IV, DSM-5 allows the diagnosis to be made even if a case does not meet full criteria at the present time, if full criteria are believed to have been satisfied at an earlier time (specified as "in partial remission"). This allows for developmental differences in symptom presentation and establishes a basis for current treatment, as long as ADHD-related impairment continues to present difficulty.

DSM-5 lists the prevalence of ADHD simply as 5% in children and 2.5% in adults. These estimates may be conservative. A recent meta-analysis of population prevalence for children yielded estimates of 6.1% using parent report and full diagnostic criteria, 7.1% using teacher report and full criteria, and 5.9% using best-estimate criteria.[11] Prevalence in adults was estimated to be 5%.

STIMULANTS

Evidence

Evidence of stimulant efficacy for child behavior disorders goes back to 1937, when D/L-amphetamine was reported to have positive effects on both behavior and interest in schoolwork.[12] Since that time, hundreds of within-subject, between-groups, and research reviews have attested to the short-term efficacy of the stimulants. Initial evidence for stimulants that are still in use today—for example, D-amphetamine[13,14] and methylphenidate—[13] is more than 50 years old. Numerous reviews have accumulated, with the general conclusion that the stimulants are effective in treating ADHD, although many individual cases respond adversely or incompletely. The general trend in research reviews is toward meta-analyses or toward a narrow focus on a subtopic.[15–17] Some of the best single-study evidence, in terms of sample size, treatment specification and fidelity, and length of outcome, comes from the Multi-modality Treatment of ADHD study (MTA) funded by the National Institute of Mental Health (NIMH).[18,19] The study provided evidence of robust response to medication using a treatment algorithm that employed adequate trials of stimulant medication. The participants, all of whom met DSM-IV criteria for ADHD, combined type, were given a double-blind trial of a low, medium, and high dosage of immediate-release methylphenidate. For 68.5% of participants who completed the trial, 1 of the dosages of methylphenidate was selected as being beneficial for maintenance treatment. Another segment of the sample (slightly >20%) was assigned either to placebo or to an openly tried dose of amphetamine. A key finding of the MTA was that medication treatment that focused on stimulants

and followed a structured titration led to higher dosing and significantly better clinical response, compared with referral to community treatment. Notably, comparative efficacy among MTA treatments was not maintained after experimental treatments were discontinued, which is consistent with the view that time-limited, acute treatment of a chronic disorder is not likely to provide durable improvement.[20]

Despite the effectiveness of the stimulants, nonstimulants play an important role, either as alternative treatments (eg, for adverse responders or nonresponders, when families prefer nonstimulants) or adjunctive treatments (because of residual ADHD symptoms or symptoms of oppositional behavior and explosive mood). Clinical data on the efficacy of atomoxetine date at least to 1998, with voluminous evidence of efficacy for ADHD symptoms appearing more recently.[21] Atomoxetine, a selective norepinephrine reuptake inhibitor, is considered to be a frontline treatment for ADHD.[22] Its comparative effectiveness with stimulants is complicated by differences in response onset and optimization of treatment. The other 2 nonstimulant treatments for ADHD approved by the US Food and Drug Administration (FDA) are alpha-2 noradrenergic agonists, and both were initially developed for treating other medical conditions, including hypertension. Efficacy of clonidine for ADHD was reported in 1985.[23] Efficacy for guanfacine for ADHD was reported in 1995.[24] Later, development of orally administered extended release formulations led to evidence of efficacy as monotherapy and as adjunctive treatment (added to stimulant treatment) for ADHD.[25–28]

Dosing

Dosing of stimulants has often been reported using weight-based ratios (ie, milligrams per kilogram). Milligram-per-kilogram dosing has largely been replaced by absolute, or "fixed," dosing (in milligram increments) for 3 reasons:

1. The differences in optimal response among individuals in the same weight category can often be larger than the differences between categories.
2. Clinical selection of dosing is simpler and less error-prone using absolute dosing.
3. The development of extended-release and multiple-ingredient products has introduced duration- and potency-based complexities into the process of weight-based calculations.[29]

Even so, it is helpful to be acquainted with some of the clinical experience of weight-based dosing. A scientific discussion of dextro- and levo-enantiometers of stimulants is beyond the scope of this article, but it is generally accepted that (a) the levo-enantiometers have fewer central nervous system (CNS) effects than dextro-enantiometers; (b) racemic mixtures of D- and L-enantiometers have roughly half the clinical potency of pure D-enantiometers[14]; and (c) amphetamine and methylphenidate are similar in potency if delivered in the same D-to-L ratio. A 2.5-mg dose

of Dexadrine (immediate-release D-amphetamine) is often reported to be a low-dose equivalent to 5 mg of Ritalin, because the former is a pure D-enantiometer and the latter is a racemic mixture. This comparison becomes less elegant when mechanisms alter the time course or bioavailability of delivery.

Stimulant dosing was influenced by the MTA, particularly regarding the importance of considering higher doses in titration. Also influential was the empanelment of experts to determine clinical algorithms for titrating medication.[30] Both approaches included pemoline, which has since been avoided because of safety concerns. A contemporary approach is to select either amphetamine or methylphenidate, and then to titrate (raise the dose in steps) to optimal or satisfactory response (in which case this becomes the initial maintenance dose). If intolerable side effects occur before satisfactory response is achieved, the alternative stimulant is selected for a similar individual dosage-range and response trial, because many individuals respond better to 1 of the stimulant classes than to the other.[31] Physicians often opt to titrate using immediate-release (IR) stimulants because of the lower cost and greater flexibility of IR dosing, and then to use IR response as a guideline to selecting an extended-release (ER) product; however, ER products are not overly difficult to titrate. Children often function better with an ER product, because of fewer practical difficulties and fewer missed doses compared with IR. This is often the case with adults as well; however, some adults prefer to dose with IR according to their perceived need for medication in the context of their specific schedules and performance demands. Dosing for adolescents is individualized. Generally, relying on repeated dosing of IR product is unreliable in clinical practice, and sustained-release medication is often helpful in both school and extra-curricular settings. Some adolescents prefer to have a say as to what times of the day or week would be suitable for medication.

Dosing is affected by the availability of evidence-based psychosocial treatments. In the MTA, concurrent protocol-driven treatments resulted in lower doses of medication when psychosocial treatment was also provided. Given concerns about short-term and long-term adverse effects of stimulants, the opportunity to reduce the dose or to avoid medication altogether is not an insignificant consideration. Physicians who choose to specialize in treating ADHD should investigate the intricacies of drug treatment, psychosocial treatment, and combined approaches and should be well aware of treatment algorithms that are not focused solely on medication.[32,33] There is ample justification for trying psychosocial treatment before medication and for including it as co-therapy.[34] Medication-only decisions are often influenced by cost, expectation of parent adherence, or misinformation about relative efficacy of medication and psychosocial treatment. Expert opinion is divided, but general consensus is that the optimal treatment for adolescent ADHD is a combined provision of medication and psychosocial treatment.

The dosage ranges in package inserts are based on dosages that were selected at the outset of clinical trials. Physicians are often unconcerned with exceeding

recommended dosages when warranted by individual response, given the relative safety of stimulants and the predetermined limitations on approved dosage ranges. Dosing of nonstimulants is more likely to follow approved ranges, but some physicians exceed those ranges also.

Side Effects

Side effect comparisons across products can be misleading. This is because side effects are captured differently across different clinical trials. It is well known that a vague, open question regarding side effects ("How have you been feeling this week? Any problems?") will elicit fewer complaints than detailed and structured ratings of specific side effects. Package inserts reflect side effects that were reported in product development, and these can be updated if new concerns arise in the postmarketing phase. However, because of methodologic differences, comparisons between individual products are something akin to comparing apples and oranges.

As a class, stimulants share common side effects. These are typically dose related, and they remit when stimulants are withdrawn. In contrast to the main therapeutic effects, which tend to be consistent across time, side effects often decrease in severity (at least partially) with continued dosing. Common side effects include insomnia/delayed sleep onset, anorexia/decreased appetite/weight loss, headache, motor tics, and irritability. Less commonly, nausea, abdominal pain, palpitations, dizziness, drowsiness, and changes in heart rate and increased blood pressure occur. Atomoxetine use is associated with similar side effects. In contrast, the alpha-adrenergic agonists tend to lower blood pressure, sometimes to the point of causing orthostatic hypotension and fainting. Somnolence and fatigue are also common side effects of these agents. Because of its greater selectivity for the alpha-2 receptor, guanfacine seems to have less severe side effects than clonidine.

Evidence of suppression or retardation of growth is mixed[35,36]; however, there is sufficient evidence that long-term treatment with stimulants retards growth that physicians should take this risk into account when weighing individual risks and benefits with families. A recent study reported dose-related slowing of growth and pubertal development in adolescent boys after 3 years of treatment with stimulants.[37] Recognition of possible effects on height is changing expert opinion on dosing toward a more conservative approach that includes drug holidays and opting for lower dosages when suitable.[38]

Toxicity

Toxicity is not a concern for current products at approved doses or for off-label doses slightly above the approved ranges. Acute stimulant toxicity because of intentional overdose is generally successfully managed with supportive treat-

ment. However, some patient characteristics increase the risk of ADHD treatments. Cases of sudden death have been reported with methylphenidate and amphetamine. Currently, the risk of stimulant-associated sudden death is believed to be limited to individuals with congenital heart abnormalities. Patients with histories of serious drug abuse, especially stimulant abuse, may be at heightened risk of abusing prescription stimulants. Special supervision or selection of nonstimulant treatments is recommended in such instances. Some stimulant medications use delivery systems (eg, oral osmotic system with Concerta, transdermal delivery with Daytrana, prodrug cleavage with Vyvanse) that make them less prone to abuse. Potential for abuse or dependency and for cardiovascular adverse events are among the risks described in black box warnings on stimulant products.

Laboratory Tests

Laboratory tests are not required before initiating approved treatments in otherwise healthy patients. Height, weight, blood pressure, and pulse should be obtained at baseline and at periodic intervals (after dose adjustments and at minimum every 6 months of maintenance). If stimulants are to be used, a cardiovascular history of the patient and the genetically related family should be obtained. Preexisting heart disease, symptoms, or positive family history (particularly for sudden death) should be followed by a referral for possible electrocardiography or echocardiography.

FDA Indications

All the drugs in Table 1 have been approved by the FDA and are indicated for treating ADHD in children and adolescents.

OTHER TREATMENTS

Several nonstimulant medications have been reported to be effective in treating ADHD, including bupropion, imipramine, and nortriptyline.[39] These have not made their way into widespread clinical use. Neurofeedback of various types has been reported as effective.[40] Confirmation of the effects of neurofeedback awaits funding of a well-designed large-scale trial.[41]

Behavioral treatments have an extensive evidence base and are often reported to yield effects in the same range as medication.[42] Behavioral parent training is directed toward changing dysfunctional parent-child interactions. In either a group or individual setting, parents are taught to give effective commands, rewards, and punishments (usually timeout or, with adolescents, withdrawal of privileges). Classroom behavior management involves educating teachers about the special needs of students with ADHD and providing behavior management skills using rewards and disincentives that are available to teachers. School-to-

Table 1
Currently approved medications for treatment of pediatric ADHD

		Maximum Daily Dosage			
Generic Name	Brand Name	Adult	Adolescents & Children	Preparations Available	Generic Available?
Amphetamine Preparations					
Short Acting					
Mixed amphetamine salts	Adderall	60 mg	40 mg (6–11 y/o) 60 mg (≥12 y/o)	Tablet: 5 mg, 7.5 mg, 10 mg, 12.5 mg 15 mg, 20 mg, 30 mg	Yes
Dextroamphetamine	Dexedrine, Dextrostat	60 mg	40 mg (6–11 y/o) 60 mg (≥12 y/o)	Tablet: 5 mg, 10 mg	Yes
Dextroamphetamine liquid	Procentra			5 mg/5 mL	No
Methamphetamine	Desoxyn	25 mg	25 mg (≥6 y/o)	5 mg	Yes
Long Acting					
Mixed amphetamine salts, extended-release	Adderall XR	60 mg	30 mg (6–12 y/o); 40 mg (13–17 y/o)		Yes
Dextroamphetamine	Dexedrine spansule	60 mg	40 mg (≥6–11 y/o); 60 mg (≥12 y/o)	Sustained-release capsule: 5 mg, 10 mg, 15 mg	Yes
Lisdexamfetamine	Vyvanse	70 mg	70 mg (≥6 y/o)	Capsule: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	No
Methylphenidate Preparations					
Short Acting					
Dexmethylphenidate	Focalin	20 mg	20 mg (≥6 y/o)	Tablet: 2.5 mg, 5 mg, 10 mg	Yes
Methylphenidate	Methylin	60 mg	60 mg (>6 y/o)	Chewable tablet: 2.5 mg, 5 mg, 10 mg	
Methylphenidate	Ritalin	60 mg	60 mg (>6 y/o)	Tablet: 5 mg, 10 mg, 20 mg	Yes

Intermediate Acting					
Methylphenidate extended release	Metadate ER	60 mg	60 mg (>6 y/o)	Extended-release tablet: 20 mg	
Methylphenidate liquid extended release	Methylin ER	60 mg	60 mg (>6 y/o)	Solution: 5 mg/5 mL, 10 mg/5 mL	
Methylphenidate sustained release	Ritalin SR	60 mg	60 mg (>6 y/o)	Sustained-release tablet: 20 mg	
Methylphenidate extended release	Metadate CD	60 mg	60 mg (>6 y/o)	Extended-release capsule: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	
Methylphenidate long acting	Ritalin LA	60 mg	60 mg (>6 y/o)	Extended-release capsule: 10 mg, 20 mg, 30 mg, 40 mg	
Long Acting					
Dexmethylphenidate extended release	Focalin XR	20 mg	20 mg (≥6 y/o)	Extended-release capsule: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	
Oral osmotic system (OROS) methylphenidate	Concerta	72 mg	54 mg (6–12 y/o); 72 mg (13–17 y/o)	OROS capsule: 18 mg, 27 mg, 36 mg, 54 mg	No
Transdermal patch methylphenidate	Daytrana	30 mg	30 mg (6–17 y/o)	Transdermal patch (Daytrana): 10 mg/9 hr (1.1 mg/hr), 15 mg/9 hr (1.6 mg/hr), 20 mg/9 hr (2.2 mg/hr), 30 mg/9 hr (3.3 mg/hr)	No
Quillivant methylphenidate HCI extended release	Quillivant	60 mg in 12 mL liquid	60 mg in 12 mL liquid	5 mg per 1 mL liquid	No
Selective noradrenergic reuptake inhibitor					
Atomoxetine	Strattera	100 mg	10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	Capsule: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	No
Alpha-adrenergic agonists					
Clonidine extended release	Kapvay	0.6 mg/day	0.2 mg	Extended-release tablet: mg, mg	No
Guanfacine extended release	Intuniv	4 mg	1 mg, 2 mg, 3 mg, 4 mg	Extended-release tablet: 1 mg, 2 mg, 3 mg, 4 mg	Yes

y/o, years old.

home notes (daily report cards) are often devised to focus on the specific behaviors that are creating school difficulties. In recent years, multicomponent behavioral treatments have been developed that simultaneously intervene with parents, teachers, and youth.[8] These treatments are generally available only at specialized centers, but the standard parent training and teacher consultation services are often available from community psychologists and other mental health professionals. Educational accommodations, although not formally considered "treatment," are often helpful for students with ADHD.

Evidence is lacking for treatments not discussed here, such as dietary adjustments and supplements, sensory integration training, and insight- and relationship-based psychotherapy. The lack of an evidence base does not prove that alternative therapies are never beneficial, only that they have not been shown as effective and therefore cannot be recommended when evidence-based treatments are available.

Case Vignettes

Cases involving ADHD as the primary diagnosis, with limited comorbidities, are typically managed with standard titration to optimal dosing of approved products. Here we present cases in which child psychiatrists at an academic medical center addressed 2 complicated cases.

CASE 1: OFF-LABEL USE OF IMMEDIATE-RELEASE GUANFACINE IN SEVERE, EARLY-ONSET ADHD AND TOURETTE SYNDROME

In Case 1, the patient, a male, was psychiatrically evaluated at age 5 and diagnosed with severe ADHD, combined type. Family history was positive for paternal depression and ADHD. Mixed salts amphetamine, mixed salts ER, and atomoxetine resulted in initially good but unsustained response. Psychiatric symptoms, including new symptoms of depressed mood and multiple tics, emerged. Atomoxetine was discontinued by the pediatrician, and the child was referred for neurologic evaluation at age 6, with the result of an additional diagnosis of Tourette syndrome and a medication adjustment to IR guanfacine twice daily, plus risperidone and oral osmotic system (OROS) methylphenidate. After another period of initial improvement, symptoms again became more severe and disruptive to functioning, at which time the child was referred to our clinic with presenting complaints of impulsivity, difficulty with transitions, social hypersensitivity, and multiple vocal tics (whimpers, squealing).

At our initial evaluation, the child was taking OROS methylphenidate 18 mg orally every morning, risperidone 0.5 mg every night at bedtime, and immediate-

release methylphenidate for breakthrough ADHD and for special school events that occurred twice weekly. Our evaluation concluded that ADHD symptoms were most impairing and that the low dose of OROS methylphenidate may have presented an opportunity for higher titration. OROS methylphenidate was increased with close monitoring of any worsening in tics. After observations of improved behavior and laboratory test results of increased prolactin and cholesterol, risperidone was successfully discontinued. Because of previous success, IR guanfacine was restarted.

The patient has done well for the past 6 years. Medication has been stable for the past 3 years with IR guanfacine, 1 mg orally twice daily, and OROS methylphenidate, 72 mg orally every day. Because of this stability, there was no inclination to replace IR guanfacine when the sustained-release product became available. Were this case to present to our clinic at this time, the ER product would be considered because of smoother pharmacokinetics. The patient is currently a freshman at a competitive college preparatory high school, receiving mostly A grades. He is also active in theater and plays the guitar. ADHD is for the most part well controlled at the higher stimulant dose. Occasional facial tics occur under stress but are not worrisome to the patient.

CASE 2: CONSERVATIVE STIMULANT TITRATION LEADING TO RATIONAL POLYPHARMACY

Case 2 involves a 13-year-old boy, an eighth-grader of Chinese-European descent. The patient had been diagnosed with ADHD and mild obsessive-compulsive disorder (OCD) at age 9. His parents were resistant to use medications. After a course of parenting classes and individual cognitive-behavioral therapy (CBT) produced only moderate improvement, parents and teachers grew concerned that the adolescent would have difficulty with the greater behavioral and cognitive demands of high school, and the case was presented to our clinic when the patient was 13.

Assessment included a history and mental status examination and included collateral information from the parents and teacher. Psychometric rating scales yielded elevated ratings for ADHD (>2 SD for parent and teacher reports, nearly 2 SD for self-report), moderately elevated ratings for anxiety, and normative ratings for depressive symptoms. Middle-school teachers were initially difficult to contact, and it was helpful to simply trade questions and answers over voicemails. The family also provided consent to use email to contact 1 teacher, and some ratings were obtained by giving the family a preaddressed envelope containing the scale for the youth to deliver to his teacher. Teachers reported that he was easily distracted by hallway noises and his classmates, he had difficulty sitting still and was constantly fidgeting, and at times he would impulsively make silly noises or blurt out answers. He had poor handwriting, frequently misplaced homework and personal belongings, frequently arrived late to classes, and often made care-

less mistakes on quizzes. Parents corroborated the teacher's reports, and they noted that at times he was "goofy" at home (their phrase for silly and impulsive speech and motor behavior). On examination, the patient constantly squirmed and fidgeted or shook his leg, and at times he would lose the focus of the conversation, asking, "Sorry, what was the question again?" At other times he lost track of his own line of thinking, saying aloud, "Hmm, I forgot what I was going to say." At the same time, he was interpersonally engaging, had a sense of humor, and appeared quite intelligent. He reported mild OCD symptoms, including some counting and checking rituals, as well as mild generalized anxiety.

The family was educated about the risks and benefits of and alternatives to treatment with stimulant medications. They reported no cardiac history and an unremarkable recent physical examination. The parents consented and the teen assented to starting a stimulant trial. IR methylphenidate, 5 mg orally every morning, was initiated, with the suggestion that the parents start it on a weekend to observe the effect on their son, and to increase to 10 mg orally every morning the next day if they noticed no effect. The following week the parents reported that they perhaps saw better focus at the 10-mg dosage, but they weren't sure, and any benefits were definitely gone by the afternoon, with possible rebound and increase in "goofiness." The formulation was switched to OROS methylphenidate, 18 mg orally every morning. Again the family reported questionable effectiveness, but they did note that the teen had a harder time with sleep initiation in the evening. The parents felt the benefits weren't worth the sleep trouble, especially because the youth had always had a hard time falling asleep. A trial of IR mixed-amphetamine salts was started at 5 mg and titrated up to 20 mg orally every morning with very good response, although this also wore off by the afternoon. The teen was switched to extended-release mixed-amphetamine salts, 20 mg orally every morning, although this again led to problems with sleep initiation. A combination of 10 mg immediate-release and 10 mg ER mixed-amphetamine salts was found to have good efficacy and brought back normal sleep pattern.

Teachers reported that all ADHD symptoms had improved except for the impulsive noises and actions, and this was corroborated by the student and his family. Considering his ongoing impulsivity, baseline difficulties with sleep initiation, and anxiety, guanfacine, an alpha-agonist, was considered as an augmentation strategy that could also help with sleep and anxiety. The family was informed about the need to watch for signs of orthostatic hypotension, and the patient was told to be especially careful when getting out of bed at night, since there is a slight risk of fainting or falling, with each dose increase. As a conservative precaution (not required as standard of care), an electrocardiogram (negative) was obtained from the pediatrician. The patient started IR guanfacine 0.5 mg orally at bedtime, and the dose was gradually increased by 0.5 mg each week in divided doses. At a dose of 1 mg every morning and 1 mg every night at bedtime, he was

sleepy at school, so dosing was shifted to 0.5 mg/1.5 mg. This helped with sleep initiation and impulsivity at school, but had minimal effect on anxiety.

The patient started reporting more severe OCD symptoms, and these persisted despite weeklong trials off the mixed-amphetamine salts (during which his ADHD symptoms would return) and trials off guanfacine (conducted to ensure that the OCD was not secondary to the stimulants or guanfacine). Compulsions to make a squawking noise developed, leading to social difficulties and internal distress, and so a diagnosis of OCD was made. The patient then reentered CBT with the same therapist, this time to specifically target anxiety and OCD symptoms. After further education and discussion with parents, fluoxetine was started at 5 mg and then increased to 10 mg after 1 week. After 4 weeks at 10 mg, the patient reported some mild relief from his OCD symptoms. The dose was increased to 15 mg and then 20 mg. At 9 weeks after initiation of fluoxetine, the patient noted significant reduction in OCD symptoms and far less anxiety, and his parents noted that he no longer made squawking noises.

Now 14 years old and a freshman in high school, the patient currently takes mixed-amphetamine salts IR, 10 mg orally every morning; mixed-amphetamine salts XR, 10 mg orally every morning; guanfacine, 0.5 mg orally every morning, 1.5 mg orally every night at bedtime; and fluoxetine, 20 mg orally every morning. His ADHD symptoms and anxiety are in nearly full remission, and his OCD symptoms are mild, and he continues to work on them in CBT. Future dosage adjustments may be considered, although the family is cautious about any dosage increases and they expressed hope of lowering or discontinuing dosing at some time in the future.

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Impulsivity, Irritability, and Depression: Antidepressants

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IMPULSIVITY, IRRITABILITY, AND DEPRESSION: ANTIDEPRESSANTS

Background

Impulsivity, irritability, and depression are among the most common symptoms addressed in psychopharmacologic treatments, particularly among children and adolescents. All 3 are also associated with a wide range of diagnoses, including disruptive behavior disorders, mood disorders, psychotic disorders, and substance use disorders either as a primary symptom or an associated feature. Each can individually or in combination contribute substantially to morbidity both in terms of subjective distress as well as functional disruption. Consequently, they are commonly significant target symptoms of medication trials, and several of the current antidepressants have demonstrated some efficacy in their treatment.[1–3] This article explores these 3 symptoms in terms of presentation and impairment and associated diagnoses, including a limited discussion of the underlying neurobiology/symptom etiology and, finally, practical considerations regarding the usage of specific agents.

Impulsivity is characterized by behavior that reflects little or no clear consideration of its consequences, is performed unreflectively, and often results in serious adverse events both to the affected individual and to others. Depending on the circumstances and associated conditions, it may or may not be associated with elevated levels of affect. Impulsivity is associated with numerous diagnoses,

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including attention-deficit/hyperactivity disorder (ADHD), where it is a primary symptom; conduct disorder; bipolar disorders, where it is an associated feature; and the cluster B personality disorders, which are characterized by interpersonal behavior patterns that are often dramatic and affectively intense.[4] It may be a component of genetic disorders, such as Prader-Willi syndrome, most often caused by a deletion in chromosome 15q12.[5] The category of specific impulse control disorders (such as intermittent explosive disorder), by definition, includes pathologies of impulse regulation.

Some authorities have conceptualized compulsive behaviors as part of a spectrum of disorders of impulse control.[6] The importance of addressing impulsivity in adolescence can be linked to associated functional impairments in adults. For example, conduct disorder in childhood is typically characterized by prominent impulsivity and is strongly associated with a range of psychiatric comorbidities, including mood disorders, substance use disorders, and the subsequent development of antisocial personality disorder in adulthood.[7]

Neurobiological research has consistently associated serotonergic dysfunction with disorders of impulse control.[8] Dopaminergic systems and noradrenergic functions have also been implicated, particularly in ADHD. In terms of neurocircuitry, dysfunction in frontotemporal and striatal regions is correlated with particular abnormalities in executive function.[9] Commonly available antidepressants interact extensively with these neurotransmitter systems. The pharmacologic properties likely account for a significant proportion of the efficacy of antidepressants in curbing impulsive behavior.

The pharmacologic prescribing strategy utilized in the treatment of impulsivity is influenced by the clinical context in which symptoms appear. The initial approach to the treatment of impulsivity in conditions such as ADHD is likely to involve psychostimulants or sympatholytics. Antidepressant agents are utilized in more complex clinical presentations involving comorbid mood and anxiety disorders or in treatment-resistant cases. Treatment of impulsivity in the context of a manic episode is likely to begin with mood stabilizers or atypical antipsychotics. These medications work to normalize expansive mood, regularize sleep disturbances, diminish general behavioral activation, and resolve psychotic features. In order to minimize the risk of inducing mania or worsening mood cycling, many physicians avoid the use of antidepressants in bipolar disorders altogether.[10–12]

This risk of precipitating mania makes it imperative to rule out bipolar disorder as the primary underlying pathology of impulsivity. Physicians should look for co-occurring or historical symptoms of euphoric mood, grandiosity, episodes of markedly increased goal-directed activities, racing thoughts, rapid speech, diminished need for sleep, or mood-congruent psychotic symptoms. The presence of 4 or more of these symptoms occurring over a 1-week period suggests

current or historical mania, and antidepressant treatment should probably be avoided.

Irritability, as a symptom, is characterized by a disposition to experience angry affect at a reduced threshold with relatively minimum provocation. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), defines irritable mood as "easily annoyed and provoked by anger."[4] This may result in varying degrees of subjective distress as well as an increased probability of overt displays of anger and, when combined with elevated impulsivity, may increase the risk of aggressive behavior. Irritability is a common symptom in psychiatric presentations, appearing as a descriptor in criteria for generalized anxiety disorder, posttraumatic stress disorder, borderline personality disorder, antisocial personality disorder, nicotine withdrawal, pathologic gambling, and schizoaffective disorder.[13] Irritability may be present in 38% to 55% of youth diagnosed with major depressive disorder,[14,15] tends to be highly nonspecific, and is observed in numerous diagnostic contexts.

Nonetheless, because of the high potential for associated aggressive behavior and attendant destructiveness, irritability is often a focus of major concern and numerous interventions. Developmentally, the symptom often plays a more central role in the presentation of psychopathology in children and adolescents as compared with adults. In mood disorders, irritability may be more prominent than the classic sad and euphoric symptom presentations in adults. Considerable controversy has existed about these differences, particularly because they have affected the diagnostic prevalence of bipolar disorder in children. The diagnostic practices of some physicians trended toward a broad utilization of irritability and rage outbursts to support a diagnosis of bipolar disorder. Recent work has suggested that many children who present with rage outbursts do not, in fact, go on to develop a bipolar disorder but rather are likely to be depressed and anxious.[16] Consequently, current practice is to emphasize the core symptoms of grandiosity and euphoria in the diagnosis of mania.

The neurobiology of irritability seems to be best understood in terms of its neuroanatomic, neurochemical, and functional aspects.[17] Anatomically, regions of the frontotemporal cortex, amygdala, and hypothalamus have been implicated. The frontotemporal regions seem to be critical in executive functions such as effective decision making and planning activities. The amygdalar areas seem to be central for the generation of emotional responses, particularly to social stimuli. The hypothalamus is extensively involved in fundamental motivational states such as hunger and sexual arousal. Irritability has been identified in the context of chronic pain syndromes, attributed to increased activity in the periaqueductal gray area. This brain region has been instrumental in the perception of somatic pain as well as of negative emotional states.[18] Several neurotransmitter systems have been implicated in amplifying or dampening irritability. Serotonin is a major neurotransmitter system central to the regulation of emotional

reactivity. Dysfunction in the serotonin system has been implicated in irritability and impulsivity. Dopamine is a neurotransmitter with a prominent role in increasing motivation and response to reward. Changes in dopamine levels and modulation of dopamine likely contribute to the etiology of behavioral dyscontrol. Furthermore, the 2 systems may interact in such a way that hypofunction of the serotonin system results in loss of adequate modulation of impulsivity and aggression and dopamine hyperfunction contributes to excess aggressive reactivity.[7] Metaphorically, this could produce a situation where there is "too much gas and not enough brake."

The particular pharmacologic strategy for treating irritability will be influenced by the clinical context and diagnostic assessment. Irritability is observed across many diagnostic categories: in mood disorders (both the unipolar and bipolar types), in schizophrenia spectrum disorders, in disruptive behavior disorders, and in cluster B personality disorder. For the reasons outlined earlier, antidepressants generally should be avoided in the setting of bipolar disorders. Irritability also can be associated with primary psychotic disorders; agents such as mood stabilizers and antipsychotic medications are recommended first-line agents in these volatile conditions. By contrast, irritability in the context of depressive disorders, trauma spectrum disorders, and schizophrenia spectrum conditions may be responsive to antidepressant therapy (from any of the different classes of antidepressants). Irritability associated with disruptive behavior disorders and autism spectrum disorders has been successfully reduced with antidepressant medications.

Depression is one of the most prevalent symptoms in psychiatry, and mood disturbances are common across multiple psychiatric diagnoses.[19] Depressed mood is the cardinal symptom in major depressive disorder, dysthymic disorder, and depression not otherwise specified. It is often a component of trauma disorders, schizophrenia spectrum disorders, disruptive behavior disorders, and anxiety disorders. Depressed mood can, like irritability and anxiety, be a relatively normal experience. It is a challenge for physicians to distinguish pathologic states from normative ones. To make the best possible diagnosis, evaluate symptoms in the context of all concurrent difficulties, with particular attention to maintaining or improving overall functional impairment. Because depressed episodes are typical in bipolar conditions and may be a more prominent feature in juvenile bipolar disorders, it is imperative that the physician inquire about current or historical features of mania. In addition, the physician should screen for the presence of suicidal ideation and of other risk factors for impulsive behavior.

The neurobiology of depression is complex, involving dysregulation of serotonergic, dopaminergic, and noradrenergic function. Neuroendocrine abnormalities have been identified in the hypothalamic-pituitary-adrenal axis that implicates corticotropin-releasing factor (a glucocorticoid). Abnormalities in mediation of inflammatory responses may also be present. Regional dysfunc-

tion in frontotemporal, hippocampal, hypothalamic, and amygdalar areas has been identified. Both strong genetic factors and a range of nongenetic factors, including psychologic trauma, neglect, and postinfectious processes, contribute to these abnormal findings in some cases.[20] Because the same regions have been involved in multiple aspects of motivation (frontotemporal cortex, hypothalamic regions, and amygdala) or the generation of negative emotional reactions to social stimuli (amygdala), impairment in these areas (and the associated circuits connecting these areas to each other) may easily contribute to motivational failure in some adolescents and perhaps excessive reactivity in others. The underlying neuroanatomy and neurochemistry are similar, in some respects, to the description of the neurobiology of irritability and aggression (see earlier).

The psychopharmacology of depression treatment, in the absence of a bipolar syndrome, typically proceeds from commonly used selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine) to serotonin and norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine). Agents such as bupropion may be used sooner in the course of treatment in patients with histories of disruptive behavior disorder without marked anxiety symptoms. Antidepressant agents are usually not the first-line drug when irritability is the predominant or prominent clinical symptom. The treatment of irritability associated with bipolar disorder is not likely to be successful with antidepressants, given the risk of inducing mania.

Which specific drug the physician selects will depend on (a) his or her familiarity and comfort with a given agent; (b) the patient's past experiences with different medications; and (c) specific concerns about potential side effects. The following is a brief summary of several of the more commonly prescribed antidepressants, dosing guidelines, and evidence supporting their usage.

Clinical Vignettes

CASE

Dario is a 13-year-old boy who comes to your office with his grandmother for outpatient psychiatric evaluation. Dario has been struggling in school, often forgetting to turn in assignments or alleging that he has lost them. His teachers have complained about his easy distractibility, mistakes in assignments, difficulty with organization, and interrupting conversations and activities. His grandmother says that Dario has "always been like this . . . since he was a young boy, he could never sit still or wait his turn."

DISCUSSION

Dario's history and ratings on current clinical scales, including the Vanderbilt ADHD Diagnostic Parent and Teacher Rating Scales, provide the information that he meets criteria for the diagnosis of ADHD, with irritability and impulsivity symptoms.[21] Dario is started on an appropriate dose of a stimulant medication (see Riddle et al for a description of stimulant medication). He has improvements in inattention as well as hyperactivity/impulsivity within the first week of medication administration, as noted by his family and teachers. Outpatient follow-up is scheduled for 2 to 4 weeks. If Dario also had depressive symptoms, bupropion, as discussed in this article, would have been an appropriate agent to target both mood and ADHD symptoms.

CASE

Wilson is a 12-year-old boy brought into the emergency department from school after screaming at an adult hall monitor without identified provocation. Wilson's mother alleges that he has been extremely irritable for about the past week. She is concerned that his new friends may be a bad influence, because Wilson has been staying out late, has been very talkative, has been unable to concentrate on schoolwork, has not been completing chores, and has shown overall poor judgment. Wilson argues with his mother, saying that he has been "fighting" with the other boys and that they are not his friends. Though Wilson has never done drugs before, he admits that he tried cigarettes for the first time a few days ago. His urine drug screen is negative.

DISCUSSION

Wilson is found to meet criteria for a manic episode, by his symptoms of irritable mood, increased speech, decreased need for sleep, and excessive involvement in pleasurable activities that have a high risk for painful consequences.[4] Treatment may include an antipsychotic (see pages 406-408) with or without a mood stabilizer (see Pakyurek et al), which is considered first-line treatment. Although Wilson is irritable and has had mood disturbances, the antidepressants discussed in this article would be contraindicated as first-line agents since they can all predispose to mania.

SPECIFIC MEDICATIONS

SSRIs

Selective serotonin reuptake inhibitors are a class of drugs that account for most antidepressant prescriptions in the United States.[22] (See Table 1.) Their primary pharmacologic action is inhibition of serotonin reuptake at the somatodentritic end of the serotonergic neural synapse. In depression, the serotonin neuron is

Table 1.
Dose range for SSRI antidepressants

SSRI	Starting Dosage	Suggested Therapeutic Range	Half-Life
Citalopram (Celexa)	Child: 10 mg Adolescent: 10 mg	10–40 mg	23–45 hr
Escitalopram (Lexapro)	Child: 5 mg Adolescent: 5 mg	5–20 mg	27–32 hr
Fluoxetine (Prozac)	Child: 5 mg Adolescent: 5 mg	5–60 mg	24–144 hr (parent) 200–330 hr (metabolite)
Fluvoxamine (Luvox)	Child: 25 mg Adolescent: 25–50 mg	25–200 mg	9–28 hr
Paroxetine (Paxil)	Child: 5 mg Adolescent: 10 mg	5–40 mg	3–65 hr
Sertraline (Zoloft)	Child: 25 mg Adolescent: 50 mg	25–200 mg	22–36 hr (parent) 62–104 hr (metabolite)

thought to have a relative deficiency of available serotonin with corresponding upregulation of presynaptic and postsynaptic receptors.[23] With initial SSRI treatment, 5HT increases in the somatodentritic area of the serotonin neuron, with delayed downregulation and desensitization of serotonin receptor, which is one mechanism of explanation for observed clinical benefit.

Side Effects. Although this class is called "selective," referring to the selective involvement on serotonin over other neurotransmitters, the class remains somewhat nonselective with regard to the myriad serotoninergic locations and system effects that result from ingestion. Stimulation of serotonin receptors in the raphe nucleus and the limbic cortex may cause anxiety and panic attack symptoms during initial dosing. Receptors in the basal ganglia are thought to be responsible for akathisialike, parkinsonian, and dystonic movements. Serotonergic system activation in the brainstem and hypothalamus may cause sleep disruptions; receptors in the spinal cord may be responsible for sexual side effects (incomplete or prolonged orgasm). Vast serotonin pathways in the gut are implicated in creating gastrointestinal cramps, diarrhea, and changes in bowel motility. Short-term studies showed increased suicidal thinking and behaviors in children, adolescents, and young adults taking antidepressants; though actual reported incidence remains rare, this is a necessary detail of monitoring and informed consent.[22]

Toxicity. Overall, SSRIs have a low risk of toxicity, with only 1 published fatality linked to fluoxetine overdose and 6 with citalopram, 5 of which had comorbid use of sedative drugs or alcohol.[22] Symptoms of toxicity include nausea, vomiting, tremor, myoclonus, irritability, electrocardiographic (ECG) changes, and seizures. A rare hypermetabolic syndrome, called serotonin syndrome, may occur from SSRIs (or other serotonergic agents), usually within 24 hours of dose changes, overdose, or medication initiation. Symptoms include nausea, diarrhea, diaphoresis, fever, hypertension, palpitations, increased muscle tone, myoclonus, hyper-reflexia,

agitation, and disorientation. Rhabdomyolysis can cause severe complications, with risk of fatality. Treatment of the serotonin syndrome involves discontinuing the offending agent and providing symptom-related supportive treatment.

Laboratory Tests. No specific laboratory tests are necessary in prescribing SSRIs or in monitoring therapeutic and toxic effects.

Indications Approved by the U.S. Food and Drug Administration (FDA). Fluoxetine has been FDA-approved for ages 8 to 17 for depression and obsessive-compulsive disorder. Fluvoxamine (age >8) and sertraline (age >7) have been FDA-approved for obsessive-compulsive disorder.

Several non-FDA indications are also pertinent, because SSRIs have been implicated in the treatment of aggressive, impulsive, and self-injurious behavior in ADHD and pervasive developmental disorders, such as autism, especially when there are comorbid mood symptoms. There are also early data that suggest efficacy regarding the use of citalopram and fluvoxamine in patients with Tourette syndrome.[22]

SNRIs

Venlafaxine (Effexor and Effexor XR) and duloxetine (Cymbalta) represent the class of serotonin and norepinephrine reuptake inhibitors.

Evidence. At least 1 open-label study suggested efficacy of venlafaxine for major depressive disorder.[24] Two double-blind studies with patients ages 8 to 17 found no separation of results from placebo when combined with psychotherapy.[22]

Dosing. In adolescents, venlafaxine may be initiated at 18.75 mg to 37.5 mg with food, and increased weekly, in 18.75-mg to 37.5-mg increments, to a maximum of 225 mg/day in divided doses. The safety and efficacy of duloxetine in adolescents has not been sufficiently evaluated to provide recommendations on dose range and safety parameters.

Side Effects. Venlafaxine has been reported to increase hostility and suicidal ideation in children (2%) as compared with placebo (1%).[22] Blood pressure monitoring is recommended, because this medication causes increased blood pressure in more than 3% of patients at starting doses, especially in the setting of preexisting hypertension.[22] Other side effects seem to be dose related, including but not limited to sedation, insomnia, disruption of sleep cycle, headache, anxiety/agitation, asthenia, breakthrough depression, hyperkinesia, seizures (<1%), tachycardia, hypotension, nausea/vomiting, anorexia, weight loss, sexual side effects, and hypomania/mania. Venlafaxine is associated with an uncomfortable withdrawal syndrome marked by asthenia, dizziness, headache, insomnia, tinnitus, nausea, "electric shock" sensations, nightmares, and depression, which can last for

more than a week.[22] Therefore, it is recommended that this medication be tapered slowly over 2 to 4 weeks or longer.

Toxicity. Toxicity is rare and most commonly reported in overdose. Symptoms include somnolence, tachycardia, QTc prolongation, and seizures. There are no documented deaths from overdose of venlafaxine or duloxetine.

Laboratory Tests. No standard laboratory monitoring is associated with SNRIs.

Indication for Use. While there are off-label uses for this class, there are no FDA-approved indications for these agents in children and adolescents. Pfizer, the manufacturer for Effexor and Effexor XR, recommends against using venlafaxine in pediatric populations because of reports of increased hostility and suicidal ideation. In spite of these concerns, in adolescents the use of SNRIs for treatment of major depression, anxiety disorders, and autism spectrum disorders is common and reported in case reports.

Bupropion

Bupropion (Wellbutrin, Wellbutrin-SR, Wellbutrin XL, Zyban) is a unique therapeutic agent in its mechanism: It primarily inhibits reuptake of norepinephrine and dopamine (to a lesser extent) into presynaptic neurons. It is the only commonly prescribed antidepressant that does not involve serotonergic neurotransmission.[23]

Evidence. A clinical trial involving 104 children and adolescents ages 6 to 16 showed good tolerance for the medication.[25] A small, unpublished open-label study found that 79% of adolescents on an average daily dose of 362 mg of bupropion exhibited improvement in depression.[22] There is some evidence to suggest that bupropion may be of benefit in adolescents with comorbid conduct disorder and substance use disorder. Because of its noradrenergic and dopaminergic effects, bupropion has been suggested to be of benefit for ADHD. Other reports have documented efficacy in seasonal affective disorder, dysthymia, chronic fatigue syndrome, and social phobia and in alleviating sexual dysfunction induced by SSRIs and SNRIs.[23] As a general statement, there is limited published evidence about indications for use, tolerability, safety, and efficacy in adolescent populations.

Dosing. Adolescent dosing has been recommended to start at 100 mg oral daily, with a suggested therapeutic dosage range of 3 to 6 mg/kg/day. It should be administered in divided dosages of no more than 150 mg/dose, with a maximum of 450 mg total daily dosage, with noted risk for generalized seizures at higher dosages as described later. Six weeks or longer may be required for full effect to be experienced.

Side Effects. The most concerning common side effect with bupropion is a lowering of the seizure threshold, especially after abrupt dose increases or use of

daily dosages greater than 300 mg. Though evidence has been lacking in adolescents, risk of seizures in adults is approximately 0.1% from 100 to 300 mg/day, with risk increasing 10-fold at dosages of more than 450 mg.[5] This is especially notable in patients with comorbid eating disorders, because of possible electrolyte disturbances. Caution should be exercised in patients with organic brain disease or who are taking other medications or have conditions that may predispose them to seizures. Headache is commonly reported after initiation (10%), as well as gait disturbances, fine tremor, myoclonus, neuralgias, myalgias, exacerbation of tics in ADHD or Tourette syndrome, insomnia, vivid dreams/nightmares, decreased REM latency and increased REM sleep. Agitation or anxiety is common, making this a poor choice if there is comorbid anxiety; possible precipitation of hypomania or mania requires attentive monitoring in patients with bipolar disorder. The dopaminergic activity of this drug may exacerbate psychotic symptoms. Alpha-1 antagonism may lead to orthostatic hypotension, dizziness, palpitations, and rebound hypertension (more likely in patients with preexisting hypertension). For unknown reasons, urticarial or pruritic rashes have been reported with this medication in up to 17% of children and adolescents, with rare cases of erythema multiforme and Stevens-Johnson syndrome.[22]

Toxicity. Toxicity from bupropion and its derivatives is rare, most commonly occurring in the setting of substantial overdose. The clinical picture may include confusion, impaired concentration, hallucinations, delusions, delirium, extrapyramidal symptoms, bradycardia, cardiac failure, and seizures. Treatment is primarily supportive; induction of vomiting if there has been recent ingestion, administration of activated charcoal, and ECG/electroencephalographic (EEG) monitoring may be indicated.

Laboratory Tests. There are no standard laboratory tests involved in monitoring treatment with bupropion.

FDA Indications for Use. Bupropion has been FDA-approved in *adults* for major depression, prophylaxis of recurrent major depression, and the depressed phase of bipolar disorder and to aid in smoking cessation (Zyban). In *adolescents*, it is most commonly used for off-label treatment of ADHD, especially if there are comorbid mood symptoms; there are no FDA-approved indications for use in adolescents.

Mirtazapine

Mirtazapine (Remeron) has a unique mechanism as a selective antagonist at alpha-2 receptors, increasing release of norepinephrine and serotonin.[23]

Evidence. One open-label study in participants ages 3 to 23 with pervasive developmental disorder demonstrated improvement in aggression, self-injury, irritability, anxiety, depression, and insomnia.[26]

Dosing. Adolescent dosing is recommended to start at 7.5 to 15 mg daily for 7 days, increasing to 15 to 30 mg. If ineffective, the dosage may be increased to 45 mg daily after 1 to 2 weeks.

Side Effects. Sedation is the most common side effect, present in 30% of patients. Mirtazapine can be associated with anticholinergic effects, including dry mouth, constipation, sweating, blurry vision, and urinary retention. Potent antihistaminergic effects are associated with an increase in appetite and with weight gain. Neutropenia and agranulocytosis have been reported, as have elevations in lipids.[5]

Toxicity. There are no documented issues of toxicity with mirtazapine or documented overdose deaths in adolescents.

Laboratory Tests. Although no screening laboratory studies are needed to initiate treatment, ongoing monitoring of complete blood cell count (specifically white blood cells), transaminases, and lipid levels is indicated given the side effects reported.

Indications for Use. Currently, mirtazapine has no FDA-approved indications in adolescents. It may be chosen if an adolescent has been refractory to other depressants. It is commonly used as monotherapy. It is also effective as an adjunct medication because of its effects on sleep and appetite, in cases where it is desirable to potentiate these effects.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are used less commonly in adolescents because of the newer and safer medications listed previously. This class includes amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Sinequan), imipramine (Tofranil), nortriptyline (Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil).

Evidence. Several controlled trials have indicated that TCAs are less effective for treating depression in adolescents than these agents are in adults. Clomipramine was effective in reducing severity of core symptoms of autism, including ritualistic behavior, anger, and aggression. Desipramine, clomipramine, and imipramine have shown some benefit to reducing hyperactivity associated with pervasive developmental disorders. Studies report clinical efficacy in the treatment of ADHD, school phobia, separation anxiety disorder, premenstrual dysphoric disorder, cataplexy/narcolepsy, pain management, and Tourette syndrome.[5,22]

Dosing. For the many named agents in this class, there is a wide variation in dosing, with a narrow therapeutic window. Because of limited efficacy and safety

in adolescents, a dosing schedule has not been included here. It is recommended to consult a specialist before initiating a TCA.

Side Effects. Drowsiness is the most common side effect, which is a reason for prescribing these medications at bedtime.[5] Cognitive dysfunction, confusion, and disorientation have been linked to the antihistaminergic/anticholinergic properties of this class. Neurologic effects may include akathisia, seizures, and myoclonus. Anticholinergic effects are also responsible for dry mucous membranes, constipation, urinary retention, and hyperhidrosis. These drugs are contraindicated in heart block because of prolongation of conduction times and resultant risk of arrhythmias, syncope, and, rarely, heart failure. There are 5 cases of deaths of prepubescent children on desipramine, possibly as a result of arrhythmias.[5,22] As with other antidepressants, it is important to monitor for precipitation of hypomania or mania, especially in patients with a history of bipolar disorder.

Toxicity. Toxicity is a significant concern with this class as a result of the narrow therapeutic window; the lethal dose is about 3 times the maximum therapeutic dose. Cardiac changes are the most concerning, with changes noted in lengthening of the QRS duration in a dose-dependent fashion. Arrhythmias may require monitoring in the intensive care unit. Because plasma levels of the drug and its metabolites may be significantly higher in children, extra caution must be observed. The FDA says TCAs are unsafe in children with a PR interval greater than 200 ms, QRS interval more than 30% above patient baseline or more than 120 ms, blood pressure higher than 140/90, or heart rate more than 130 beats/min at rest.[22] Toxicity or overdose is considered a medical emergency.

Laboratory Tests. TCAs have meaningful plasma levels that can be checked; below-therapeutic levels are associated with incomplete or poor response, and above-therapeutic levels are associated with toxicity. Because of the adverse effects with this class, vital signs and ECGs are recommended before initiation, during titration if clinically indicated, and every 3 to 6 months once steady state has been reached.

FDA Indications for Use. Clomipramine has been approved for OCD in children and adolescents ages 10 and older. Imipramine has been approved for enuresis. Other off-label indications have been implied as described previously.

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) are an older class of antidepressants that are seldom used in children, primarily because of limited evidence, concerning side effects, and dietary interactions with tyramine-containing foods. Monoamine oxidases are endogenous enzymes that break down dopamine, serotonin, epinephrine, and norepinephrine; inhibition of these enzymes results

in increased endogenous concentrations of these neurotransmitters.[23] These medications include phenelzine, isocarboxazid, tranylcypromine, selegiline, moclobemide, and brofaromine. There are no FDA-approved indications for adolescents.

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Treatment of Psychosis in Children and Adolescents: A Review

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TREATMENT OF PSYCHOSIS IN CHILDREN AND ADOLESCENTS: A REVIEW

Recognition and psychopharmacological treatment of psychosis in children and adolescents remains challenging. This is partly because of limited research available for this age group, at least until recently, and partly because of a relatively small number of recognized psychotic disorders in younger age groups. Indeed, estimates indicate that only up to 1% of all patients with schizophrenia have an onset before age 10 years, and less than 5% have an onset before age 15 years.[1] However, when psychosis secondary to a variety of diagnoses and disorganized thinking is taken into consideration, the numbers increase significantly.

A BRIEF HISTORY

More than a century ago, German psychiatrist Emil Kraepelin differentiated the psychosis of manic depression, which is marked by episodic illness alternating with times of relatively intact function, from the psychosis of what he termed *dementia praecox*, with its long-term progressive deterioration.[2] A few years later, the Swiss psychiatrist Eugen Bleuler coined the term *schizophrenia* and emphasized the loss of associations in thought process and the schism of thought, emotion, and behavior. In 1949, in his quest to find a more effective anesthetic, the French surgeon Henri Laborit serendipitously introduced the first antipsychotic, chlorpromazine, which was found to calm patients with schizophrenia.[3]

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EPIDEMIOLOGY

The prevalence of schizophrenia in the general population is about 1%, with a male-to-female ratio of 1.4:1. Higher rates are observed in cities, in migrant groups, and for winter births.[4] The prevalence of early-onset schizophrenia has not been well studied.[5]

GENERAL CONCEPTS AND DEFINITIONS

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) requires positive and negative symptoms to make the diagnosis of schizophrenia. *Positive symptoms* refer to an excess or distortion of normal function and include hallucinations, delusions, and disorganized behavior (eg, catatonia) or speech. *Negative symptoms* refer to a loss of normal function and include affective flattening, poverty of speech, and loss of motivation. To meet diagnostic criteria, at least 2 positive symptoms or 1 positive and 1 negative symptom must be present for 1 month (or less if successfully treated) unless hallucinations are continuous or delusions are bizarre. There must also be 6 months of failure to meet age-appropriate social, academic, or occupational goals or loss of function in these areas. Finally, these symptoms cannot be better accounted for by a mood, substance, medical, or pervasive developmental disorder.[6] The essential features of the diagnosis remain the same in the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition.

Although not a component of the DSM-IV-TR diagnostic criteria for schizophrenia, cognitive deficits usually accompany positive and negative symptoms. These include degradations in memory, attention, executive function, and processing. Cognitive deficits generally precede psychosis, are consistent and persistent across fluctuations in positive and negative symptoms, fit a typical profile, and may have the greatest impact on function.[7]

To count as diagnostic for schizophrenia in the DSM-IV-TR, positive symptoms must occur in the absence of insight into their pathological origin—that is, when the individual believes in the veracity of the content of the psychosis. In practice the presence or absence of insight is sometimes difficult to ascertain, and the positive symptoms of schizophrenia can be conceptualized as a continuum. On one end are attenuated symptoms (with retained insight), and on the other are fully developed clinical picture (with absent insight). Attenuated symptoms include hallucinations that are infrequent, cause low levels of distress, and are readily identified as coming from one's own mind or imagination or as transient delusional thoughts that are readily dismissed and do not significantly affect behavior or functioning.

For the sake of early identification and intervention, the category of ultra high risk (UHR; also referred to as clinical high risk) has been developed. The cate-

gory refers to individuals who (1) have exhibited attenuated positive psychotic symptoms in the past year; or (2) exhibit brief, full-fledged, self-limited psychotic symptoms lasting less than a week; or (3) have schizotypal disorder or a first-degree relative with a psychotic disorder and have experienced a substantial (30% decrease on the Global Assessment of Function scale) functional decline over the past year.[8]

Very early-onset schizophrenia (VEOS) refers to onset before age 13 years, whereas *early-onset schizophrenia (EOS)* refers to onset before age 18 years. Thus, VEOS is a subtype of EOS. *Childhood-onset schizophrenia (COS)* refers to onset at 12 years of age or younger, and *adolescent-onset schizophrenia (AOS)* refers to onset between the ages of 13 and 17.[9]

PRESENTATION AND COURSE

A rich fantasy life is normative for children, and reports of psychotic-like experiences are common; for example, a recent study revealed that 35% of school-age children reported auditory hallucinations and 30% reported paranoia.[10] By themselves, these reports do not seem to impart a risk for developing a psychotic disorder later in life.[11]

In children and adolescents, psychosis usually presents as a component of another psychiatric illness. These can include, in order of prevalence, major depressive disorder, bipolar disorder, anxiety disorders, and substance use disorders, followed last by schizophrenia spectrum disorders.[12] Similarly, youth with pervasive developmental, cognitive, and personality disorders can also present with psychosis.

The course of schizophrenia can be divided into the prodrome, acute, recovery, and residual phases.[5] Generally, 5 years of prodromal symptoms precede the first full-fledged positive symptom of schizophrenia. *Prodrome* refers to this period, which is often marked by difficulties with emotion (depression, lack of self-confidence, lack of energy, anxiety, worry), cognition (trouble with thinking and concentration), motor (restlessness and slowness), and socialization (withdrawal, distrust).[13] Thus, the prodrome differs from UHR, although adherence to this distinction is not always in the literature. The prodrome ends at the first full-fledged positive symptom, starting the acute phase. More than a year usually passes before the index psychiatric hospitalization.[13] The recovery phase usually follows, marked by negative symptoms and significant impairment. Some will progress to the residual phase with lesser impairment. Approximately 25% of patients recover within 6 years, but about 60% develop chronic schizophrenia, with ongoing positive or negative symptoms.[13]

Most UHR individuals do not develop schizophrenia. The risk of progression from UHR to full-fledged psychosis increases with time: 22% at 1 year, 29% at 2

years, and 36% after 3 years.[14] Still, presenting with prodromal symptoms already indicates significant psychiatric illness and functional deficits. Comorbidity in UHR individuals is the rule: 55% have a mood disorder; 38%, an anxiety disorder; 25%, a substance use disorder; 13%, attention-deficit/hyperactivity disorder; and 40%, a cluster A personality disorder (paranoid, schizoid, or schizotypal).[15]

DIFFERENTIAL DIAGNOSIS AND MEDICAL WORKUP

Psychosis can also present as a symptom of nonpsychiatric illness. The differential diagnosis for this is quite broad. Metabolic (eg, hepatic failure, renal failure, and imbalances of serum sodium and calcium), endocrine (eg, Addison disease, Cushing disease, and thyroid dysfunction), autoimmune (eg, systemic lupus erythematosus), infectious (eg, herpes simplex and human immunodeficiency virus), neurologic (eg, complex partial seizures and Wilson disease), genetic (eg, fragile X syndrome), and substance use (intoxication and withdrawal, as well as poisoning) are all illness categories potentially implicated in psychosis.[16]

Because there is no laboratory, imaging, or psychological test to make the diagnosis of schizophrenia, the initial medical evaluation should focus on ruling out nonpsychiatric causes of psychosis while at the same time establishing baseline indices to monitor for side effects of medication treatment. Routine workup typically includes a physical examination with a detailed neurological examination, complete blood cell count, comprehensive metabolic panel, thyroid function tests, and toxicology screen. Development of psychosis very early in childhood or rapid deterioration of function should prompt more detailed investigations, and these are generally guided by specific symptoms (eg, genetic testing with dysmorphic physical features and brain imaging with neurological deficits).[5] In the absence of signs or symptoms that prompt further workup, additional investigations rarely reveal a nonpsychiatric cause.[17]

TREATING THE ULTRA HIGH-RISK PATIENT

Several studies have investigated second-generation antipsychotics (SGAs) and SGAs with cognitive-behavioral therapy (CBT) to prevent UHR youth from progressing to full-fledged psychosis. Overall, these studies suggest that SGAs reduce the severity of prodromal symptoms and that an SGA plus CBT may delay progression, but none of these treatments prevent progression. Dropout and treatment adherence were significant issues, and medication tolerability (eg, weight gain with olanzapine) likely played a role. Studies that examined CBT alone suggest that it also delays progression, is better tolerated, and may be similar in efficacy to supportive psychotherapy.[18–20]

Although there are no controlled trials of selective serotonin reuptake inhibitors (SSRIs) in the prodrome, this class of medication shows promise. A naturalistic

study prospectively followed UHR youth for about 2 years. In the cohort treated with SSRIs, none progressed to psychosis. In the cohort treated with SGAs, 43% progressed to psychosis and the treatment was highly associated with medication nonadherence.[21] A later naturalistic, prospective study at the same site demonstrated that SSRI treatment improved verbal learning and sustained attention, whereas patients treated with SGAs saw deterioration in these domains.[22] These studies suggest that the more favorable side effect profile of SSRIs leads to greater adherence and therefore efficacy.

One randomized controlled study examined the use of omega-3 fatty acids in concentrated fish oil in UHR individuals. Fish oil taken for 3 months protected against progression to full-fledged psychosis (4.9% in the treatment group progressed to psychosis vs. 27.5% in the placebo group), was associated with fewer symptoms and better function, and was well tolerated. Interestingly, some of these differences persisted for 9 months after the treatment was stopped.[23]

Because of the relatively low rate of progression from UHR to full-fledged psychosis and the limited benefit and poor tolerability of SGAs in preventing progression, they are not considered first-line treatments. Targeting these comorbid disorders with more benign evidence-based treatments (including CBT, SSRIs, and fish oil), while monitoring for the emergence of full-fledged psychosis, is recommended and likely to decrease distress and improve function.

SUICIDE RISK

Between 23% and 42% of patients with schizophrenia will attempt suicide in their lifetime,[24] and 4.9% succeed.[25] During the prodrome, 25% will have suicidal ideation, and 7.5% will attempt suicide, usually violently. Younger age of onset of prodromal symptoms and depression were risk factors for attempt, and any attempt predicted later risk.[26] The risk is highest at the onset of psychosis, and very close monitoring is needed during this period.[27] CBT shows some efficacy in suicide risk reduction after the first episode of psychosis.[28]

Case Vignette

CHIEF COMPLAINT: "I AM NOT SURE WHAT IS HAPPENING TO ME."

Mariah (her name has been changed to protect her anonymity) was a 15-year-old white female who presented to the Sacramento Early Diagnosis and Preventive Treatment (EDAPT) Clinic for adolescents who are UHR or have recent-

onset psychosis. She reported that 3 years ago she began having strange experiences. She had intermittently, alternately, and with varying degrees of insight or certainty endorsed the Cotard delusion (in which she felt as though she did not exist), paranoia (feeling as though she was being watched), and a sense of time dilation (feeling as though everything was slowed down). She also reported auditory (hearing ringing in her ears), visual (seeing a blinding white light), and tactile (feeling a light touch on her skin) hallucinations. She reported feeling sad, and this was associated with poor sleep and fatigue. There was no history of emotional, physical, or sexual trauma. Her parents recalled noticing a decline in social and academic function about 2 years ago. Despite this, she managed to keep a small group of close friends and was not failing any classes. At presentation, her thought process was circumstantial, and her behavior was somewhat disorganized.

Mariah had no history of psychiatric disorder. Other than mild asthma, she had always been medically healthy. There was a family history of schizophrenia in her maternal grandmother and uncle, and her brother had attention-deficit/hyperactivity disorder. There were no complications during her mother's pregnancy or delivery, and she met developmental milestones on time. She had experimented with marijuana on 2 occasions in the past.

Physical and neurological examinations were unremarkable. Baseline laboratory studies, including a comprehensive metabolic panel, a complete blood cell count, and thyroid studies, were all within normal limits.

Mariah was enrolled in the EDAPT program. A team of experts, including psychiatrists, psychotherapists, social workers, and teachers, met weekly and discussed Mariah's needs and progress. She received individual, family, and group psychotherapy. An education plan was developed to foster academic progress. Some of the treatment occurred in Mariah's home. She was started and maintained on fluoxetine, 10 mg orally each morning, as well as omega-3 fatty acid supplementation with concentrated fish oil, both of which she tolerated well. For the first month of her treatment she also received clonazepam, 0.25 mg orally twice daily, to address anxiety, and this was weaned over a week without issue.

At the conclusion of Mariah's 18-month treatment, she and her parents reported significant improvement with her symptoms overall. Her delusions and hallucinations had resolved completely. Her anxiety was gone, and her sadness was much improved. She was sleeping regularly and no longer tired. She made the honor roll at school, and she seemed more appropriately socially engaged. There was still some intermittent circumstantiality in her thought process, but this did not seem functionally limiting or bothersome to her. She continues to be seen intermittently for follow-up to monitor for recurrence or worsening of symptoms.

TREATMENT OF FULL-FLEDGED PSYCHOSIS

Antipsychotic medications are indicated to treat schizophrenia in children and adolescents. The SGAs aripiprazole, olanzapine, quetiapine, and risperidone are FDA-approved for ages 13 to 17 years for schizophrenia. Risperidone is often considered first because it has the most empirical data and is generic. Otherwise, the side effect profile generally guides the decision, but other factors, such as cost, patient, or family preference and physician's familiarity with an agent, can also be considered. Weight gain may limit olanzapine's use as a first-line agent.[5] If weight is a significant concern, aripiprazole seems safest in this regard.[29] Concern for neurologic and cardiovascular complications usually limits use of haloperidol and other first-generation antipsychotics. A rule of thumb for dosing is *Start low and go slow.* If a medication is insufficiently effective after a 6-week trial with adequate dosing, reevaluate the diagnosis. Alternative explanations for symptoms or comorbid illness may lead to considering other treatments and classes of medication. If the diagnosis remains the same, it is reasonable to switch to a different antipsychotic. Finally, in treatment of refractory patients, a trial of clozapine may be indicated (Table 1).[30]

There are relatively few studies of psychosocial interventions in the treatment of schizophrenia in children and adolescents.[5] It is well established that psychoeducation for families and key social networks is effective in preventing rehospitalisation.[31] CBT has become widely used in the United Kingdom and is increasingly used in the United Sates as well. One promising approach is cognitive remediation to address attention, memory, and problem solving. Two earlier studies demonstrated some efficacy.[32,33] A more recent 2-year randomized controlled study indicated that cognitive and social remediation produced superior gains in cognitive and social function, as well as in employment, activities of daily living, leisure, and relationships.[34]

The literature on psychosocial interventions for adults suggests efficacy for a variety of treatments, and youth should also benefit from them.[5] Focused social skills training improves overall function in the community. Support in procuring and maintaining employment, including on-the-job assistance, is effective. Education about nutrition, portion control, meal planning, and exercise are effective means of weight loss. CBT can reduce positive and negative symptoms. Providing support and psychoeducation to families reduces relapse and hospitalization and improves medication adherence and family relationships.[35]

MONITORING

Before initiating treatment with an antipsychotic, obtain a personal and family history of diabetes, dyslipidemia, seizures, and cardiac issues. Eliciting a history of these should prompt additional workup with consideration given to specialist consultation.[30]

Table 1
Antipsychotic medications

Medication	Indication	Age	Starting Dosage	Titration	Goal Dosage	Maximum Dosage
Aripiprazole	Schizophrenia	≥13 yr	2 mg/day	2 mg/day for 2 days; then 5 mg/day for 2 days; then increase in 5-mg increments	10 mg/day	30 mg/day
Haloperidol	Psychosis	3–12 yr	0.025–0.05 mg/kg/day divided BID or TID	0.5 mg/day every 5–7 days	Not given	0.15 mg/kg/day
Haloperidol	Psychosis	≥13 yr	0.5–2 mg BID or TID	Not given	Not given	100 mg/day
Olanzapine	2nd line for schizophrenia	≥13 yr	2.5–5 mg/day	Increase in 2.5- to 5-mg increments	10 mg/day	20 mg/day
Quetiapine	Schizophrenia	≥13 yr	25 mg BID	Increase as clinically indicated	400–800 mg/day divided BID or TID	800 mg/day
Risperidone	Schizophrenia	≥13 yr	0.5 mg/day	Increase by 0.5 mg/day every 3–7 days	3 mg/day	6 mg/day
Thioridazine,	Psychosis	≥2 yr				

BID, 2 times per day; FGA, first-generation antipsychotic; TID, 3 times per day.

Vital signs, including height, weight, blood pressure, and heart rate, should be obtained at baseline and at 1, 2, 3, and 6 months of treatment, and every 6 months thereafter if stable, although it is good practice to obtain this information at each appointment. Body mass index (BMI) can be calculated and plotted on the appropriate chart at baseline, 1, 2, and 3 months, and every 3 months thereafter if stable. The Abnormal Involuntary Movement Scale should be administered at baseline and periodically thereafter.[5]

Laboratory studies usually include fasting blood glucose and fasting lipid panel repeated at 3 months and every 6 months thereafter if stable. If there are clinical signs of hyperprolactinemia (menstrual irregularity, gynecomastia, or galactorrhea), obtain a fasting prolactin level and consider referral to a specialist. The manufacturer of quetiapine recommends baseline ophthalmologic examination and periodic reexamination because of the risk for cataracts. Clozapine has special monitoring requirements and should be prescribed by a child and adolescent psychiatrist.[5]

After a systematic review, Pringsheim et al recommended additional monitoring, including liver function tests for olanzapine, prolactin level for risperidone and olanzapine, and thyroid-stimulating hormone for quetiapine.[36]

TREATMENT OF SIDE EFFECTS

Because side effects are common, treatment should begin with a frank discussion weighing the risks and benefits of an antipsychotic. Using the lowest effective dosage will help minimize side effects. If a side effect occurs, consider lowering the dosage or changing agents. Periodically discussing the diagnosis and treatment rationale with patients and their caregivers is an important part of informed consent and may enhance treatment concordance.

Several neuromuscular side effects are associated with antipsychotic treatment:

- Acute dystonic reaction:

Acute dystonia is a sustained muscle contraction leading to twisting movements and abnormal postures, usually involving the head, neck, and trunk muscles. Although uncomfortable, dystonia usually responds to anticholinergic agents, such as benztropine (0.02–0.05 mg/kg twice daily) or diphenhydramine (ages 2–11: 1–2 mg/kg every 6–8 hours, not to exceed 50 mg/dose or 300 mg/day; ages 12 and older: 25–50 mg every 6–8 hours, not to exceed 300 mg/day orally or 100 mg/dose and 400 mg/day intramuscular [IM] or intravenous [IV]).

- Akathisia:

Akathisia is a subjective state of restlessness with a need to move. In children this may present as anxiety or irritability. Treat with propranolol (1–2 mg/kg/day

divided every 8 hours) or clonazepam (in children weighing less than 30 kg, start 0.01–0.03 mg/kg/day divided every 8–12 hours, titrated 0.25–0.5 mg every 3 days up to 0.2 mg/kg/day; in children weighing more than 30 kg, start 0.5 mg 3 times daily; may increase by 0.5–1 mg/day every 3 days to a maximum of 20 mg/day). When using clonazepam, monitor for paradoxical agitation.

- Tardive dyskinesia:

Tardive dyskinesia is a writhing and repetitive movement of the mouth, lips, tongue, or distal limbs. Vigilance for this is important because the disorder can be permanent. Treatment may entail decreasing or stopping the antipsychotic medication, with consideration given to clozapine if continued treatment is necessary.[37]

Because weight gain is common, all patients and their caregivers should receive counseling regarding lifestyle interventions (including a healthy diet and exercise). BMI greater than the 90th percentile or an increase in 5 BMI units in patients obese at the start of treatment should prompt more intensive interventions and monitoring.[30] CBT targeted to a healthy lifestyle and a nutritionist consultation can be helpful. There is emerging evidence that metformin can slow weight gain and even effect weight loss. Start at 250 mg daily given with food and gradually titrate over 3 to 4 weeks to minimize gastrointestinal side effects, which usually subside within this time frame.[38]

Patients with elevated fasting blood glucose, dyslipidemia, hyperprolactinemia, and abnormal thyroid-stimulating hormone level should be referred to a specialist. Patients with mild hypertension can be followed weekly, and if blood pressure remains elevated over 2 or more readings, the patient should be referred to a specialist.[39]

Neuroleptic malignant syndrome is a rare but potentially life-threatening complication of antipsychotic treatment that requires referral to an emergency department. It is a type of delirium that often presents with autonomic instability and muscle rigidity, usually after antipsychotic treatment initiation or dose increase. Elevations of creatinine kinase and myoglobinuria are also associated. Diligence for symptoms can facilitate quick treatment that includes discontinuing the antipsychotic and initiating supportive measures.[40]

INTEGRATED CARE FOR ULTRA HIGH-RISK YOUTH AND EARLY PSYCHOSIS IN CHILDREN AND ADOLESCENTS

It is useful to recognize that the treatment of UHR youth or new-onset psychosis in children and adolescents involves multiple modalities implemented in a coordinated fashion by a multidisciplinary treatment team. This approach has become standard practice in many systems of care, including the National

Health Service in the United Kingdom, where all individuals with recent onset of psychosis are entitled to evaluation and treatment by a specialized early psychosis treatment team. Providing this form of integrated care is more challenging in the United States; however, some states, such as Oregon and California, have provided support for the establishment of these systems at the state and county levels, respectively. Future efforts to make such integrated comprehensive care more widely available, particularly for those who are privately insured, will be bolstered by additional mental health services research addressing the efficacy and cost effectiveness of this approach.

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Bipolar Disorder in Adolescence

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PREVALENCE, DIAGNOSIS, COURSE OF ILLNESS

The prevalence of bipolar disorder was approximately 1% in a community sample of 1709 adolescents ages 14 to 17 years.[1] Most youths experienced a depressive episode as the onset mood episode, and the mean age of onset of this first episode was 11.75 years. The National Comorbidity Survey Replication—Adolescent Supplement (NCS-A) surveyed 10,123 adolescents ages 13 to 18 years, along with their parents. The prevalence of bipolar disorder in this community sample was 2.9%.[2]

The diagnosis of bipolar disorder in children and adolescents is based on the same *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, (DSM-5) criteria that are required for an adult diagnosis.[3] The criteria for bipolar I disorder include at least 1 manic episode, which is defined as an elevated, expansive, or irritable mood and increased goal-directed activity or energy lasting at least 1 week during which at least 3 of the following symptoms are present: grandiosity, decreased need for sleep, increased or pressured speech, flight of ideas, distractibility, increased goal-directed activities, and excessive involvement in risky activities. If only an irritable mood is present, at least 4 additional manic symptoms must be present. If the patient requires hospitalization, symptoms may be present less than a week. Bipolar II disorder is a less severe form of bipolar disorder in which symptoms are present at least 4 days per week and do not cause functional impairment.

Bipolar I disorder in youth is a chronic disorder. A 4-year prospective longitudinal study of 86 children and adolescents with bipolar I disorder, mixed or manic,

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showed a 4-year recovery rate of 87% and a remission rate of 64%.[4] An 8-year naturalistic study of 115 youths with bipolar I disorder showed a recovery rate of 87.8% and a relapse rate of 73.3% after recovery during the 8-year follow-up.[5]

The earlier the age of onset of illness, the worse the prognosis. The Course and Outcome of Bipolar Youth (COBY) study followed 413 youths ages 7 to 17 years, diagnosed with bipolar disorder, for 4 years, to assess recovery and relapse rates.[6] Approximately 2.5 years after the index mood episode, 81.5% of the participants had fully recovered, but 62.5% of these had a syndromal recurrence 1.5 years later. Younger age at onset and family history of mood disorders were just 2 of the factors associated with poorer outcomes. Similarly, a retrospective study of adults with bipolar disorder found that those adults with onset of mood symptoms prior to age 13 had a more severe course of illness.[7] Controversy exists among physicians on whether nonepisodic irritability (severe mood dysregulation [SMD]) predicts later diagnosis of bipolar disorder. However, SMD has been shown to be more predictive of unipolar depression than bipolar disorder.[8] The 5th edition of the DSM includes a diagnosis of disruptive mood dysregulation disorder. This diagnosis is characterized by severe recurrent temper outbursts, occurring more than 3 times a week, along with a persistently irritable or angry mood for at least 12 months.[3]

Case Vignette

WS is a 15-year-old boy with a history of attention-deficit/hyperactivity disorder who presents to the clinic with his mother for a diagnostic evaluation. His mother is concerned because WS has been extremely irritable for the last month. He has also been staying up most nights on the computer in his room, often getting only 2 or 3 hours of sleep a night. He is not tired the next day; rather he seems to have an excess of energy. His grades have dropped dramatically over the last month, and he is now failing 3 classes. WS says he has been angry most of the time, and he reports having very little motivation to do schoolwork, instead choosing to spend hours on his computer. He reports feeling much more distracted than usual, especially at school. With his mother out of the room, he admits that he has been staying up all night and chatting with adult women. He says he feels giddy when he engages in his nighttime activities. He says he has thought about stealing his mother's car to drive a few states away to meet one of the women he met online. He speaks very quickly. He denies auditory or visual hallucinations.

WS's mother says his behavior the last month has been out of character for him. She says when he was 12, he saw a therapist briefly for some mild depressive symptoms with irritability, which resolved after a few months. Since then, there are times when he will become slightly irritable and have difficulty sleeping, but they have never lasted longer than a few days or caused him difficulties in other

aspects of his life, such as school. WS has been on a stimulant medication since age 7 for symptoms of hyperactivity, impulsivity, and inattention, and he has been stable on his current dosage for the past 2 years. Family history is significant for bipolar disorder (patient's father), major depressive disorder (patient's mother), and ADHD (1 of the patient's 3 siblings).

This case illustrates several important points:

1. The patient presents with a predominantly irritable mood. It is less common for bipolar disorder to present with classic, episodic euphoria in children and adolescents.[9] Bipolar more frequently presents with mixed or rapid-cycling mood symptoms, commonly including irritability, which can make accurate diagnosis more difficult. However, symptoms of hypersexuality, flight of ideas, and decreased need for sleep make a diagnosis of bipolar disorder more likely.
2. The patient has a history of a depressive episode when he was 12. The index episode in bipolar disorder is most commonly depressive.[10] When a patient presents with depressive symptoms, it is necessary to screen for any symptoms of mania, either current or in the patient's history. The Mood Disorder Questionnaire for Adolescents (MDQ-A), which is completed by a parent, is a useful screening instrument for manic symptoms in adolescents.[11] Even if the patient does not initially present with any manic symptoms, it is important for the physician to continue monitoring for the development of these symptoms, especially when a family history of bipolar disorder exists.
3. The patient's father has bipolar disorder. First-degree relatives of patients with bipolar disorder are at increased risk for a mood disorder. The risk of bipolar disorder in offspring is 4% if one parent has bipolar disorder and 25% if both parents have bipolar disorder.[12] When a patient presents with a family history of bipolar disorder, the physician should be careful to assess for a history of mood symptoms, including symptoms of depression, mania, and hypomania.
4. The patient has a diagnosis of ADHD. It is common for children and adolescents with bipolar disorder to have comorbid ADHD.[13] This can make an accurate diagnosis difficult for the physician because ADHD and bipolar disorder share some symptoms (distractibility, increased activity, and talkativeness are some examples). It is important to remember that bipolar disorder is primarily a mood disorder, and mood symptoms should be significant. Grandiosity and hypersexuality are symptoms that suggest a diagnosis of bipolar disorder versus ADHD. Increased activity is goal directed in mania, and speech is pressured. Additionally, thought processes are not always linear and can be difficult to follow in mania. This should not be the case in a patient with ADHD. The patient in the case described here has evidence of hypersexuality (chatting with women online) and flight of ideas, suggesting a diagnosis of bipolar disorder.

PHARMACOTHERAPY

Physicians generally select an atypical antipsychotic or traditional mood stabilizers such as lithium or divalproex for treatment of youth with bipolar disorder. Five medications are FDA-approved for the acute treatment of bipolar I disorder, manic or mixed, in children and adolescents. Of these, 4 are atypical antipsychotics and 1 is lithium. The physician must decide which of these medications to select first in the treatment of an adolescent with bipolar disorder. The Treatment of Early-Age Mania study (TEAM study) was designed to determine whether an atypical antipsychotic (eg, risperidone), lithium, or divalproex is most effective in the treatment of children and adolescents with bipolar I disorder, manic or mixed.[14] This randomized 8-week trial included 279 participants ages 6 to 15 years. Response rates (Clinical Global Improvement of much or very much improved) were significantly higher for risperidone (68.5%) compared with lithium (35.6%) and divalproex (24.0%). There was no statistically significant difference between the response rates of lithium and divalproex. The findings from this study support the use of an atypical antipsychotic as the initial medication choice for an adolescent with bipolar disorder.

Atypical Antipsychotics

There is much evidence supporting the use of atypical antipsychotics in the acute treatment of adolescents with bipolar disorder. Correll et al conducted a comparative analysis of the efficacy of antipsychotics and mood stabilizers in the treatment of youth with bipolar disorder.[15] Atypical antipsychotics showed a significantly greater improvement as assessed by the Young Mania Rating Scale (YMRS).[16] The effect size was 0.65 for atypical antipsychotics and 0.24 for mood stabilizers.

Aripiprazole, risperidone, and quetiapine are FDA-approved for the treatment of bipolar I disorder, mixed or manic, in youth ages 10 and older, whereas olanzapine is FDA-approved for ages 13 and older. FDA approval of the atypical antipsychotics was based on double-blind, placebo-controlled studies ranging in duration from 3 to 4 weeks.[17–20] In general, response rates (defined as a 50% improvement in manic symptoms) for the atypical antipsychotics are about 50% to 60% in the acute treatment of bipolar disorder in youth.

Ziprasidone and clozapine are not FDA-approved for the treatment of bipolar disorder in youth under age 18 years. One controlled study supported the efficacy of ziprasidone in youth ages 10 to 17 years with bipolar disorder.[21] Clozapine has not been examined in a controlled study. Given its significant side effects and need for blood cell count monitoring, clozapine should only be considered in youth who have failed to respond to other atypical antipsychotics and mood stabilizers.[22]

Dosing

The recommended dosing guidelines for atypical antipsychotics in children and adolescents are outlined in Table 1.

Adverse Events and Monitoring

Adverse events associated with atypical antipsychotics are covered in Pakyurek et al, along with monitoring recommendations.

Traditional Mood Stabilizers

Although traditional mood stabilizers are commonly used to treat bipolar disorder in youth, this use is largely based on efficacy and safety data in adults. The few placebo-controlled studies executed in the pediatric population have not shown results as robust as the atypical antipsychotic studies. Only one traditional mood stabilizer, lithium, has FDA approval for the treatment of bipolar I disorder in adolescents.

Lithium

Lithium is FDA-approved for the acute treatment of bipolar I disorder, mixed or manic, in youth 12 to 17 years old. FDA approval was granted based on evidence of efficacy in adults, not on pediatric studies. In a study funded by the National Institute of Mental Health (NIMH), 154 youths ages 7 to 17 years with a diagnosis of bipolar I disorder, manic or mixed, were treated with lithium, divalproex, or placebo for 8 weeks.[23] Lithium was not found to be significantly superior to placebo. In the previously cited TEAM Study, the response rates were significantly higher in the youth treated with risperidone (68.5%) than those treated with either lithium (35.6%) or divalproex (24%).[14] There was no significant difference between the response rates of lithium or divalproex.

Table 1.
Clinical use of atypical antipsychotics in children and adolescents

Medication	Typical Starting Dosage (mg)	Target Dosage (mg/day)
Clozapine	25 twice daily	200–400
Olanzapine	2.5 twice daily	10–20
Quetiapine	50 twice daily	400–600
Risperidone	0.25 twice daily	1–2
Ziprasidone	20 twice daily	80–120
Aripiprazole	2.5–5.0 at bedtime	10–25

Data from Kowatch RA, DelBello MP. Pharmacotherapy of children and adolescents with bipolar disorder. *Psychiatr Clin North Am*. 2005;28:385–397, with permission from Elsevier.

Divalproex

Despite evidence showing its efficacy with the treatment of bipolar disorder in the adult population, divalproex is not FDA-approved for the treatment of bipolar disorder in children and adolescents. Even so, this medication has historically been used widely in clinical practice for this purpose. Early studies (including chart reviews, open-label studies, and small comparison studies) showed promising results; however, randomized controlled trials have shown mixed results. A double-blind, randomized, placebo-controlled study examined the efficacy of divalproex extended release for bipolar disorder in children and adolescents.[24] In this 4-week multisite study, 150 youths aged 10 to 17 years with a diagnosis of bipolar I disorder, manic or mixed, were treated with either divalproex ER or placebo. Divalproex ER was not superior to placebo on the primary efficacy measure of change in YMRS score from baseline to endpoint.

In the previously cited NIMH study by Kowatch, the response rate in the divalproex group was 56%, which was significantly greater than the response rate in the placebo group.[23]

Three studies compared divalproex with atypical antipsychotics.[14,25,26] In these studies, divalproex was not shown to be superior to the atypical antipsychotics. Response rates for divalproex ranged from about 30% to 50%, compared with 70% to 80% for the atypical antipsychotics.

Carbamazepine

Carbamazepine is not FDA-approved for use in pediatric bipolar disorder, and there are no large controlled studies of its efficacy in this population. In a small comparator study, response rates were 38% in the carbamazepine group compared with 53% and 38% in the divalproex and lithium groups, respectively.[27]

Oxcarbazepine

Oxcarbazepine is not FDA-approved for the treatment of bipolar disorder in children and adolescents. One double-blind, 7-week, randomized, placebo-controlled trial examined the efficacy of oxcarbazepine in the treatment of pediatric bipolar disorder.[28] No significant difference was found between oxcarbazepine and placebo in change in mania ratings from baseline to endpoint.

Topiramate

Topiramate is not FDA-approved for the treatment of bipolar disorder in any age group, though it has been used clinically for this purpose. A pilot double-blind, placebo-controlled study examined the efficacy of topiramate in the treatment of pediatric bipolar disorder.[29] This 4-week, multicenter study was prematurely discontinued after other studies of topiramate failed to show efficacy in adult bipolar patients. Topiramate did not separate from placebo in this study.

Lamotrigine

Lamotrigine is not FDA-approved for the treatment of bipolar disorder in children and adolescents, and there are no large controlled studies of its efficacy in this population. In a small, open-label study of lamotrigine in patients with pediatric bipolar disorder, the efficacy of lamotrigine was examined for the treatment of elevated mood in bipolar disorder.[30] Although the study did demonstrate significant reductions in mania rating scores, almost half the participants did not complete the 12-week trial, and 15 participants developed skin lesions during the trial.

Dosing

The recommended dosing guidelines for the traditional mood stabilizers in children and adolescents are outlined in Table 2.

Adverse Events and Monitoring

Lithium

The narrow therapeutic index of lithium necessitates close monitoring for potential adverse events and signs of toxicity. Early signs of toxicity may include neurologic symptoms such as dysarthria, ataxia, and motor coordination difficulties, and severe toxicity may lead to seizures, coma, or death.[31] Side effects commonly seen with lithium treatment in children and adolescents include hypothyroidism, tremor, polyuria, polydipsia, nausea, acne, and weight gain.[32] Additionally, abdominal pain, sedation, and diarrhea have been reported in

Table 2
Clinical use of mood stabilizers in children and adolescents

Medication	Typical Starting Dosage (mg)	Target Dosage	Therapeutic Serum Level
Carbamazepine	7 mg/kg/day	Based on response and serum level	8–11 μg/L
Lamotrigine	12.5 mg/day	Based on response	N/A
Lithium	25 mg/kg/day (2–3 daily dosages)	30 mg/kg/day (2–3 daily dosages)	0.8–1.2 mEq/L
Oxcarbazepine	150 mg twice daily	20–29 kg (900 mg/day) 30–39 kg (1200 mg/day) >39 kg (1800 mg/day)	N/A
Topiramate	25 mg/day	100–400 mg/day	N/A
Valproic acid, divalproex sodium	20 mg/kg/day (2 daily dosages)	20 mg/kg/day (2–3 daily dosages)	90–120 μg/mL

Data from Kowatch RA, DelBello MP. Pharmacotherapy of children and adolescents with bipolar disorder. *Psychiatr Clin North Am*. 2005;28:385–397, with permission from Elsevier.

the pediatric population. Over time, lithium may cause nephrogenic diabetes insipidus as result of its effects on the distal tubules and antidiuretic hormone. Possible cardiac side effects include benign electrocardiogram (ECG) findings (T-wave flattening) and more serious conduction disturbances, such as sinoatrial block and tachycardia.[31] Younger children may be more sensitive to certain neurologic effects of lithium, including cognitive dulling and headaches.[33] In pregnant female adolescents, there is the additional risk of congenital cardiac malformations, namely, Ebstein anomaly with fetal exposure in the first trimester.[31]

Baseline laboratory studies should include complete blood cell count, thyroid function tests, electrolyte levels, renal function tests, serum calcium level, and a pregnancy test (females). Additionally, it is also recommended that an ECG be obtained at baseline because of potential cardiac conduction disturbances, even in youth without preexisting cardiac disease, and yearly thereafter.[31] Renal function tests should be ordered every 2 to 3 months in the first 6 months of treatment, then every 6 months thereafter. Thyroid functioning should be checked every 6 months throughout the duration of treatment.[33] Lithium serum levels should be obtained with each dosage increase, and then every 3 months after a stable, therapeutic dosage is reached.[31]

Anticonvulsants

Divalproex

Common side effects of divalproex in children and adolescents include weight gain, sedation, nausea, and tremor. Pancreatitis, hepatic toxicity, thrombocytopenia, and hair loss are seen less commonly.[31] Liver function tests and complete blood cell count, including platelets, should be obtained at baseline and every 6 months thereafter. The risk of neural tube defects during pregnancy and a possible association with the development of polycystic ovarian syndrome (PCOS) necessitate caution when using divalproex in female patients. A urine pregnancy test should be obtained at baseline and every 6 months thereafter. Female patients should be monitored for symptoms of PCOS, such as menstrual irregularities, hirsutism, and acne.[33]

Carbamazepine

Carbamazepine induces the metabolism of other drugs as a result of its stimulation of the P450 isoenzyme system, and it may decrease levels of oral contraceptives and other anticonvulsants, such as lamotrigine. Common side effects in children and adolescents include dizziness, ataxia, sedation, nausea, vomiting, and blurred vision.[32] It has also been associated with agranulocytosis, aplastic anemia, hyponatremia, hepatotoxicity, and Stevens-Johnson syndrome.[31] Monitoring recommendations are similar to those for divalproex but also include checking for hyponatremia.

Oxcarbazepine

Common side effects in children and adolescents treated with oxcarbazepine include dizziness, nausea, fatigue, somnolence, and rash. Hyponatremia is also a possible side effect.[28] Oxcarbazepine is a 10-keto analog of carbamazepine, and it seems to have a slightly lower risk of hyponatremia and drug-drug interactions than carbamazepine.[33] Monitoring recommendations are the same as those for carbamazepine.

Topiramate

Topiramate has been associated with weight loss in children and adolescents, making it a potentially beneficial adjunctive treatment to other agents that cause significant weight gain. Other common side effects include appetite suppression and sedation. Additionally, paresthesias, glaucoma, and metabolic acidosis have been reported.[31] Word-finding difficulties have been reported commonly in adults taking topiramate, and this has also been seen in the pediatric population.[32] Monitoring guidelines are similar to those proposed for the other anticonvulsants.

Lamotrigine

Common side effects of lamotrigine in children and adolescents include somnolence, headache, nausea, tremor, and dizziness. Rashes are seen in about 12% of patients. More rarely seen are severe cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. This risk is greater in children and adolescents younger than 16 years, and a slower titration schedule may decrease this risk. The metabolism of lamotrigine is inhibited by valproic acid, and concomitant treatment requires lower doses of lamotrigine.[32] Monitoring guidelines are similar to those proposed for the other anticonvulsants.

Combination Medication Treatment

Because response rates for monotherapy treatment of bipolar disorder in youth are approximately 50% to 60%, some adolescents will require combination medication treatment to effectively treat mania.

Aripiprazole and quetiapine are FDA-approved as adjunctive treatment to valproate and lithium for the treatment of bipolar I disorder, manic or mixed, in adolescents. This approval was based not on an adjunctive treatment study in the youth population but on extrapolation from adult data.

There have been a few studies that examined combination medication treatment and medication augmentation for adolescents with bipolar disorder. These studies show that combination medication may improve response rates from 50% to 85%.

In a 6-week trial, 30 youths aged 12 to 18 years old were treated with divalproex plus placebo or combination divalproex and quetiapine.[34] A significantly greater

reduction in mania rating scores from baseline was found for the combination group versus the divalproex monotherapy group. The most common side effects in both groups were sedation, nausea, headache, and gastrointestinal irritation, with sedation significantly more common in the divalproex plus quetiapine group.

The efficacy of combination treatment with risperidone plus lithium (Li+Risp) or divalproex (DVPX+Risp) was assessed in a 6-month, open-label study of 37 youths ages 5 to 18 years diagnosed with bipolar I disorder, manic or mixed.[35] Participants in both treatment groups experienced significant improvement in mania rating scores from baseline to endpoint, with no significant difference between the 2 groups. The most commonly reported side effects included weight gain, sedation, nausea, increased appetite, and stomach pain, with no significant difference between the 2 groups.

The efficacy of risperidone augmentation in lithium nonresponders was assessed in a 12-month, open-label study of children and adolescents with preschool-onset bipolar disorder, manic or mixed.[36] Risperidone was added to lithium at any time after 8 weeks in participants who did not respond to lithium monotherapy. Among the lithium nonresponders, 85.7% showed significant response to risperidone augmentation.

Medication Treatment Duration

Clinical consensus is that medication should be continued for at least 12 to 24 months after sustained remission of 12 to 24 or more consecutive months.[37] Medication should be tapered slowly over approximately a 3-month period. The physician should monitor the adolescent for signs of recurrence of illness including symptoms of mania or depression. The adolescent's parents should be advised of the symptoms of mania and depression and contact the physician if the adolescent exhibits any of these symptoms.

OTHER TREATMENT OPTIONS

Adjunctive Therapy: Cognitive-Behavioral and Psychoeducational Approaches

Adjunctive psychotherapy may be helpful in addition to pharmacotherapy when managing bipolar disorder in children and adolescents. One proposed therapy is child- and family-focused cognitive-behavioral therapy (CFF-CBT). Objectives include psychoeducation, cognitive restructuring, affect regulation, social skills training, and improvement of communication and coping skills. A pilot study examined the efficacy of this therapy in 26 youths ages 6 to 17 years with bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified.[38] The study showed CFF-CBT administered in group format to be helpful in reducing

manic symptoms and improving participants' psychosocial functioning after treatment.

Another proposed adjunctive therapy for use in this population is multifamily psychoeducational psychotherapy. This therapy focuses on educating family members about the disorder, course of illness, prognosis, medications, and management. This can be presented to individual families or as part of a multifamily workshop. One goal of this therapy is to reduce expressed emotion (EE) in families, because high EE has been associated with higher rates of relapse in patients with mood and psychotic disorders.[39] One randomized controlled trial examined the efficacy of multifamily psychoeducational psychotherapy for mood symptoms in 156 children, 70% of whom had bipolar disorder.[40] Participants assigned to the multifamily psychoeducational psychotherapy plus treatment as usual showed significant improvement in mood severity scores from baseline to endpoint when compared with participants in the wait list control plus treatment as usual group.

SUPPORT GROUPS/OUTSIDE RESOURCES

In addition to these interventions, families may benefit from outside support, and there are many resources available online. Following is a noninclusive list of outside resources physicians may find beneficial for patients' families:

The Balanced Mind Foundation: http://www.thebalancedmind.org

Ryan Licht Sang Bipolar Foundation:
http://www.ryanlichtsangbipolarfoundation.org/

Depression and Bipolar Support Alliance: http://www.dbsalliance.org/

National Alliance on Mental Illness (NAMI): www.nami.org

National Institute of Mental Health (NIMH): http://www.nimh.nih.gov

American Academy of Child and Adolescent Psychiatry, section for families: http://www.aacap.org/cs/forFamilies

Mina K. Dulcan, MD. *Helping Parents, Youth, and Teachers Understand Medications for Behavioral and Emotional Problems: A Resource Book of Medication Information Handouts.* American Psychiatric Publishing; 2007

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Considering Biomedical/CAM Treatments

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INTRODUCTION

An increasing number of parents, physicians, and nonphysician clinicians are using complementary and alternative medicine (CAM) treatments in pursuit of their children's health and well-being. A recent National Health Statistics Report estimated that nearly 12% of children in the United States used CAM therapy in the past 12 months of that year.[1] Of these, the most common use of CAM was in natural products consisting of herbs and dietary supplements. Such a trend has brought forth numerous studies and reviews of the safety and effectiveness of CAM treatments. It is important, therefore, for physicians and families to be aware of the variety of alternative treatments available for children with psychiatric disorders.

The challenge of defining CAM is to encompass all its extensive, variable modalities. The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM treatment as a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. These can include vitamin supplements, dietary restrictions, and manipulative therapy such as acupuncture. In this review, the term *biomedical treatments* is used in exchange for the term *CAM* as reference to integrative treatments that may be translational and provide health and medical benefits. Currently, there are 4 broad areas of focus for biomedical treatment: gastrointestinal abnormalities, immune dysfunctions, detoxification abnormalities, and nutritional deficiencies.

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This article summarizes recent findings on various biomedical treatments with the goal of exposing physicians and patients to the rising use of biomedical/CAM treatments in children with psychiatric disorders. In discussing each biomedical treatment, there will be a brief description of its mechanism and use, followed by a review of the most relevant studies on different psychiatric disorders that seem to benefit from it. The biomedical treatments summarized in this article do not exhaust all those that have been tried but are those for which research evidence exists. Families are eager to use biomedical treatments, whereas many physicians do not feel well informed about the different biomedical treatments that are available. This review highlights the evidence and the prominence of knowing more about the most common biomedical/CAM treatments in use today.

VIGNETTE #1: BEN

Ben is a 6-year-old boy with moderately impairing autism spectrum disorder (ASD) who is receiving applied behavioral analysis (ABA) treatment at school and home and speech and language therapy at school. He has no significant behavioral problems, but does not initiate social interaction with other children, is mildly anxious on occasion but does not "melt down," and is making slow but steady progress in his treatment programs. However, Ben has difficulty falling asleep at night, and his parents consult you to consider what they can do about his sleeping patterns and to see if there are any medications that might alleviate his chronic constipation and help him progress faster in treatment. You suggest the family consider a trial of melatonin starting at 2 to 3 mg and increasing up to 9 to 10 mg if needed 30 to 60 minutes before his bedtime for his initial insomnia. You also suggest adding 1 g of omega-3 per day, and consider adding a high-potency multiple vitamin, and probiotics 2 to 3 times a day. You suggest there are no conventional medications with an indication for the difficulties experienced by Ben at this time, but there are several undergoing clinical trials that may be helpful in the future. If the melatonin is not successful, there are several conventional medications, with some side effects such as daytime sedation and weight gain, that can be considered if necessary for his sleep.

BIOMEDICAL/CAM TREATMENTS

The list of potential biomedical/CAM treatments is long and most have inadequate evidence to judge potential efficacy. For the purpose and length of this article, the biomedical treatments with the most published evidence and efficacy are briefly discussed.

Omega-3 Fatty Acids

Omega-3 fatty acids are a type of polyunsaturated fatty acid (PUFA), long-chain orthomolecules that are essential for brain health and growth. They are nutrients

that primarily function in cell membranes, where they are integrated as phospholipid molecules aiding in synaptic plasticity and neuroprotection.[2]

Omega-3 has been widely studied as a treatment for attention-deficit/hyperactivity disorder (ADHD) since deficiencies in PUFA were found in children with ADHD more than a decade ago.[3] A review in 2007 found that of the 5 double-blind placebo-controlled studies of omega-3 for children with ADHD reported at that time, only 2 saw significance over placebo in behavioral measures.[4] A more recent review from the Cochrane Review compared the efficacy of PUFA with other forms of treatment or placebo and found no significant evidence for improvement in ADHD symptoms, although combined omega-3 and omega-6 supplementation showed some benefit.[5] In a series of double-blind placebo-controlled studies testing the safety and efficacy of omega-3, it was found that phosphatidylserine, a component of the phospholipid, enriched with omega-3 (PS omega-3) may reduce symptoms of ADHD in a subgroup of emotionally and behaviorally dysregulated children.[6] In this study, 200 children with ADHD were given either PS omega-3 or placebo for 15 weeks, with an open-label extension for an additional 15 weeks. The result was a reduction in the Global Restless/Impulsive subscale of Conners' Parent and Teacher Rating Scales (CRS-P), and improvement in the Parent Impact—Emotional (PE) subscale of the Child Health Questionnaire (CHQ). The treatment was safe and well tolerated, but more double-blind randomized controlled studies are needed to confirm efficacy.

Omega-3 treatment is often studied as a potential treatment for autism spectrum disorder. So far, a review by Lofthouse et al identified only 2 published double-blind placebo-controlled trials of omega-3, both without statistical significance.[7] However, the small sample sizes of these studies do not provide enough evidence to dismiss the efficacy of omega-3. For instance, one randomized controlled trial studied 27 children ages 3 to 8 with ASD using 1.3 g/day of omega-3 fatty acids or placebo for 12 weeks.[8] Hyperactivity as measured by the Aberrant Behavior Checklist improved 2.7 points in the omega-3 group compared with 0.3 points in the placebo group.

Although data are scarce, omega-3 has shown potential for treating mania and depression symptoms in children. In an open-label trial in 2007, 20 children ages 6 to 17 with bipolar disorder took omega-3 fatty acids for 8 weeks. Researchers found reductions in the Young Mania Rating Scale in 35% of the subjects.[9] A review in 2007 concluded that omega-3 seems to most benefit mood disorders such as major depressive disorder and bipolar disorder.[4]

One double-blind, placebo-controlled study of omega-3 in children with Tourette syndrome included 33 children who received either omega-3 or olive oil as placebo for 20 weeks. Researchers found that although omega-3 did not significantly reduce mean tic scores on the Yale Global Tic Severity Scale

(YGTSS), more subjects taking the omega-3 were considered responders than placebo.[10]

Although the use of omega-3 for mental disorders is widely explored, the limited sample size in the double-blind, placebo-controlled trials suggests further study is needed to make sound recommendations. If found effective, omega-3 offers a safe, tolerable, and affordable treatment option for psychiatric disorders in children.

_N_-acetylcysteine (NAC)

NAC is an antioxidant and a glutamatergic modulator that inhibits the release of glutamate, the most abundant excitatory neurotransmitter in the brain.[11] Research pointing to the potential efficacy of NAC in treating schizophrenia, bipolar disorder, and obsessive-compulsive disorder has surfaced from the research that suggests redox imbalance and abnormal glutamatergic pathways could be models for certain aspects of these psychiatric disorders.[11] Other studies have found NAC to be effective in treating grooming disorders such as skin-picking and nail-biting,[12] but studies in children have limited exploration.

To date there are only 2 published studies on the effect of NAC on children, 1 on cannabis dependence and the other on autism. The study involving children with autism was a 12-week, double-blind, placebo-controlled randomized trial of NAC.[13] Thirty-three subjects ages 3.2 to 10.7 years were randomized and NAC was initiated at 900 mg daily for 4 weeks, then twice daily for the next 4 weeks, and 3 times daily for 4 weeks thereafter. Compared with placebo, NAC resulted in significant improvements on the ABC irritability subscale ($F = 6.80$; $P < .001$; $d = 0.96$). Given the small sample size, this study will need to be replicated to produce adequate evidence to routinely recommend NAC for the treatment of ASD.

The other double-blind, placebo-controlled trial of NAC was in 116 cannabis-dependent adolescents 15 to 21 years old, who were randomized to an 8-week trial of NAC treatment with weekly cessation counseling. Interestingly, those who were treated with NAC had twice the odds of having negative urine tests for cannabinoid compared with placebo.[14] NAC was also found to be safe and tolerable in this study.

The very limited number of studies on NAC for children with mental disorders motivates future research to evaluate its efficacy as a neuroprotective glutamatergic modulator.

Melatonin

Melatonin is an endogenous neurohormone best known for regulating circadian rhythm. It is released by the pineal gland in response to decreasing levels of light

and peaks in the middle of the night to cause drowsiness. Melatonin is synthesized from serotonin through a series of metabolic pathways starting with L-tryptophan, and abnormalities in these pathways have been reported in insomnia as well as noncircadian disorders such as autism.[15] In addition to having neuroprotective properties, melatonin has antioxidant and antiinflammatory properties as well.[15]

Sleep problems are common in children with ASD. A recent article reported 50% to 80% prevalence of sleep problems in children with ASD, compared with 9% to 50% in age-matched, typically developing children.[16] Given the large percentage of melatonin deficiency that is observed in children with ASD, many studies have investigated melatonin treatment for sleep disturbance in ASD.[16] A meta-analysis by Rossignol & Frye reported 9 studies that found at least 1 study showing abnormality in melatonin levels, 4 studies with correlations between melatonin levels and ASD symptoms, and 5 studies with gene abnormalities associated with decreased melatonin production.[15] Further, of 18 melatonin treatment studies, there were 5 randomized controlled trials in which sleep duration was increased by 44 minutes and sleep onset latency was decreased by 39 minutes, but nighttime awakenings were unchanged. Side effects were minimal to none.

Of the more recent studies, it was found that a 4-week treatment with melatonin following a 1-week baseline period resulted in an increase in the mean total sleep time of 21 minutes, shortened sleep onset latency by 28 minutes, and early sleep onset time by 42 minutes for children with autism and fragile X syndrome.[17]

In 2011, a study of 22 children with ASD examined the effects of 3 months of treatment with up to 10 mg of melatonin. Researchers found that although total sleep time and sleep latency were significantly improved, the number of nighttime awakenings were not.[18] Furthermore, in 2012 researchers administered 1 to 6 mg of melatonin to 24 children with autism for 14 weeks and found that it was safe and effective for improving sleep, behavior, and parental stress.[19] This study was unique in that it identified the most effective doses of melatonin—the doses at which children with ASD responded best—as 1 and 3 mg, but not 6 mg, laying the groundwork for future clinical trials and care.

Another disorder with associated insomnia is ADHD. In one study in 2013, researchers asked parents of 46 children with ADHD to complete the Children's Sleep Habits questionnaire, Conners' Parent Rating scale, and the Pediatric Quality of Life inventory. They found that 87% of children with ADHD had sleep problems, compared with 61% in the control group.[20]

There is a lack of double-blind, placebo-controlled trials of melatonin use in children with ADHD. One randomized trial of the effects of 3 or 6 mg of melatonin on 105 children with ADHD found that it increased total sleep time but had no effect on behavior or cognitive performance.[21]

One case report documents rapid relief of insomnia and mania in a 10-year-old boy with bipolar disorder after 15 months of melatonin treatment[22]; however, no recent published trials of melatonin for children with bipolar disorder exist. Considerable evidence points to abnormal sleep-wake cycles in children with bipolar disorder, thereby proposing sleep disturbances to be a potential target for treating symptoms of the disorder.[22]

Double-blind, placebo-controlled randomized trials of melatonin for children with neurodevelopmental disorders found that it increased total sleep time.[23] However, Gringras et al later found that although melatonin reduced the time it took for children to fall asleep, they woke up earlier as well, pointing out that sleep latency, not total sleep time, may be a more clinically and statistically significant measure of the effect of melatonin.[23]

Small sample sizes, variability in sleep assessments, and lack of follow-up limit the conclusiveness of these studies, but overall melatonin seems to improve sleep and is one of the best-studied biomedical treatments for children with psychiatric disorders. The safety, tolerability, and affordability of melatonin credit its promise as a biomedical treatment.

Methyl B_{12} Injection

Methyl B_{12} is a vital cofactor for the regeneration of methionine from homocysteine by providing methyl groups for the transmethylation and transsulfuration metabolic pathways.[24] Methyl B_{12} deficiency causes reduced synthesis of transsulfuration pathway products, including glutathione and cysteine, which may lead to reduced antioxidant capacity and cytotoxic effects.[24] A recent report of vitamin B_{12} deficiency in clinical practice shows demyelination and neurologic issues,[25] implying the role of B_{12} in psychiatric disorders.

There are very few studies of methyl B_{12} in children. A pilot study in 2004 found that injections of high doses of vitamin B_{12} led to increased levels of glutathione in children with autism. After this finding, a double-blind, placebo-controlled, randomized crossover trial in 2010 found that methyl B_{12} treatment for children with autism led to no significant differences in behavioral tests or glutathione levels between active and placebo groups.[24] However, in the same study, 9 (30%) subjects demonstrated clinically significant improvement on the Clinical Global Impression—Severity (CGI-S) scale and at least 2 additional behavioral measures. More notably, these responders exhibited a significantly increased ratio of reduced glutathione to oxidized glutathione, which may represent decreased oxidative stress and alleviated symptoms in a subgroup of children. The supplement was well tolerated and many families continued the injection more than 2 years after the trial.

One other case report of a 16-year-old boy from Turkey with vitamin B_{12} deficiency and mood disorder symptoms demonstrated reduced psychotic features

after just 1 week of treatment with 500 μg of methyl B_{12} and 0.5 mg of risperidone a day. When vitamin B_{12} levels were raised to normal, risperidone was stopped and injectable vitamin B_{12} was continued for 3 months. A follow-up after 6 months revealed no recurrence of psychiatric symptoms.[26]

Although information on methyl B_{12} and the association between vitamin B_{12} levels and psychiatric disorders such as autism are sparse, randomized control trials are inadequate to fully determine its efficacy.[25] The limited number of side effects of methyl B_{12} in children, if found effective, would allow it to be a safe biomedical treatment.

Digestive Enzymes

Digestive enzymes as a biomedical treatment have been largely focused on children with ASD, who exhibit gastrointestinal disturbances in up to 91% of different study populations.[27] Although there is no published evidence that probiotics or digestive enzymes are effective in treating ASD, their use for treating gastrointestinal (GI) symptoms and their safety profile suggest that they should be considered in alleviating GI problems in ASD.

Abnormal intestinal permeability values among patients with autism is reported at 37% compared with neurotypical subjects at 5%, and GI symptoms, such as constipation and diarrhea, were present in 47% of children with autism.[28] Another study evaluated duodenal biopsies in 199 individuals with autism including children and found that lactase activity was low in 24% of children older than 5 years and 1.7-fold lower for boys than girls in those younger than 5 years old.[29] This suggests that addressing lactase deficiency and intolerance may help with abdominal pain and discomfort that often accompanies aberrant behaviors in ASD.

Only 1 double-blind placebo-controlled crossover trial for enzyme therapy in children has been reported. It involved a 6-month treatment for 43 children with ASD ages 3 to 8 years old.[30] The study did not show clinically significant improvement in behavior as measured by the Global Behaviour Rating Scales,[31] the Rescorla Language Development Survey, and other tests for GI symptoms and sleep quality. However, a small but statistically significant improvement in the food variety score suggests that digestive enzymes could have improved maldigestion and helped reduce food selectivity, which often poses stress and difficulties for children with autism and their families.

Curemark (www.curemark.com) is currently testing the use of pancreatic digestive enzymes to treat psychiatric disorders such as autism and ADHD in children. Their product, Luminenz CM-AT, is an enzyme designed to enhance protein digestion and absorption of essential amino acids. CM-AT has been approved by the US Food and Drug Administration (FDA) for Fast Track, which

expedites the review of new drugs that have the potential to treat serious conditions. Curemark notes that it has reached its targeted enrollment for their CM-AT Phase III trial of a total 170 children with autism ages 3 to 8 years at 18 sites. The Curemark study seems promising but further conclusions await the published results.

Gluten-Free, Casein-Free Diet

The gluten- and casein-free (GFCF) diet has drawn attention since the 1970s, when researchers began to speculate that dietary intervention could affect mental health. The scientific rationale for such dietary interventions was first raised from models relating congenital metabolic conditions, such as phenylketonuria (PKU), and symptoms of psychiatric disorders such as schizophrenia.[32] Since then, there have been numerous associations between neurologic conditions, particularly autism, and immune reaction associated with diet.[33]

Testimonials from parents of children with ASD claim that gluten- and casein-restricted diets are markedly effective, leading to their children acquiring language and showing much improvement in social relatedness.[34] Overall, diet efficacy among children whose parents reported the presence of GI symptoms, food allergy diagnoses, and suspected food sensitivities included greater improvement in ASD behaviors, physiologic symptoms, and social behaviors compared with children whose parents reported none of these symptoms ($P < .05$).

A preliminary double-blind clinical trial has been reported of 15 children with ASD ranging from 2 to 16 years of age whose urinary peptide levels were collected over 12 weeks while they were on the GFCF diet.[34] No statistical significance was observed in the results for urinary peptide levels of gluten ($P = .44$) and casein ($P = .11$) even though several parents reported noticeable improvement. The authors note that these insignificant results may be a result of the small sample size and a heterogeneous group of children. Parents of 9 children decided to keep their children on the GFCF diet even though there was no empirical support for continuing. Another, more recent single-blind randomized controlled trial of gluten- and casein-free diets enrolled 26 children on the diet and 29 controls ages 4 to 10 years old. Researchers found significant improvement on the Autism Diagnostic Observation Schedule (ADOS) and Gilliam Autism Rating Scale (GARS) behavioral assessments. However, the lack of a placebo arm undermines the conclusions and calls for further double-blind, placebo-controlled trials.

The GFCF diet has also been studied in children with ADHD as a result of various reports of an association between celiac disease and psychiatric disorders, including ADHD.[34] One study from Italy enrolled 67 participants ages 7 to 42 on a GFCF diet for at least 6 months and found significant improvement in the assessment of ADHD-like symptoms, deeming that celiac disease should be part

of the ADHD symptom checklist.[34] However, a more recent study refutes such a claim, showing that in 362 patients ages 5 to 15, serum levels of transglutaminase and immunoglobin A and G, used to detect celiac disease, were similar in ADHD and control groups.[35] Thus, the study's authors concluded that neither screening for celiac disease nor implementation of a GFCF diet seems necessary.

The effects of a GFCF diet in children with other psychiatric disorders have not been reported.

As described, there are inconsistencies between parent reports and the results of clinical trials for a GFCF diet in children with autism and ADHD, warranting future research with larger sample size and randomized controlled trials.

Memantine

Memantine, an uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, is a medication approved by the FDA for the treatment of moderate to severe Alzheimer disease.[36] The drug is believed to protect against neuronal degeneration by blocking the NMDA receptor from excessive activation by glutamate.[36] Although memantine is only approved for Alzheimer disease, numerous studies have assessed the off-label use of memantine for the treatment of psychiatric disorders such as depression, schizophrenia, obsessive-compulsive disorder (OCD), and developmental disorders.[36]

A growing body of evidence suggests that ASD may involve abnormal glutamatergic signaling, including altered levels of glutamate, glutamate receptors, and glutamate transporters, any of which may be associated with increased excitotoxic damage mediated through the glutamatergic NMDA receptor.[37] A recent 10-week, double-blind, placebo-controlled trial tested memantine as an adjunctive treatment to risperidone in children with autism.[38] Of the 40 children who were randomized, half were assigned risperidone plus memantine and the other half risperidone plus placebo. The results showed a significant reduction in the subscale for irritability, stereotypic behavior, and hyperactivity on the Aberrant Behavior Checklist—Community.

The safety, tolerability, and effectiveness of memantine have also been evaluated in children with ADHD. A pilot, open-label 8-week trial of memantine (10 or 20 mg/day) in 16 children ages 6 to 12 found no adverse effects and yielded improvements on the ADHD-IV and CGI-S scales, more so in the 20 mg/day group compared with the 10 mg/day group.[39] Other studies for adults with ADHD have shown similar benefits,[40] but further randomized controlled trials for children have yet to be reported.

Glutamatergic abnormalities are also associated with OCD. There is a recent case study of a 15-year-old boy with comorbid OCD and Asperger syndrome

who demonstrated significantly improved symptoms of OCD after adding memantine to an ongoing treatment of fluoxetine.[41] This case report supports previous adult studies on the success of memantine as an add-on to serotonin reuptake inhibitors (SSRIs) for reducing obsessive-compulsive symptoms by up to 50%.[42]

One retrospective, open-label study found that memantine may also benefit pervasive developmental disorder (PDD) symptoms. Treatment at 2.5 to 20 mg/day improved aspects of social withdrawal, inattention, and irritability in 11 out of 18 children and adolescents with PDD.[43]

Additionally, ongoing evaluation of memantine for effectiveness in other psychiatric disorders, such as Tourette syndrome, anxiety, bipolar disorder, and Down syndrome, is underway.[44,45] Memantine's generally well-tolerated response in children promises potential usefulness in a variety of childhood mental disorders.

Oxytocin

Oxytocin is a neuropeptide shown to play an important role in the regulation of the social behaviors. It functions in the central nervous system (CNS) as a neuromodulator to facilitate bonding, trust, and social recognition.[46] In the peripheral nervous system, it serves to promote childbirth and breastfeeding.

Oxytocin has been most aggressively studied in children with ASD. Genetic studies have shown that patients with autism have decreased expression in the part of the gene that controls expression of the oxytocin receptor, as a result of significant increases in methylation in that part of the gene.[47] Therefore, polymorphism in the oxytocin receptor gene is postulated to present risk for autism. One double-blind, placebo-controlled, randomized crossover study of intranasal oxytocin in 16 male participants with autism, ages 12 to 19 years, found improvement in the ability to recognize others' emotions.[46] Another recent pilot study reported that long-term administration (7 months) of intranasal oxytocin is a safe and promising therapy for early adolescents with ASD.[48] Six of the 8 participants showed improved scores on the communication and social interaction domains of the ADOS—Generic. Several additional studies to test whether oxytocin nasal spray can improve social interaction and communication in children with ASD are underway. Oxytocin was well tolerated, and no serious adverse effects were reported.

Chelation

Chelation is a process of detoxifying and removing heavy metals from the blood. According to proponents, chelating agents will rid the body of toxic metals, such as mercury and lead, to prevent suppression of enzymes and myelin degenera-

tion.[49] Oral intake of chelating agents such as DMSA (2,3-dimercaptosuccinic acid), a synthetic organosulfur compound, with periodic elemental analysis of urine from subjects and controls are suggested for successful detoxification.[7]

The benefit of chelation in children has mostly been focused on ASD, based on the unproven theory that higher levels of mercury in the blood of children with ASD cause autistic symptoms.[7] A 2-part, double-blind randomized study involved 65 children with ASD who received 1 round of DMSA for 3 days and, based on which participants had high urinary excretion of toxic metals, were randomly assigned to receive either 6 additional rounds of DMSA or placebo.[49] DMSA was reportedly well tolerated and resulted in high excretion of heavy metals, normalization of glutathione in blood, and improved assessments of ASD symptoms. Subjects demonstrated improvements in language, cognition, and sociability in 5 different assessment tools (Autism Treatment Evaluation Checklist [ATEC], Pervasive Developmental Disorder Behavior Inventory [PDD-BI], Severity of Autism Scale [SAS], the Autism Diagnostic Observation Schedule [ADOS], and the Parent Global Impressions [PGI]). Another more recent study from Germany supported these earlier findings by yielding a slight improvement in the Childhood Autism Rating Scale after DMSA chelation treatment.[50] Further studies with more double-blind, placebo-controlled designs are needed to confirm these results and general safety.

Although reported risks of diarrhea, fatigue, and even seizures and a recent warning from the Institute of Medicine (IOM) make chelation controversial, the process is able to successfully remove excessive heavy metals in children. To date, there are inadequate randomized controlled trials to verify the safety or completely dismiss the benefits of chelation.

Acupuncture

Acupuncture, which involves the use of needles or pressure to specific points on the body, is used widely in traditional Chinese medicine and increasingly within the Western medical paradigm. Scientific research has determined that acupuncture raises beta-endorphins, serotonin, and noradrenaline, which may improve symptoms of depression and anxiety.[51] A review by Jindal, Ge, and Mansky examined 31 journal articles, including 23 randomized controlled trials, and concluded that acupuncture has very low risk in children and is most effective against nausea and vomiting, but too few studies on other symptoms exist to render proper conclusions.[51]

Of the limited number of studies of acupuncture for children, Jindal, Ge, and Mansky reported 1 randomized trial of 40 children ages 5 to 16 with nocturnal enuresis (the involuntary loss of urine in children older than age 5) who took part in a 6-month treatment of either laser acupuncture or desmopressin, a well-established treatment of nocturnal enuresis using a synthetic vasopressin.[51]

Results showed that 65% of children receiving acupuncture treatment were completely dry, compared with 75% in children treated with desmopressin. This study implies that acupuncture could be considered as an alternative, noninvasive therapy for children with nocturnal enuresis.

Acupuncture has been proposed as a possible treatment for ASD symptoms, but its clinical significance and safety are not thoroughly understood or researched. A more recent review reported 10 trials that involved 390 children with ASD ages 3 to 18 years and treatment duration from 4 weeks to 9 months in Hong Kong, mainland China, and Egypt.[52] Of these 10 trials, 2 compared acupuncture with sham acupuncture and found no difference in the primary outcome of core autistic features, although some aspects of the secondary outcomes of communication and linguistic ability, cognitive function, and global functioning were improved. Six trials compared needle acupuncture as a supplement with conventional treatment but could not demonstrate effectiveness of acupuncture for improving core autistic symptoms, though one trial reported that patients in the acupuncture group were slightly more likely to have improvement on the Autism Behavior Checklist post-treatment total scores. There are also reports of adverse effects, including bleeding, crying, irritability, sleep disturbance, and hyperactivity. Overall, the review concluded that current evidence is not adequate to support the use of acupuncture for treatment of ASD. The evidence to date supports the need for randomized controlled trials in children as well as adults with ASD.

Acupuncture has shown mixed results in the treatment of ADHD. One randomized controlled study from China reported improvements in symptoms of ADHD in 180 children.[53] However, a review published a year later of randomized controlled trials comparing acupuncture with placebo found no evidence of benefits for symptoms of ADHD.[54]

Positive effects of acupuncture in anxiety, neurosis, and depression have been reported in randomized controlled trials of adults from China and Germany, but no major trials in children have been reported.[55]

Iron

Iron is a cofactor for many enzymes involved in dopaminergic neurotransmission and plays an important role in cognitive and behavioral development.[56] Iron deficiency is demonstrated to alter oligodendrocyte wrapping for myelination, dopamine metabolism, and neuronal and glial energy metabolism in the hippocampus.[56] In fact, several reports have shown that infants with iron deficiency anemia have persistent cognitive and neurochemical abnormalities.[57] A recently published study found that ferritin levels for children and youths (n = 108) in a community mental clinic was significantly lower than those of the same-aged national sample, confirming previous findings.[58] Furthermore,

Calarge and Ziegler found that iron depletion and deficiency was prevalent in 45% and 14%, respectively, for children and adolescents treated with risperidone, suggesting that iron supplementation may alleviate adverse symptoms associated with antipsychotics.[57]

Children with ASD often have severe food selectivity and restricted diets, which put them at risk for nutritional deficiencies. In the United States and other parts of the world, including the United Kingdom, Canada, and Turkey, low ferritin levels in the blood was found in 7% to 52% of children with ASDs.[59] The study in the United States recruited 222 participants from 5 sites within the Autism Treatment Network, and found iron deficiency in 8% of the population.[59] Given the side effects and risk of toxicity with overdose of iron treatment, more large-scale, carefully designed studies are needed to confirm the prevalence of deficiency and the benefits of supplementation.

Several studies have found serum ferritin levels and symptoms of ADHD to be inversely related, suggesting iron deficiency as a potential target for treatment of ADHD.[60] A double-blind, placebo-controlled, randomized study of 52 children with ADHD who were already receiving psychostimulants found that zinc supplementation increased serum ferritin levels and reduced baseline inattention, hyperactivity/impulsivity, and total ADHD symptom scores.[60] This study was conducted on the grounds that zinc supplementation optimizes response to psychostimulants in children.[60] The results agree with past findings that screening for iron deficiency and optimizing response to psychostimulants help reduce symptoms of ADHD.[61] It has also been shown that children with ADHD and restless leg syndrome or sleep disorders are at a higher risk for having iron deficiency.[61] However, open-label trials have shown both significant and nonsignificant results in measures of ADHD symptoms. Although the link between ADHD symptoms and serum ferritin levels is still unclear, current research is not sufficient to rule out the possibility that iron deficiency may contribute to psychiatric disorders.

These studies highlight a possible association between iron deficiency and psychiatric disorders in children, which warrants further research. Unfortunately, studies relating iron deficiency to other psychiatric disorders in children have not been reported.

Zinc and Copper

Zinc and copper, along with iron, are main metals critical for the functioning of the CNS and synaptic transmission. They stabilize proteins and transcription factors and serve as cofactors for metallochaperones that are key in enzyme catalysis.[62] Abnormal levels or lack of biometals such as zinc and copper have been linked to neurodegenerative disorders affecting not only adults, but also children.[62]

Zinc has been found to be associated with GABA and glutamate regulation, particularly through anxiolytic activity, modulating GABAergic inhibition and seizure susceptibility. Alterations in levels of GABA and GABA receptors in ASD indicate that the GABAergic system responsible for synaptic inhibition may be involved in autism. In a recent study, researchers administered vitamin B_6 and zinc to 79 children with autism, 52 with pervasive developmental disorder not otherwise specified (PDD-NOS), and 21 with Asperger syndrome.[63] After treatment, it was found that individuals with autism and PDD-NOS had significantly lower levels of copper and that awareness, receptive language, focus and attention, and hyperactivity all improved.

Other uses of zinc have been suggested in the treatment of ADHD, as previously mentioned in the Iron Deficiency section.[60] However, a systematic review in 2013 investigated zinc for treatment in children and adolescents with ADHD found that in the only well-controlled and randomized trial, according to the baseline zinc level, using zinc, either alone or in combination with stimulants, did not improve ADHD.[64]

Zinc is regarded as relatively safe and generally well tolerated when taken at recommended doses. Adverse effects such as metallic taste, nausea, vomiting, or diarrhea have been observed.

Magnesium

Magnesium (Mg) has been considered in the treatment of psychiatric disorders throughout the last 3 decades because of its modulatory role in a subtype of the NMDA receptor that is crucial in various cortical functions.[65] Mg is often used in combination with other components, such as vitamin B_6 and zinc. Research has tied Mg deficiency to a number of psychiatric disorders in children, particularly autism.

The link between Mg and ASD began in the 1980s, when Barthelemy et al found that combined treatment of Mg and vitamin B_6 produced a decrease in autistic behaviors in 3 double-blind crossover studies.[65] Since then, a number of studies have supported the initial findings; however, reviews have criticized their methodological shortcomings, including the lack of data for analysis, only slight statistical significance between the treated and placebo groups, and small sample sizes.[65] Interest seems to have waned after this initial surge of studies.

In the more recent years, an extensive study by Rimland and Edelson of 5780 children and adults with autism found that improvement was noted in 47% of subjects receiving B_6 and Mg treatment.[66] However, methodology was once again questioned as the study was conducted online by volunteers, suggesting a high rate of anecdotal and biased data. There is one recent case report, however,

of a 9-year old boy with autism who responded to dimethylglycine and a combined vitamin B_6 and Mg treatment with a 48% reduction in communication and sociability issues.[67] No other current cases have been reported.

The vitamin B_6 and Mg combination has also been tested in children with ADHD. Beginning in 1997, it was found that Mg treatment in 50 hyperactive children led to an increase in Mg content in their hair along with a decrease in hyperactivity.[68] Since then, an open-label study from France reported that in 52 children with low Mg^{2+} levels and hyperactivity, vitamin B_6 and Mg supplementation reduced aggressive behavior and instability in 1 to 6 months.[68] An observational study has been reported of Mg in combination with zinc and omega-3 or omega-6 fatty acids in 810 children with ADHD for 12 weeks.[69] Results showed a considerable reduction in symptoms of ADHD as assessed by the SNAP-IV Teacher and Parent Rating Scale.

Inositol

Inositol is a carbohydrate widely found in nature that serves as a precursor for phosphatidylinositol, the second messenger for a subtype of serotonin receptors.[70] In the mid 1990s, it was reported that inositol treatment was effective in the treatment of depression, panic disorder, and obsessive-compulsive disorder.[70,71] Since then, very few clinical trials of inositol have been conducted.

There is only 1 published controlled double-blind crossover trial of inositol for children with ASD, in which 200 mg/kg per day administered to 9 children with autism demonstrated no benefit.[72] A more recent study has pointed out that lack of inositol in the amygdala may contribute to social impairment in children with ASD.[73] No other studies of inositol treatment in children with other psychiatric disorders have been reported.

St John's Wort

St John's wort, or *Hypericum perforatum*, is an herbal treatment widely used for depression. It is proposed that the mechanism of action of St John's wort is caused by the inhibition of reuptake of certain neurotransmitters. An extensive review from the Cochrane Review analyzed 29 trials including 18 comparisons with placebo and 17 comparisons with synthetic standard antidepressants, and found that available evidence showed St John's wort is superior to placebo in patients with major depression.[74]

Most studies of St John's wort are in adults; however, there is 1 study involving 101 children with depression treated with St John's wort for 4 weeks with an optional extension to 6 weeks.[75] Parents' and physicians' ratings on the effectiveness of treatment as "good" or "excellent" was 72% after 2 weeks, 97% after 4 weeks, and 100% after 6 weeks. However, missing data resulted in a final evalua-

tion with only 76% of the initial sample. Despite such shortcomings, treatment was tolerable, without adverse events, and yielded positive results.

Another randomized controlled trial of St John's wort found no significant differences in ADHD-IV rating scale score from baseline to week 8 between treatment and placebo groups.[76] However, it was found that the St John's wort extract in the study had degraded, so little can be determined based on this study alone.

Although no other studies for children have reported benefit from St John's wort, recent adult studies pointing to reduced symptoms of depression,[41] along with its safety and tolerability, encourage further studies.

CONCLUSION AND FUTURE DIRECTIONS

It is desirable for physicians and families to work together to review promising biomedical treatments that are safe and tolerable, have a rationale for use, and fit with the family's values. So far the biomedical treatments most studied are omega-3, melatonin, and the biometals, including iron, zinc and copper, and Mg. However, other hopeful treatments, such as NAC and methyl B_{12}, lack sufficient clinical trials in children to properly draw conclusions regarding efficacy. The studies mentioned in this review push for more double-blind, randomized, placebo-controlled trials to truly decipher the effectiveness of the variety of biomedical treatments available today. Despite the limited amount of information, it is clear that many parents of children with psychiatric disorders are willing to use and have been using alternative biomedical treatments for years.

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Why Adolescents Use Substances of Abuse

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INTRODUCTION

Adolescents use mind-altering substances for experimentation and for coping with emotions and cognitions that they are unwilling or unable to tolerate.[1] Unfortunately, they tend to use illicit substances in the presence of other adolescents or young adults who often do not have an accurate understanding of the consequences of intoxication. Myths and mistruths are shared and incorporated into ritualized use. Some are harmless, such as the belief that ecstasy (MDMA) causes somatic effects "by making your spinal cord bleed." Others are fatal, such as the belief that opiates are safe in overdose because they are a prescribed medication.

Adolescence is a period of great social and biological changes, and experimentation with behaviors and perception is common. The availability of abusable substances leads many to experiment with substance use. Intoxication provides a momentary change in perception of the internal and external world. In the case of substances of abuse, the experience is also filled with emotional salience. Unfortunately, adolescents discount the risks of substance use and often underestimate the potential sequelae of their pursuit of an altered state. Additionally, they are driven to seek out novelty, which itself can be intoxicating and reinforcing.

The likelihood of developing a substance use disorder (SUD) is inversely proportional to risk aversion in adolescence. Ironically, intoxication tends to decrease risk aversion, making it both a means to its own end and a multiplier of risk exposure liability. An important example of this is the reduction of adolescent safe-sex practices while intoxicated. Other examples of life-altering behaviors facilitated by intoxication include theft, causing bodily harm, sexual imposition, vehicular accidents, and suicide attempts.

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ADOLESCENCE IS A MOVING TARGET

Adolescence is a process of brain maturation, and the high levels of brain plasticity during this period render the brain vulnerable to reinforcing substances, causing an overdevelopment of emotional salience to factors associated with use through an increasingly automatic cognitive process. This is accomplished largely through communication among the nucleus accumbens (the brain's sine qua non of addiction), the orbitofrontal cortex, the amygdala, and the hippocampus. Reinforcing substances trigger an increase of dopamine in the nucleus accumbens, the activation of which causes the sensation of novelty, accompanied by a curious affinity for the same novelty. The nucleus accumbens interfaces with the amygdala, adding a sense of vital importance to the experience and tagging the memories in a way that prioritizes their recollection. This tagging process is thought to be a mechanism behind the development of substance-related cues and resultant craving. The nucleus accumbens also interfaces with the orbitofrontal cortex, an area strongly involved in decision-making, mediated through the excitatory neurotransmitter glutamate. With consistent, repeated exposure to reinforcing substances, these glutamatergic pathways are reinforced, strengthening the signal to the orbitofrontal cortex, making the decision to use increasingly automatic. Understanding the automaticity that develops in the *decision to use* circuit helps the physician to understand a severely addicted youth describing the use of intoxicants without being aware of the decision to do so.

DUALLY DIAGNOSED

Psychiatric comorbidity with SUDs tends to be the rule rather than the exception.[2] An example commonly encountered in substance-using youth is attention-deficit/hyperactivity disorder (ADHD), which is marked by high levels of impulsivity and poor decision-making, a combination that naturally leads to substance experimentation and use. An adolescent with ADHD is more likely to engage in substance use. When untreated, ADHD commonly leads to poor self-esteem and poor academic achievement, which are also risk factors for substance use. When ADHD is effectively treated with psychostimulants, the increased risk of problematic substance use caused by ADHD decreases.[3]

RISK FACTORS

Factors that increase the risk of developing an SUD are both genetic and environmental. A family history of SUDs can include a genetic vulnerability and inappropriate modeling. To date, addictions to most abused substances have a 40% to 55% penetration rate into subsequent generations. Parenting styles that include significant intoxication around children or openly suggests substance use as a way to cope with adversity and pain add to the burden.

Developing a mental illness during adolescence increases the risk of experimentation and self-medication. Personal traits associated with substance use include inattention, impulsivity, negative affective states, and emotional reactivity. Temperament qualities associated with substance use include aggression, sensation seeking, low harm avoidance, an inability to delay gratification, low achievement, and a lack of religiosity.[4] Adverse childhood events, including physical and sexual abuse, violence, being bullied or victimized, or serious illness increase the risk of problematic substance use. Parental discord is highly disconcerting to adolescents and children and increases the risk of substance use.

Low academic performance can result in social isolation and low self-esteem. In a national survey of high school students in the United States with a D or lower grade point average, 52% had used tobacco, alcohol, or other drugs, whereas 56% of teens with an A average had never tried any of these substances.[1] Whether low before substance use begins or low as a result of substance use, as academic effort is deprioritized, the risk of abusing substances is increased. Likewise, a teen who works so much that school becomes a hindrance to maintaining employment is at risk for substance use.

Involvement with the criminal justice system is a risk factor for substance use equal to dropping out of high school. Growing up as a sexual minority (eg, lesbian, gay, bisexual, or transgender) in a community that is intolerant of alternatives to heterosexuality increases the risk of substance use. Although organized athletic involvement is protective against most substance use, it actually increases the risk of using smokeless tobacco, alcohol, and anabolic steroids. Additional risk factors for substance use include an absence of normative peers, pro-drug social norms, and relaxed enforcement of laws and policies.

PROTECTIVE FACTORS

Just as risk factors exist for the development of SUDs, so do protective factors. Chief among the protective factors against teen substance use is engagement by a parent or parental figure. The research on teen substance use by the National Center on Addiction and Substance Abuse (CASA) demonstrates that 80% of adolescents are influenced by their parent's concerns and views about substance use.[1] Parental disapproval decreases the likelihood of teen substance use. Parents can engage their teen by monitoring their activities and social contacts. Teens who perceive that they are not being closely monitored are more likely to drink alcohol or use cannabis. Engaging in pro-social activities reduces the risk of substance use. Aspiring to an academic or career goal, participating in clubs, and being involved in a religious community are examples of pro-social activities that reduce the risk of substance use. Athletics involvement actually increases the risk of using smokeless tobacco, alcohol, and anabolic steroids and decreases the risk of using other substances.[1]

WHICH ONE IS THE GATEWAY?

Kandel's 1975 paper introducing the gateway theory of drug addiction illustrated the same series of events that studies have continued to show: Adolescent substance use begins with nicotine and alcohol.[5] In the 1970s neither of these socially sanctioned substances were considered "drugs," despite being referred to as such in the original article. They are the most common first 2 steps in the gateway theory of addiction. Nicotine and alcohol use increase the likelihood of using cannabis. Cannabis is the second gateway, and earlier use of cannabis does increase the likelihood of using any other illicit substance.[6,7]

SUBSTANCES USED BY ADOLESCENTS

Nicotine

Nicotine is the prototypical drug for the study of addictive properties. It produces short-lived, reinforcing experiential improvements in cognition and focus. Because its effects are brief and reinforcing, it is used with frequent dosing intervals. The adolescent brain is highly susceptible to the reinforcing effects of nicotine. Nicotine is so reinforcing that during 4 years of observation, 40% of teens who tried nicotine once were using it daily 4 years later.[8] Interestingly, teen nicotine use is a marker for reacting more severely when under stress.[9] Additionally, teen smokers have higher levels of novelty-seeking and they have more difficulty waiting for a reward, even when waiting means a greater reward.[10]

Routes of Administration. Nicotine is most commonly consumed by using tobacco. Tobacco is smoked as cigarettes, chewed as oral tobacco, or inhaled as snuff. Nicotine is also available in nontobacco forms such as lozenges, gum, transdermal preparations, and inhalant vapors.

Safety. In overdose, nicotine can cause cardiotoxicity. In lower dosages, nicotine does not cause significant morbidity.

Treatment. Nicotine replacement therapy shows benefit in some teens but adds no benefit if combined with cognitive behavioral therapy (CBT).[11] Bupropion may help with early symptoms of nicotine abstinence. Contingency management (CM)—rewarding the meeting of treatment goals with prizes—is an effective nonpharmacologic intervention for smoking cessation.[12] CM adds to the effectiveness of bupropion.[13] Interestingly, although not commonly practiced, aversion therapy can decrease adolescent tobacco use. One form involves the youth delivering an electrical shock to himself or herself every time a cigarette is used, using a faradic device. A second method involves adolescents smoking consecutive cigarettes one after another until they vomit.

Alcohol

Alcohol is commonly found in many parts of the world, making it the second most widely used substance globally. It acts throughout the brain and at a variety of receptor types, a property that differentiates it from many substances of abuse. Alcohol's intoxicating effects come largely from acting as an agonist of GABAa and acetylcholine receptors. Alcohol itself is reinforcing, because of its effect on mu-opioid receptor input into the nucleus accumbens. Because of its disinhibiting effects, alcohol use in adolescence is commonly paired with the pursuit of other reinforcing, hedonic, and risky activities. Its use also habituates the user to the effects of acute intoxication. Using alcohol in the company of other teens normalizes its use as a leisurely pursuit. In the event that no serious repercussions result, teens may learn that intoxication and illegal activity (where drinking is illegal for minors) are acceptable. Unfortunately, by binding at the GABAa receptor, alcohol is an effective anxiolytic. For this reason many teens consume alcohol to avoid anxiety.[14,15] Not surprisingly, a teen's age of first drink predicts allostatic (stress) load later in life.[16]

Routes of Administration. Alcohol is found in a variety of beverage forms, including beer, wine, and liquor. Additionally, many products contain varying concentrations of ethyl alcohol. Examples include hand sanitizer, mouthwash, and liquid fabric softener. These nonbeverage forms of alcohol can be abused by opportunistic youth.

Safety. Alcohol is neurotoxic. It decreases respiratory drive with acute intoxication, making it dangerous in overdose, especially when mixed with other respiratory depressants. Intoxication in youth is associated with injuries, including fatal motor vehicle accidents.

Treatment. Both disulfiram (alcohol sensitization) and naltrexone (craving reduction) therapies have been shown to benefit adolescents with problematic drinking.[17] Screening, brief intervention, and referral to treatment (SBIRT; http://www.attcnetwork.org/regcenters/index_nfa_sbirt.asp) is an effective treatment plan for teens who misuse alcohol.

Cannabis

Cannabis seems to be the most widely available "drug" (ie, nonalcohol intoxicant) in many parts of the world. Delta-9-tetrahydrocannabinol (THC) gives cannabis its intoxicating effects. THC receptors are found throughout the cerebral hemispheres. THC does not cause respiratory depression because of the absence of THC receptors in the midbrain. The cannabinoid system is complex and is only beginning to be understood. THC is best thought of as a hallucinogen. Illusions (a misperception of external stimuli) are more common than hal-

lucinations (a perception not based on external stimuli) with cannabis use. However, hallucinations can occur and are a prominent feature in the development of cannabis-influenced schizophrenia. Cannabis use in adolescence increases the likelihood of developing symptoms of schizophrenia. Cannabis use predicts a poorer prognosis regarding treatment outcome for schizophrenia. Early age of cannabis use is associated with moving on to other illicit substance use.[18] Cannabis use causes memory deficits in adolescents.[19]

Routes of Administration. Cannabis is most often smoked or, increasingly, vaporized (heated to a temperature that causes the THC to aerosolize but below the temperature that causes the plant material to burn). In the hashish form (THC resin harvested from plant material), it does not burn easily and is often mixed with tobacco in cigarettes. THC is fat soluble and can easily be combined with butter and cooking oils used in baking. Baking with cannabis allows for consumption of THC without risking exposure to reactive hydrocarbons. When aerosolized or smoked, a high concentration of THC is delivered to the bloodstream over a brief period through gas exchange in the lungs. However, when eaten, THC is slowly absorbed from the gastrointestinal tract, resulting in a slower buildup of THC concentrations in the bloodstream.

Safety. THC does not seem to be neurotoxic; it dysregulates serotonin, dopamine, and acetylcholine systems. Psychosis associated with cannabis use places the user at significant risk of injury and assault from others. Cannabis is commonly smoked; its reactive hydrocarbons are as damaging to lung parenchyma and arteriolar intima as those generated by pyrrolizine tobacco. Cannabis (the plant) is a mélange of substances, and cannabidiol (CB) has very different effects from THC. CB receptors are located in the peripheral (non–central nervous system) tissues. CB is not intoxicating. It raises the seizure threshold (is anti-epileptogenic) and decreases inflammation in humans and decreases atherosclerosis in mice.[20]

Treatment. No established pharmacologic treatments exist for cannabis use disorders. The Cannabis Youth Treatment study demonstrated the low cost and high effectiveness of motivational enhancement therapy followed by 5 cognitive behavioral therapy sessions or of employing the adolescent community reinforcement approach for 12 to 14 weeks.[21] A single screening and a brief intervention, giving feedback on cannabis use, in the emergency department doubled the rates of abstinence 12 months later.[22]

Inhalants

Intoxicating inhalants are found in many common household products. The ease of obtaining inhalant intoxicants increases their liability for abuse. Various types of inhalants are used by adolescents. Solvents, paints, and glues commonly contain toluene or benzene, which act at acetylcholine and GABA receptors, resulting in a stuporous intoxication. The mechanism of action for nitrous

oxide's intoxicating effects is poorly understood. Acute intoxication results in a short-lived and intense psychedelic experience. Petroleum products cause anticholinergic toxicity. Large doses of inhalants commonly lead to loss of consciousness, significantly increasing the risk of anoxic brain injuries, accidents, and assault.

Routes of Administration. Inhalants are consumed through the respiratory system, a process referred to as "huffing." They are commonly housed in a container designed to maximize the amount of intoxicating substance delivered. Solvents are commonly absorbed into rags that are placed in or over the mouth. Spray paint or adhesives are commonly applied to the inside of a bag that is then placed over the nose and mouth. Nitrous oxide is commonly placed in balloons and then inhaled. It is also found as a propellant in cans of computer keyboard cleaner and whipped cream cans.

Safety. Toluene and benzene are neurotoxic.[23] Long-term exposure leads to T-lymphocyte infiltration along the brain's white matter tracts and cerebellum. Loss of hearing, sight, taste, and balance ensue with prolonged exposure. Extended nitrous oxide abuse inhibits absorption of vitamin B_{12} from the diet through oxidative inactivation, leading to the development of peripheral neuropathies. "Huffing" leaded gasoline/petrol can cause lead poisoning. Inhalants cause significant intoxication, increasing the risk of accident or injury.

Treatment. No pharmacologic treatments exist for inhalant use disorders. Nonpharmacologic treatments include motivational interviewing (MI) and CBT.

Opioids

Adolescent opioid use is becoming a significant problem, fueled by drug availability and the misperception of safety by teenage naïveté. Studies in the United States have repeatedly shown that youth get most experimental/illicit opioids for free from friends or relatives.[1] A commonly believed mistruth among teens is that opioid analgesics are medicines and therefore are not dangerous in overdose. Most of the intoxicating and reinforcing effects are caused by opioids binding to the mu-opioid receptor. Mu-opioid receptors are found in the nucleus accumbens and amygdala, rendering opioids incredibly reinforcing.

Route of Administration. Opiate analgesics are commonly swallowed orally. They can also be crushed into a powder that is either snorted or dissolved in water and injected. Heroin can be smoked, snorted, or injected. Many teens find the idea of snorting or smoking heroin more palatable than injecting it.

Safety. Opioids are lethal at high doses, causing depressed respiratory drive. Intravenous use of opioids is associated with the transmission of infectious diseases, thromboembolic injury, and vegetations on cardiac valves.

Treatment. As with adults, medication-assisted therapy results in less illicit opioid use and a lower overdose rate.[24] Long-term studies support the use of both buprenorphine and methadone in adolescents.[25] In clinical studies, 64% of opioid-dependent youth who were prescribed medication-assisted therapy progressed in their recovery as long as the opioid replacement medication was taken. Relapse rates doubled once the replacement opioid was stopped.[26]

Stimulants

Adolescent stimulant use is most problematic when it involves cocaine or amphetamines, especially methamphetamine and methylenedioxymethamphetamine (MDMA, ecstasy). Stimulant intoxication tends to increase impulsivity and risk-taking behaviors. There is a spectrum of stimulant potency. Methamphetamine and cocaine are extremely potent and result in large amounts of norepinephrine and dopamine availability in the synapse. Other amphetamines are also potent but less so than methamphetamine. Methylphenidate is a nonamphetamine stimulant whose potency is less than amphetamines.

Route of Administration. Cocaine and methamphetamine can be insufflated as fine powders, pyrolyzed as base salts, or injected parenterally. Many amphetamines are available as pharmaceutical-grade tablets and capsules that can be taken orally.

Safety. Stimulants pose many risks to the adolescent user. Cocaine is cardiotoxic and becomes even more so in the form of ethyl cocaine, which results from using cocaine and alcohol together. Methamphetamine is neurotoxic, causing significant long-term cognitive deficits and increasing the likelihood of experiencing psychosis later in life. MDMA seems to be neurotoxic, and it temporarily renders serotonin receptors inaccessible. Hyperthermia and seizures are significant concerns with acute MDMA intoxication, particularly given the association of using MDMA while dancing in closed spaces at raves.

Treatment. No pharmacotherapies consistently show efficacy for stimulant dependence. Stimulant replacement therapies look promising and may represent converting illicit self-medication of ADHD to legitimate treatment. A novel cocaine vaccine shows promise in clinical trials.[27] Given as a series of boosters rather than a single-dose vaccine, the serum is flooded with anticocaine antibodies that opsonize any cocaine introduced to the bloodstream, preventing it from crossing the blood-brain barrier.

CONSEQUENCES OF ADOLESCENT SUBSTANCE USE

Sadly, a number of unfortunate consequences accompany adolescent substance use. Teens are often risk takers at baseline, and those risk-taking behaviors increase with intoxication. Many teens combine intoxication with sexual activity. Twenty percent of adolescents endorse pairing substance use with sexual activity. While intoxicated, teens are more likely to use the withdrawal method and less likely to

use a barrier method, rendering them vulnerable to sexually transmitted diseases and pregnancy.[28] Intoxication increases the risk of accident and injury, the leading causes of death for adolescents. Even with equal increases in blood alcohol concentration, intoxicated teens are more likely than adults to be involved in a motor vehicle accident. Substance use is also associated with an increased risk of premature death from homicide or suicide. Significant injury can result from fighting, which is more likely to occur when intoxicated. Prohibitive laws make most adolescent substance use illegal, and engaging in it increases the risk of involvement with the criminal justice system. Intoxication increases a teen's vulnerability to physical or sexual assault. Early substance use increases the risk of developing an addiction. Initiating substance use during adolescence increases the risk of developing an SUD compared with initiating as an adult. Developing an addiction has significant consequences for academic and career trajectories. Problematic use of many substances causes end-organ damage and serious illness.

MOTIVATIONAL INTERVIEWING

Many well-studied, robust nonpharmacologic treatments for adolescent substance use disorders exist. Motivational Interviewing (MI) is a patient-centered, directive approach to eliciting behavioral change.[29] MI respects patient autonomy and approaches sensitive subjects in a nonjudgmental fashion. This "caring and curious" approach engenders trust. By not raising the patient's defenses, MI elicits honesty and accuracy. In this way it is as much an *interviewing* method as it is a *treatment* method. When implemented therapeutically, information gathered in the interview is used to elicit verbal statements relating to change by pairing the patient's reasons to make the change with his or her reasons to not make a change. MI is the gold standard therapeutic approach to the treatment of SUDs.

ADOLESCENT COMMUNITY REINFORCEMENT APPROACH

A slightly more involved, evidence-based application of MI is the adolescent community reinforcement approach (ACRA). ACRA approaches the adolescent with the nonjudgmental, autonomy-respecting "spirit" of MI. The interview in ACRA includes a functional analysis of substance use (Table 1). The functional analysis identifies internal and external triggers, as well as short- and long-term consequences. Trigger identification provides targets for relapse prevention. Pairing short-term *positive* consequences with long-term *negative* consequences develops discrepancies that tend to favor not using.

Pro-social behavior is heavily emphasized in ACRA. Pro-social behaviors are those that are culturally sanctioned, healthy, and performed when not intoxicated. This ranges from folding laundry to going to a play, to joining a sports team, to helping an elderly community member. Pro-social behavior is consistently reinforced because it is not compatible with substance use. The emphasis on pro-social behaviors reinforces healthy activities as "normal."

Table 1
Contents of a functional analysis of substance use

External triggers	Where, when, and with whom do you use?
Internal triggers	What are you feeling or thinking before and after using?
Behaviors	What and how much do you use?
Short-term *positive* consequences	What do you like about it?
Long-term *negative* consequences	What problems does it cause in school, with parents, emotionally, legally, etc.?

From Godley SH, Meyers RJ, Smith JE, et al. *The Adolescent Community Reinforcement Approach for Adolescent Cannabis Users, Cannabis Youth Treatment (CYT) Series, Volume 4.* DHHS Pub. No. (SMA) 07-3864. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2001, reprinted 2002, 2003, and 2007.

In ACRA, goals of treatment are defined by the youth. This engenders a sense of ownership of the treatment. The physician helps to maintain focus on realistic, time-bound goals. These parameters make measurement of progress toward any given goal possible. ACRA emphasizes the principles of positive psychology in helping to define goals. Goals that are stated negatively often lack a measurable variable and are also dissuasive by nature. For example: "I don't want to go back to jail" can be rephrased by the physician as "I want to keep my freedom by not getting arrested or violating probation." By gently nudging the goal in the direction of pro-social, safe, and healthy behavioral change, the physician is strategically positioning the teen for success. Progress is measured over time and used as a discussion point with the teen, celebrating positive change.

Both MI and ACRA reinforce personal responsibility for teen choices and behaviors. They also celebrate pro-social choices and behaviors. This is one way to engender trust, because teens with SUDs commonly live in a social environment that rarely celebrates them.

Drug testing, an important element of any treatment of SUDs, including ACRA, offers the chance to highlight the results of personal choices. Described as a test to *prove that you are doing what you say you are doing*, an alliance is offered. Allied in the service of the treatment goals, resistance is avoided between the teen and the provider. Discussing the results of the drug test with the teen is vital to contextualizing his or her choices. ACRA emphasizes performing a functional analysis of any relapses to substance use. A behavioral chain of events that led up to the relapse can identify triggers. Reviewing alternatives to substance use helps the teen to learn from the experience (Figure 1).

One way that ACRA differs from other interventions is its emphasis on improving communication. ACRA emphasizes 3 rules for communication (Table 2). ACRA communication supports empathy, taking personal responsibility, and offering to help. This method of communication is mature and effective and can be learned. Many teens learn that they are able to navigate relationships more easily and get

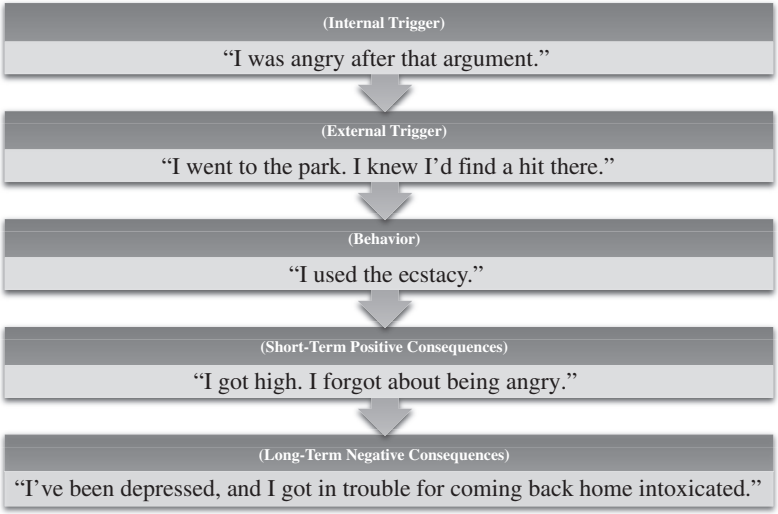

Fig 1. Behavioral Chain of Events. From Godley SH, Meyers RJ, Smith JE, et al. *The Adolescent Community Reinforcement Approach for Adolescent Cannabis Users, Cannabis Youth Treatment (CYT) Series, Volume 4*. DHHS Pub. No. (SMA) 07-3864. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2001, reprinted 2002, 2003, and 2007.

Table 2
Communication Rules in ACRA

Give an understanding statement	"I realize that you wanted me to clean my room today."
Take partial responsibility	"I didn't do my part, and that is disappointing to you."
Offer to help	"If I take 5 minutes to quickly remove the biggest part of the mess, can I go to a movie with my friends and clean it all up when I get back?"

From Godley SH, Meyers RJ, Smith JE, et al. *The Adolescent Community Reinforcement Approach for Adolescent Cannabis Users, Cannabis Youth Treatment (CYT) Series, Volume 4.* DHHS Pub. No. (SMA) 07-3864. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2001, reprinted 2002, 2003, and 2007.

their needs met more accurately. At times, the adolescent's parent can benefit greatly from also being taught ACRA-consistent communication. When the teen and the adult both accept responsibility and offer to help, conflict can be avoided.

ACRA also facilitates communication about important areas of teen life by measuring "happiness." With the use of a happiness scale (Table 3), the teen can communicate satisfaction and dissatisfaction through a rating scale for 16 items. The ACRA happiness scale is a 10-point Likert scale ranging from completely unhappy (0) to completely happy (10). The lowest scoring items (ie, most dissatisfied with) can be prioritized as targets of clinical focus.

Table 3
Components of the happiness scale used in the Cannabis Youth Treatment Study

Marijuana use/nonuse	
Alcohol use/nonuse	0 1 2 3 4 5 6 7 8 9 10
Other drug use/nonuse	0 1 2 3 4 5 6 7 8 9 10
Relationship with boyfriend or girlfriend	0 1 2 3 4 5 6 7 8 9 10
Relationships with friends	0 1 2 3 4 5 6 7 8 9 10
Relationships with parents or caregivers	0 1 2 3 4 5 6 7 8 9 10
School	0 1 2 3 4 5 6 7 8 9 10
Social activities	0 1 2 3 4 5 6 7 8 9 10
Recreational activities	0 1 2 3 4 5 6 7 8 9 10
Personal habits (eg, getting up in the morning, being on time, finishing tasks)	0 1 2 3 4 5 6 7 8 9 10
Legal issues	0 1 2 3 4 5 6 7 8 9 10
Money management	0 1 2 3 4 5 6 7 8 9 10
Emotional life (feelings)	0 1 2 3 4 5 6 7 8 9 10
Communication	0 1 2 3 4 5 6 7 8 9 10
General happiness	0 1 2 3 4 5 6 7 8 9 10
Other	0 1 2 3 4 5 6 7 8 9 10

From Godley SH, Meyers RJ, Smith JE, et al. *The Adolescent Community Reinforcement Approach for Adolescent Cannabis Users, Cannabis Youth Treatment (CYT) Series, Volume 4.* DHHS Pub. No. (SMA) 07-3864. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 2001, reprinted 2002, 2003, and 2007.

SUMMARY

In summary, adolescent substance use is associated with a variety of risks. Using a nonjudgmental and collaborative approach to treating adolescent substance users can yield positive results. Motivational interviewing and the adolescent community reinforcement approach are evidence-based, nonpharmacologic treatments for teens with substance use disorders.

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