Report of the Working Group on Psychotropic Medications for Children and Adolescents:

Psychopharmacological, Psychosocial, and Combined Interventions for Childhood Disorders: Evidence Base, Contextual Factors, and Future Directions

American Psychological Association
750 First Street, NE
Washington, DC 20002

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Working Group on Psychotropic Medications for Children and Adolescents

Members

Ronald T. Brown, PhD, ABPP, Chair

Temple University

David Antonuccio, PhD, ABPP

University of Nevada School of Medicine

George J. DuPaul, PhD

Lehigh University

Mary Fristad, PhD, ABPP

Ohio State University

Cheryl A. King, PhD, ABPP

University of Michigan

Laurel K. Leslie, MD, MPH

Children's Hospital of San Diego

William E. Pelham Jr., PhD

University at Buffalo, The State University of New York

John Piacentini, PhD, ABPP

University of California, Los Angeles

Benedetto Vitiello, MD

National Institute of Mental Health

APA Staff

Children, Youth, and Families Office

Mary Campbell, Director

Gabriele McCormick

Efua Andoh

Report of the Working Group on Psychoactive Medications for Children and Adolescents. Psychopharmacological, psychosocial, and combined interventions for childhood disorders: Evidence base, contextual factors, and future directions

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Preface

The Report of the APA Working Group on Psychotropic Medications for Children and Adolescents was completed over a two-year period—a time of rapid changes in the field of child and adolescent mental health. It has been a particularly challenging time for mental health care providers and caregivers as they struggle in their quest to determine the appropriate treatments for children and adolescents. The volatile nature of developments surrounding various pharmaceuticals, resulting in advisories and black box warnings, has complicated their decision-making process. Against this backdrop, the American Psychological Association commissioned this working group and charged it with reviewing the literature and preparing a comprehensive report on the current state of knowledge concerning the effective use, sequencing, and integration of psychotropic medications and psychosocial interventions for children and adolescents. This review includes a comparative examination of the risk–benefit ratio of psychosocial and pharmacological treatments and the range of child and adolescent psychopharmacology, including the appropriateness of medication practice.

Clearly, the challenge for the working group has been the rapid and constant change of research in this field. While we have made every attempt to include the most recent data, we fully acknowledge the burgeoning nature of literature regarding psychopharmacological and psychosocial treatment for children and adolescents. We believe that this report represents an important snapshot in time. A compendium such as this provides a starting point in understanding the practice and science of pediatric psychopharmacology within the context of psychosocial approaches to treatment and in addressing important questions critical to the psychological well-being of children, adolescents, and their families. We do not present this report as the definitive word on the subject but rather as a basic framework for future

developments as mental health care providers and families strive to enhance the quality of life for children and adolescents.

Finally, this report could not have been accomplished without the unwavering support and efforts of Gabriele McCormick. Her editing of the entire document and assistance in writing and rewriting the document are most appreciated by the entire working group.

Ronald T. Brown, PhD

Chair

APA Working Group on Psychotropic Medications for Children and Adolescents

Executive Summary

There has been an increased recognition of the prevalence and substantial morbidity associated with child and adolescent mental disorders. Estimates suggest that up to 15% of children and adolescents suffer from a mental disorder of sufficient severity to cause some level of functional impairment (Roberts, Atkinson, & Rosenblatt, 1998; Shaffer, Fisher, Dulcan, & Davies, 1996). Of concern are data indicating that only one in five of these children receive services provided by appropriately trained mental health professionals (Burns et al., 1995; Centers for Disease Control, 2004; U.S. Department of Health and Human Services, 1999). For many of these interventions, the short-term efficacy for decreasing symptoms is fairly well demonstrated. Evidence supporting the acute impact of treatment on daily life functioning and the long-term impact on both symptoms and other functional outcomes is less well documented.

Given a recent increase in the number of efficacy studies of psychosocial, psychopharmacological, and combined interventions for mental health disorders in youth, including several recent clinical trials sponsored by the National Institutes of Health (NIH) (Vitiello, 2006), and growing public recognition of the existence of these disorders, the APA Working Group on Psychotropic Medications for Children and Adolescents was charged with reviewing the literature and preparing a comprehensive report on the current state of knowledge concerning the effective use, sequencing, and integration of psychotropic medications and psychosocial interventions for children and adolescents. In preparing its report, the working group reviewed the existing literature in peer-reviewed journals (included as part of MEDLINE and PsycINFO), as well as Food and Drug Administration (FDA) data concerning safety. For the psychological disorders most prevalent in children and adolescents, the various psychosocial, psychotropic, and combination treatments were reviewed, including the effect of each therapy, the strength of evidence for its efficacy, and the limitations and side effects of each treatment in

the short- and the long-term. An Efficacy Summary Table for treatments targeting each type of child psychopathology appears at the end of each section.

Disorders included in the report are attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), Tourette and tic disorder, obsessive–compulsive disorder (OCD), anxiety disorders, depression and suicidality, bipolar disorder, schizophrenia spectrum disorder, autism spectrum disorder, and elimination disorders. Information regarding specific psychosocial, psychopharmalogical, and combined treatments for each disorder can be found in the main report.

Safety

Especially salient to this review are issues of safety, particularly with respect to psychotropic medications in the pediatric population. Within childhood populations, there are vast developmental differences that influence physiological, cognitive, behavioral, and affective functioning. The unique issues in child and adolescent psychopharmacology must be considered when prescribing and monitoring medication effects at home and at school. The acceptability of the risk–benefit profile for any intervention involves value judgments as to the cost of harm-related and psychiatric-related adverse events. Recent safety concerns about antidepressants in the pediatric population illustrate several of the ethical issues related to clinical research and the dissemination of findings. For many other psychotropic agents, issues of safety have not been explored, particularly for long-term usage.

Diversity

Issues of diversity, including gender, race/ethnicity, sexual orientation, physical disability, socioeconomic status, culture, and religious preference may moderate response to treatment and influence treatment choice and adherence. There is, however, a paucity of data concerning these possible moderators. Where there are published data with regard to treatment efficacy,

the working group has taken care to review these studies. Further research examining treatment effects and outcomes by diversity variables is necessary.

Conclusions

Despite recent advances in treatment research, significant knowledge gaps remain. The evidence base for treatment efficacy is somewhat uneven across disorders, with some of the most severe mental health conditions of childhood, including bipolar disorder and schizophrenia, receiving proportionally less attention from treatment researchers. Most of the evidence for efficacy is limited to acute symptomatic improvement, with only limited attention paid to functional outcomes, long-term durability, and safety of treatments. Few studies have been conducted in practice settings, and little is known about the therapeutic benefits of intervention under usual, or real-life, conditions. The benefits of some behavioral treatments have been well documented through numerous single-subject design studies and group crossover designs for some low-prevalence disorders, although there is a relative dearth of well-controlled randomized clinical trials supporting their effectiveness. The interpretation of study findings for a number of disorders is also limited by specific design features, including inadequate statistical power, choice of control group, and lack of an intent-to-treat analytical strategy.

Relatively few studies have addressed the sequencing and integration of different interventions—that is, which of the treatment alternatives should be first-line—and little empirical evidence is available to guide the management of initial treatment nonresponders. In spite of the high rates of diagnostic comorbidity in childhood, few studies have addressed the treatment of youngsters with multiple disorders or other complex presentations.

It is the opinion of the working group that the decision about which treatment to use first be in general guided by the balance between anticipated benefits and possible harms of treatment choices (including absence of treatment), which should be the most favorable to the child. It is recommended that the safest treatments with demonstrated efficacy be considered

first before considering other treatments with less favorable side effect profiles. For most of the disorders reviewed herein, there are psychosocial treatments that are solidly grounded in empirical support as stand-alone treatments. The preponderance of available evidence indicates that psychosocial treatments are safer than psychoactive medications. Thus, the working group recommends that in most cases psychosocial interventions be considered first. The acute and long-term safety and efficacy data that are available for each disorder will be central to this determination.

It should also be acknowledged that there are cultural and individual differences about how to weigh safety and efficacy data, and consumers (i.e., families) might weigh them differently. Ultimately, it is the families' decision about which treatments to employ and in which order. A clinician's role is to provide the family with the most up-to date evidence, as it becomes available, regarding short- and long-term risks and benefits of the treatments. As the evidence base continues to grow, the ultimate goal will be to provide information that will allow families to apply their own preferences about how to weigh safety and efficacy in order to make an informed choice with regard to treatment on behalf of their child.

Recommendations

A summary of each section is provided below. Specific recommendations for each category can be found in the main report.

- **Research and Funding**

  To advance knowledge in the field and improve the lives of children and adolescents and their families, it is recommended that researchers, research funding organizations, and other stakeholders, including those who establish funding priorities, work together to strengthen the evidence base for the treatment of child and adolescent psychopathology.

- **Professional Education**

  It is recommended that (a) predoctoral training of professional psychologists include a broad-based education in the various evidence-based treatments discussed in this review, (b) postdoctoral training further the development of skills in the implementation of evidence-based psychosocial interventions and general knowledge of evidence-based psychopharmacological and psychosocial treatments, and (c) continuing education for child and adolescent practitioners and training faculty emphasize contemporary evidence-based strategies in the treatment and management of childhood disorders.

- **Public Education**

  To improve recognition and understanding of childhood mental illness and its treatment, it is recommended that professional organizations, the medical community, federal agencies, foundations, private industry, health care organizations, accrediting bodies, and other stakeholders commit to educating the public about these disorders and appropriate treatments that have been empirically demonstrated to be both safe and effective.

- **Service Delivery**

  It is recommended that policymakers, professional organizations, educational and training institutions, and providers develop policy and implement practices ensuring that youth with mental health disorders are identified and have access to evidence-based (to be consistent with above and APA policy), safe, reimbursable treatments.

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Overarching Goals: Introduction

There has been an increased recognition of the prevalence and substantial morbidity associated with child and adolescent mental disorders. In particular, the *Report of the Surgeon General's Conference on Children's Mental Health: A National Action Agenda* (U.S. Public Health Service, 2000) has renewed public attention on the issue and identified children's mental health as a national priority. Prevalence estimates for childhood disorders range from 17.6% to 22% (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), with up to 15% of children and adolescents suffering from a mental disorder severe enough to cause some level of functional impairment (Roberts, Atkinson, & Rosenblatt, 1998; Shaffer, Fisher, Dulcan, & Davies, 1996). Of concern are data indicating that only 1 in 5 of these children receive services provided by appropriately trained mental health professionals (Burns et al., 1995; Centers for Disease Control [CDC], 2004; U.S. Department of Health and Human Services, 1999). The renewed interest coupled with the increased recognition of mental disorders in children and adolescents has been paralleled by an increased use of psychotropic medications for children (Zito et al., 2002). This increase has led to closer public and scientific scrutiny of the efficacy and safety of these medications.

Spurred by this increasing attention, the number of scientific studies of treatment efficacy with children has risen dramatically (Vitiello, 2006). Support for pediatric treatment research has ranged from an increase in program announcements and requests for applications from NIH. In the last decade, an approximate threefold increase in the proportion of the National Institute of Mental Health (NIMH) funding levels for clinical trials has been paralleled by an increase in pharmaceutical-sponsored clinical trials as a result of congressional legislation (Vitiello et al., 2004). In fact, there has been an increase in research in investigating several modalities at the same time. Moreover, several recent federally sponsored clinical trials have addressed the

efficacy of psychosocial, psychopharmacological, and combined interventions for childhood disorders.

Prompted by an increase in the number of efficacy studies for treatment of mental health disorders in youth and growing public recognition, research efforts are increasingly focusing on issues of safety. Since the first use of psychotropic medication in children nearly 7 decades ago, safety concerns have been present (R. T. Brown & Sammons, 2002). For example, concerns were raised about the use of stimulants in the 1970s (O'Leary, 1980) and the use of specific selective serotonin reuptake inhibitors (SSRIs) when they emerged in the early 1990s (C. A. King et al., 1991). More recently, these issues have risen to the forefront of public awareness, particularly with regard to the use of psychotropic medications for the treatment of depression in children and adolescents. The 2003 decision by the United Kingdom to contraindicate the use of most antidepressants in children (Whittington, Kendall, & Pilling, 2005) was followed by scrutiny of safety data from clinical trials in the United States and the FDA's mandated cautionary warning of these medications.

Given this changing landscape, the APA Working Group on Psychoactive Medications for Children and Adolescents (WGPMCA) was charged with reviewing the literature and preparing a comprehensive report on the current state of knowledge concerning the effective use, sequencing, and integration of psychotropic medications and psychosocial interventions for children and adolescents. Psychosocial interventions represent a range of treatments across targets (e.g. youth, families, teachers) and across areas of functioning. Psychosocial interventions are the evidence-based alternative and complementary interventions to medications, and medications cannot be appropriately evaluated without considering the alternatives. Therefore, this review includes a comparative examination of the risk–benefit ratio of psychosocial, psychopharmacological, and combined treatments.

For the purposes of this report, the premise of "evidence-based practice" is defined as set forth in the Institute of Medicine (IOM) report in 2001: practice that "involves the integration

of best research evidence with clinical expertise and patient values." The working group recognizes that this is a narrow definition of evidence-based practice but believes it was necessary to employ this narrower definition in order to meet the charge of conducting a consistent, comparative analysis of psychotropic medications relative to psychosocial interventions. The working group believes it is in concert with the *APA Policy Statement on Evidence-Based Practice in Psychology* (American Psychological Association, 2005). This report relies on the best available evidence in the scientific literature and reports the best evidence available for each major class of child and adolescent disorder. The authors acknowledge that the strength of the available evidence is variable across disorders and that, for some disorders, the samples enrolled in clinical trials are not necessarily representative of the children and adolescents seen in usual-care settings, where consideration must be given to factors such as gender differences, race/ethnicity, socioeconomic status, sexual orientation, and co-occurring disorders.

In approaching this task, the existing literature in peer-reviewed journals (included as part of MEDLINE and PsycINFO) was reviewed. Available FDA data concerning safety were also closely examined. This review is organized in accord with the nosology put forth in the fourth edition (text revision) of the *Diagnostic and Statistical Manual* (*DSM–IV–TR*; American Psychiatric Association, 2000), and its conceptual framework considers acute, long-term, and adverse outcomes associated with various psychosocial and pharmacological interventions, the efficacy and safety of these interventions, as well as contextual variables that may affect their use and risk–benefit ratios. It should also be noted that the review focuses on symptoms of disorders, as well as functional outcomes, and rates the strength of evidence and magnitude of effect with regard to treatment modalities. While careful assessment is critical for treatment, assessment and diagnostic issues are not included (for a review, see Mash & Hunsley, 2005).

The review first describes the contextual factors that may enrich understanding of these issues. In the second section (Disorders and Interventions), a review of psychosocial,

pharmacological, and combined interventions for each childhood and adolescent disorder is presented. It should be noted that *preschoolers* are defined as children 5 years old and under, *children* as ages 6–12, and *adolescents* as ages 13 and above. Included are discussions of strength of evidence, side effects, diversity issues, a risk–benefit analysis, and future directions. The review concludes with recommendations for training and professional practice, further research, public education, and public policy.

DEFINITIONAL AND METHODOLOGICAL CONSIDERATIONS

This section considers methodological and definitional issues pertinent to the evaluation of the potential benefit (efficacy and effectiveness) and potential harm (safety) of the treatments reviewed.

Evaluation of Benefit

A treatment or combination of treatments is considered to be efficacious if carefully conducted scientific studies show that it has a positive effect on one or more outcomes of primary importance and interest. Taking a more dimensional approach, efficacy is defined as the potency of an intervention, as assessed under highly controlled conditions (Bower, 2003). Efficacy studies are usually conducted in university or university-affiliated settings, where it is possible to closely safeguard internal validity. When a promising treatment emerges, efficacy studies are necessary as one component of the treatment development process, prior to broad dissemination efforts. They may be conducted prior to, at the same time as, or in integration with effectiveness studies (discussed below), which evaluate the effects of treatments under conditions approximating usual care (Wells, 1999).

Advances in the evidence base for clinical practices typically follow a progression from descriptive case reports to case series and open trials and ultimately to controlled single subject, crossover, and between-group trials. Several methodological features determine the scientific rigor or strength of treatment studies and the extent to which findings provide definitive or even interpretable information concerning the targeted treatment's efficacy. These features include, but are not limited to, subject flow (enrollment, intervention allocation, follow-up, data analysis), randomization procedures, control conditions (wait list, no treatment, placebo, active treatment), assessment procedures (e.g., independent "blind" evaluators), specification of

treatment details (format, strength, duration, dose), issues related to treatment integrity and fidelity (e.g., highly trained providers; fidelity assessments), and data analysis strategies (e.g., intent to treat). A Consolidated Standards of Reporting Trials (CONSORT) statement is available to assist investigators in outlining and reporting the design, conduct, analysis, and interpretation of their clinical trials (Begg et al., 1996; Moher, Schulz, & Altman, 2001). It is extremely important when interpreting and reporting findings that investigators carefully consider and discuss the potential generalizability of findings.

As discussed by Kaslow and Thompson (1998) and more recently by Weisz, Jensen Doss, and Hawley (2005), substantial methodological weaknesses exist in many child and adolescent treatment studies. In their recent analysis of 236 youth psychotherapy outcome studies conducted across a 40-year period (1962–2002), Weisz et al. (2005) found that inadequate sample sizes and the absence of procedures to enhance treatment fidelity may have resulted in less than optimal tests of treatment efficacy in many studies. Moreover, studies have often failed to examine alternative explanations for positive findings, such as positive expectancies, therapeutic alliance, and attention (Jensen, Weersing, Hoagwood, & Goldman, 2005).

Because the research design and methodological strength of treatment studies vary enormously and yet are critical to the interpretation of findings concerning treatment efficacy, this review includes an *Efficacy Summary Table* for treatments targeting each type of child psychopathology. These tables report the level of efficacy for each treatment according to effect sizes (a = .20 or less; b = .21 to .50; c = .51 to .80; d = .81 and above) using the guidelines put forth by Cohen (1988) for between-group designs. For other designs, appropriate effect sizes were considered. Tables also report the strength of evidence available for making this determination (1 = no control group; 2 = comparison group but not a controlled trial; 3 = controlled clinical trial; 4 = replicated controlled clinical trial).

More than 1,000 efficacy studies have demonstrated substantial benefits for psychotherapy and medication, delivered using structured treatment protocols and under systematically controlled conditions across a wide variety of child and adolescent mental health problems (Kazdin, 2000; Weisz & Jensen, 2001). Unfortunately, growing evidence suggests that outcomes achieved in real-world community settings pale in comparison to those obtained in evidence-based clinical trials for both psychotherapy (e.g., Weersing & Weisz, 2002) and medication (Jensen et al., 1999; MTA Cooperative Group, 1999). In fact, both prospective controlled trials and meta-analytic reviews suggest that traditional psychotherapy delivered in real-world community settings is on average no more effective than minimal or no intervention at all (Weiss, Catron, Harris, & Phung, 1999; Weisz, Donenberg, Han, & Weiss, 1995). With regard to psychopharmacology, Jensen et al. found notable discrepancies between medication utilization of stimulants in community pediatric practice and current evidence-based guidelines. For example, the frequent use of polypharmacy in the community far outstrips the few published studies to support this practice (Zonfrillo, Penn, & Henrietta, 2005). This failure of positive findings from research-based treatments to generalize to community settings, sometimes referred to as the efficacy-effectiveness paradox (Curry & Wells, 2005), presents a significant challenge to the mental health research and treatment communities.

A number of factors underlie the efficacy–effectiveness paradox. First, as noted above, *efficacy* studies are designed to test the impact of treatment under optimal conditions (Connor-Smith & Weisz, 2003) and reflect design elements uncharacteristic of typical clinical practice. This may include the use of treatments specifically crafted to address the targeted disorder, experienced and highly-trained therapists, careful monitoring of treatment, and selection of less complicated and highly motivated patients. In contrast, *effectiveness* studies seek to test the impact of treatments provided in real-world clinical settings by community therapists with varying levels of specialized expertise and limited oversight and delivered to a group of patients

relatively heterogeneous with respect to clinical presentation and level of complexity (Connor-Smith & Weisz, 2003; Curry & Wells, 2005).

Safety and Ethical/Legal Issues

Issues of safety in treatment studies are increasingly being scrutinized, with recent calls for safety outcomes to be as rigorously measured and monitored as efficacy outcomes. This is evidenced in the recent requirement of data and safety monitoring plans for all federally funded clinical trials as well as heightened public awareness of safety issues. It is the position of this working group that the highest possible safety standards should be applied to pediatric treatment studies. It should be noted that ethical practice requires a partnership with the individual being treated. This concept is embodied in many statutes across the various states that address issues such as a minor's legal right to consent to treatment, to give assent, to exercise a veto over treatment or otherwise have a meaningful say in treatment decision-making. Concerns are especially pronounced for older children, who, according to existing empirical research, make medical decisions that are comparable to those of their adult counterparts. Accordingly, the developmental status of children and youth requires particular attention in this context of their input into the process.

Consider, for example, a 16-year-old who does not want the untoward, sexual side effects of a particular medication but whose parents want the medication administered. Alternatively, consider a 14-year-old who desperately wants the medication to alleviate symptoms but whose parents do not want the medication administered because of its potential effect on pubertal development. It would seem ethically responsible to offer patients and their parents psychoeducation concerning all psychosocial and pharmacological treatments. While a complete review of ethics regulating the treatment of minors is not possible within the scope of

this report, Schouten and Duckworth (1999) provided a comprehensive review of legal and ethical constants for both psychosocial and psychopharmalogical treatments.

Safety of psychotropic medications in children cannot be inferred from adult data (Vitiello, 2003). More research is necessary on children's and parents' motivation for research participation, effectiveness of the informed consent and assent process, the possibility of persistent consequences of exposure to experimental treatments and placebos, and validation of the concept of minimal risk (Vitiello, 2003).

Methodologies for assessing safety are currently being developed and redesigned in order to help standardize the collection of safety data (Greenhill et al., 2003). Measuring both efficacy and safety in a clinical trial has implications for study design. Larger sample sizes and longer durations may be necessary for identifying potentially rare (e.g., SSRI-triggered suicidality) or slowly emerging (e.g., stimulant height suppression for ADHD) problems, and there is a need to standardize the definition for adverse events, degree of severity, ascertainment methods, and recording procedures (Vitiello et al., 2003).

Safety issues are particularly salient with respect to psychotropic medication. Whether one subscribes to the Hippocratic dictum "first, do no harm" or takes a risk–benefit approach to treatment, it is impossible to discount possible unwanted treatment effects. A population perspective that asks “How many children should benefit from a psychotropic medication to justify one extra child harmed?” must be considered. One method for quantifying this question is calculating the NNTB (numbers needed to benefit one additional child) (Sackett, Richardson, Rosemberg, & Haynes, 2000) and the NNTH (number needed to treat to cause harm in one additional child) to help researchers and clinicians weigh the relative costs and benefits of psychopharmacological and psychosocial interventions alone or in combination (Whittington et al., 2004).

The acceptability of the risk–benefit profile for any psychotropic medication thus involves value judgments as to the cost of harm-related and psychiatric-related adverse events. For

example, in the case of antidepressants, the risk of increased suicidality appears to be relatively low (i.e., 2 extra suicidal patients for every 100 treated with an SSRI compared with a placebo), and no patients actually completed suicide in the FDA database of controlled trials, but given the potentially serious implications of suicidality, even low-rate events are clinically important. It is also important to note that the vast majority of clinical trials have addressed monotherapy, and there are almost no data concerning adverse events associated with combining psychotropic medications. This issue seems to be especially relevant given the high rate of combined pharmacological use in the community (Safer, Zito, & Dos Reis, 2003).

The debate over the possible link between the newer antidepressants and suicidality has focused public attention on the ethical and legal issues surrounding the provision of pediatric mental health care. These issues include the public's need for trust in the research and regulatory processes that determine both the efficacy and safety of pediatric mental health treatments and the clinician's role in providing ethical care to youth and their families.

Recent safety concerns about antidepressants illustrate several of the ethical issues related to clinical research and the dissemination of findings from clinical studies. These issues include potential miscoding of data, selective reporting and publication bias, lack of reliable and valid assessment of adverse effects, and failure to apply validated, empirical methodology to the examination of adverse events. A recent review has urged caution in interpreting trials in children sponsored by the pharmaceutical industry, given evidence of selective reporting and a failure to publish negative results (T. Kendall, Pilling, & Whittington, 2005). Bias is not likely limited to financial conflicts of interest or research involving the pharmaceutical industry. Other influences (e.g., interest in career advancement, professional affiliation, training and experience, theoretical orientation, and funding source) may also result in bias (Levinsky, 2002). A collaborative agreement reached by the top medical journals now requires that all clinical trials be publically registered in order for them to qualify for publication (De Angelis et al., 2004) to help address the issue of publication bias. In the end, total transparency, with all raw data

involving human subjects, may be the only solution that will ensure that all the data are available and considered for meta-analysis (Antonuccio, Danton, & McClanahan, 2003).

Developmental and Contextual Considerations

Historically, interventions for child and adolescent psychopathology have been drawn from the adult literature and adapted to meet the developmental needs of children, with varying degrees of success (R. T. Brown & Sammons, 2002). Given the salience of developmental processes to our understanding of children and adolescents, a brief review of this topic follows. As noted by others (for reviews, see R. T. Brown & Sawyer, 1998; Werry & Aman, 1999), youth differ both qualitatively and quantitatively from adults. Developmental psychology generally suggests that there are various periods during childhood and adolescence in which children evidence different cognitions and behaviors, including early childhood (infancy, toddlerhood, primary school years), middle-childhood or the elementary school years, preadolescence, early adolescence, and late adolescence.

Even within childhood populations, however, there are vast developmental differences that influence physiological, cognitive, behavioral, and affective functioning. Each of these areas of functioning varies by age and has an important influence on outcomes for children, particularly with regard to school performance and socialization. For example, adolescents have the potential to be more active and cognitively engaged in their treatment than their younger counterparts and are apt to be better informants with regard to adverse side effects and potential benefits of medication both at home and at school. It should be noted that a corpus of research in pediatric psychology exists that suggests rather poor adherence with traditional pharmacological treatments (e.g., antibiotics) and even worse adherence with psychotropic agents (for a review, see LaGreca et al., 2003). This adherence rate has been shown to differ across age groups (e.g., adolescents), ethnic groups, and socioeconomic status. Adherence

rates are of particular concern because of their possible effect on the titration of medication on the part of the provider. Issues of adherence may also result in family conflict, or more specifically, parent–child conflict (LaGreca et al., 2003). It is anticipated that most studies of psychotropic agents will be of the standard of clinical trials; however, such controlled environs are not always standard when children are prescribed medication within the family environment. It is recommended that future studies provide an examination of various interventions designed to advance adherence rates for children and adolescents both to psychosocial and psychopharmalogical treatments.

Development also has implications with respect to medication titration and management. Physiological differences in children and adolescents across the age span can result in markedly different rates of medication absorption, distribution in the body, and metabolism among youth of different ages and among adults (R. T. Brown & Sammons, 2002). Children are also less able than adults to accurately describe changes in their physiological and psychological functioning that may be associated with the use of psychotropic medications, the course of these changes over time, and the adverse effects of these agents. In addition, when treating children and adolescents with medication, caregivers typically are responsible for both the decision to use pharmacotherapy and the administration of medication. In the school setting, it may be the school nurse or the teacher who administers medication. As a result, caregivers' attitudes, as well as those of school personnel, toward medication may influence children's use of medication and adherence to medical regimens. For these reasons, the unique issues in child and adolescent psychopharmacology must be considered when prescribing and monitoring medication effects at home and at school for pediatric populations.

It is important to bear in mind, as R. T. Brown and Sawyer (1998) pointed out, use of psychotropic medication is typically only one element of a child's treatment program. Frequently, psychotropic medications are used for the purpose of reducing children's symptoms and increasing functional behaviors both at school and at home, thereby making the children more

amenable to other psychosocial, social, or educational interventions. The effects of development on participation in these additional interventions and the appropriate sequencing of psychosocial and psychotropic interventions during different developmental windows remains an under-researched area.

Diversity Issues

Gender, race/ethnicity, sexual orientation, physical disability, socioeconomic status, culture, and religious preference may moderate response to treatment and influence treatment choice and adherence. This report has taken care to review studies of published data with regard to treatment efficacy; however, the paucity of data concerning these possible moderators in comparison to data on treatment choice or utilization is notable. Limited data exist on the interaction of these factors and the impact and effectiveness of pharmacological agents, and, in the majority of studies available, participants were White boys. More research is needed on the ways in which issues of diversity play an ever-increasing role in the diagnosis and/or misdiagnosis of individuals (e.g., the underdiagnosis of ADHD in girls; for a review, see Hinshaw, March, & Abikoff,1997). In addition, while emerging literature is just beginning to suggest culture as a mediator in response to psychosocial and pharmacological treatments, this area should be studied carefully in the future. While it is recognized that issues such as linguistic differences, immigrant status, lifestyle and health concerns, and use of indigenous healers contextualize the use of medication by children and adolescents, again, the paucity of data concerning these possible moderators in pediatric populations is notable.

Very little work has been done in the pediatric population regarding differential metabolism of medications by gender and race/ethnicity. One exception was a study conducted by Campbell et al. (1997) in a prospective investigation of neuroleptic-related dyskinesias in children with autism that revealed dyskinesias were higher among females than among their

male counterparts. This investigation is important because it demonstrates that gender may be a viable risk factor for specific adverse effects associated with psychotropic agents in pediatric populations. In the adult literature, there is a corpus of research to suggest differential rates of metabolism of psychotropic medications among races/ethnicity. For example, African American individuals suffer from a greater frequency of toxicities associated with lithium carbonate, while individuals from Taiwan may respond more favorably to these agents (Strickland, Lin, Fu, Anderson, & Zheng, 1995; Yang, 1985). Even more compelling are data suggesting differential rates of metabolism with antidepressant medication among Asian American individuals compared with other ethnic groups and findings of greater toxicities among African American individuals compared with Asian Americans, Latinos, and Whites (for reviews, see R. T. Brown & Sawyer, 1998; Phelps, Brown, & Power, 2002). Similar findings have been revealed for anxiolytic agents. Clearly, the adult literature indicates differential absorption, pharmacokinetics, and toxicities as a function of ethnicity, and further work needs to be conducted in this area. Moderating effects of age, ethnicity, and gender have been found for a number of psychosocial interventions and are summarized in Section II of this review.

Assessment Issues

This review is premised on three assumptions: (a) psychopathology can be accurately diagnosed in children and adolescents, (b) interventions (whether psychopharmacological or behavioral) are clearly described and followed, and (c) outcomes are measured accurately. In other words, stating that a particular intervention is likely to work for children and adolescents with a particular disorder assumes those individuals are reliably distinguished from individuals not having that particular disorder or from individuals having other disorders. When it is declared that a particular intervention has a positive outcome, it is assumed that the intervention was implemented as described and that the outcome (e.g., the reduction of symptoms from

preintervention to postintervention) is reliably and accurately measured. Should these assumptions be invalid, it would be foolish to claim that treatment X works for condition Y as measured by outcome Z. Unless conditions, treatments, and outcomes are measured accurately (i.e., reliably) and appropriately (i.e., validly), one cannot presume to draw conclusions about whether or not a given treatment works, how well, and for whom.

Research in assessment suggests that the assumptions of diagnostic precision, intervention fidelity, and outcome accuracy are imperfectly realized (see Mash & Hunsley, 2005). With respect to *DSM–IV–TR* diagnoses, highly trained clinicians typically show close agreement when distinguishing psychopathology from normative behaviors (e.g., Klin, Lang, Cicchetti, & Volkmar, 2001) but much less agreement when assigning specific (and in the case of multiple disorders, primary) diagnoses. For example, differential diagnosis of attention-deficit disorder (ADD) from oppositional defiant disorder (ODD) continues to complicate diagnosis of the most common problem (i.e., ADD) confronting children and adolescents (Barkley, 2003; Root & Resnick, 2003). Furthermore, depth of information about a case may increase the confidence that a clinician has in diagnosis, but it does not necessarily increase diagnostic accuracy (Gutkind et al., 2001). Concerns about diagnostic accuracy are likely to overestimate the accuracy actually achieved in practice with children and adolescents because (a) research typically uses clearly specified diagnostic protocols with trained professionals, whereas experienced clinicians tend to rely on less structured diagnostic processes (Aegisdottir, White, & Spengler, 2006; Garb, 2005); and (b) the focus of most research has been on adult clients, who are typically better able to provide information to clinicians than are children and adolescents.

The degree to which a given treatment or intervention is actually implemented is also imperfect. Failure to take medication as directed is the most common problem in treatment of many psychological disorders (e.g., Byrne, Regan, & Livingston, 2006), and it is difficult to assess treatment fidelity even in motivated adults (Bauman, 2000). Because many children and adolescents receive interventions from others (e.g., teachers, parents), researchers must

assess the degree to which those adults adhere to intervention protocols. Unfortunately, assessment of intervention fidelity finds that interventions, even when delivered by trained professionals who agree to implement them, are often delivered at unacceptably low levels of accuracy (e.g., Wickstrom, Jones, LaFleur, & Witt, 1998). Furthermore, professionals' self-assessments of adherence to treatment programs are often unrelated to observers' assessments of treatment adherence (e.g., Noell et al., 2005). Therefore, conclusions regarding intervention efficacy must be tempered by evidence suggesting wide variability in intervention integrity.

Finally, the accuracy with which outcomes are measured varies, in part as a function of the measure (e.g., different instruments have different reliabilities) and because different sources of information vary in judgments about children's and adolescents' behavior and affect. Differences in raters, settings, and the domain of behavior being observed can be substantial (Achenbach, McConaughy, & Howell, 1987) and lead to markedly different conclusions about the degree to which individuals express psychopathology (Achenbach, Krukowski, Dumenci, & Ivanova, 2005). This is particularly problematic for those evaluating outcomes for children and adolescents, as outcome measures typically rely on adult observations.

Therefore, research on assessment suggests important constraints on the degree to which researchers and clinicians can draw conclusions about what works, for whom it works, and how well it works. Although these constraints do not invalidate the evaluation of efficacy for psychotropic and other treatments used with children and adolescents, they do suggest conclusions should be tempered by an understanding of variability with respect to diagnostic accuracy, intervention fidelity, and outcome measurement. Furthermore, assessment research suggests that practitioners should institute assessment practices to measure and ensure diagnostic accuracy, treatment fidelity, and outcome precision when applying research-based interventions to their clients.

DISORDERS BY INTERVENTION

This literature review focuses on specific mental health disorders that practicing psychologists and other professionals caring for children and adolescents encounter. It examines the most prevalent disorders using the nomenclature employed in the *DSM–IV*. For each disorder, the various psychosocial, psychotropic, and combination treatments are reviewed, including the effect of each therapy, the strength of evidence for its efficacy, and the limitations and side effects of each treatment in the short- and long-term. While many studies focus on symptom management and others investigate functional outcomes, both are addressed in this review. Each section also presents the information described above in table form.

The review begins with attention-deficit/hyperactivity disorder (ADHD) because of its high prevalence and the volume of available research. Subsequent sections review oppositional defiant disorder (ODD), conduct disorder (CD), Tourette and tic disorder, obsessive–compulsive disorder (OCD), anxiety disorders, depression and suicidality, bipolar disorder, schizophrenia spectrum disorder, autism spectrum disorder, anorexia nervosa and bulimia nervosa, and elimination disorders.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate levels of inattention, impulsivity, and/or overactivity that result in chronic functional impairment across settings (American Psychiatric Association, 2000). Approximately 5% of the school-aged population in the United States can be diagnosed with this disorder (American Psychiatric Association, 2000), with a male to female ratio ranging between 2:1 to 6:1

(Biederman, Lopez, Boellner, & Chandler, 2002). ADHD typically emerges early in life and is a chronic disorder that places children and adolescents at higher than average risk for academic, behavioral, and social difficulties. Thus, treatment must begin early in life, address multiple areas of functioning, and be implemented across settings and over long periods of time.

The most widely studied treatments for ADHD include psychostimulant medication (e.g., methylphenidate), behavior modification strategies, and their combination. There is widespread agreement that pharmacological intervention with a central nervous system (CNS) stimulant (Greenhill & Ford, 2006; Spencer et al., 1996; Swanson, McBurnett, Christian, & Wigal, 1995), behavior modification (Pelham, Wheeler, & Chronis, 1998), and the combination of the two (American Academy of Pediatrics, 2001a) are evidence-based, short-term treatments. There is some debate about the amount of evidence in support of each of these and about their relative effectiveness, but all three approaches have a solid evidence base accumulated over the past 3 decades. Other treatments, such as nonstimulant medication (e.g., atomoxetine, clonidine), academic intervention, and social skills strategies, have also been studied, and some evidence supporting their effectiveness exists, but less than for the three primary strategies.

Psychosocial Interventions

Behavior Therapy

Since the 1970s, a large number of studies have shown that behavioral interventions cause short-term amelioration of ADHD symptoms and impairment and that these acute effects are comparable in most domains to those obtained with low to moderate doses of stimulant medication (Pelham & Waschbusch, 1999). In contrast to the results of studies of stimulant medication that focus on improving the core symptoms of ADHD, studies of behavioral treatments have focused on improving the key domains of impairment associated with ADHD

and thought to mediate long-term outcomes: parenting practices, peer relationships, and academic/school functioning (Pelham, Fabiano, & Massetti, 2005). Thus, behavioral treatments and studies thereof have involved behavioral parent training (Anastopoulos, Shelton, & Barkley, 2005), classroom interventions—both behavioral and academic (DuPaul & Stoner, 2003)—interventions for problems with peers (Mrug, Hoza, & Gerdes, 2001), and often two or three of these components. Notably, studies of behavioral treatment have shown beneficial effects of intervention throughout the age range from preschool to adolescence (e.g., Evans, Pelham, & Grudberg, 1995; Pisterman et al., 1989). At the same time, the literature is most abundant on elementary-aged children, and there is much more research with younger children than with adolescents, where more is needed (Smith, Waschbusch, Willoughby, & Evans, 2000).

Parent Training

Many studies have shown that behavioral parent training, typically consisting of 8 to 12 group or individual sessions, improves parenting skills, children's behavior in key domains in the home setting (e.g., noncompliance with parental requests, not following rules, defiant/aggressive behavior) and ADHD symptoms (Anastopoulos, Shelton, DuPaul, & Guevremont, 1993). Studies have typically lasted a matter of months, with effects usually measured at treatment termination or after follow-up periods of a few months. The magnitude of effects is typically moderate to large, with within-subject designs yielding larger effects than between-group designs (Pelham & Fabiano, in press; Pelham, Wheeler, & Chronis, 1998). Effects were larger on the key domains of impaired functioning noted above than they were on *DSM* symptoms of ADHD (e.g., MTA Cooperative Group, 1999a, 2004a). Positive effects were found regardless of comorbidity, and in some studies, the impact of parent training was greatest when comorbidities were present (e.g., Hartman, Stage, & Webster-Stratton, 2003; Jensen et al., 2001; Lundahl, Risser, & Lovejoy, 2006). Arguably, behavioral parent training is the most well-validated intervention for children with aggression/conduct problems (Brestan & Eyberg,

1998), given that the vast majority of children with conduct problems also have ADHD and that parent training effects are at least as large if not larger for comorbid ADHD/CD children than for children with CD alone (Bor, Sanders, & Markie-Dadds, 2002; Lundahl et al., 2006); behavioral parent training with comorbid aggressive ADHD children is one of the most well-validated interventions in the field of child therapy. Although most studies have focused on children between 6 and 12 years of age, studies have shown similar changes in both younger children (e.g., Bor et al., 2002; Pisterman et al., 1989; Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001) and adolescents (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001).

Classroom Interventions

Behavioral classroom interventions for ADHD have also been very widely studied over the past 3 decades (e.g., O'Leary, Pelham, Rosenbaum, & Price, 1976), are widely used in school settings (Walker, Ramsey, & Gresham, 2003/2004), and are solidly evidence based (DuPaul & Eckert, 1997; Pelham & Fabiano, in press; Pelham et al., 1998). There are many different types of classroom interventions for ADHD (DuPaul & Stoner, 2003), ranging from daily report cards (DRC) to point/token systems, and include classwide and schoolwide programs, as well as individual, foci. As with studies of parent training, these studies have typically targeted ADHD symptoms and associated functional difficulties (e.g., not following classroom rules, disruptive behavior, noncompliance with teacher requests, not getting along with classmates). The majority of the dozens of studies have investigated relatively intensive programs (e.g., point system and time out) in special class settings (e.g., Abramowitz, Eckstrand, O'Leary, & Dulcan, 1992; Carlson, Pelham, Milich, & Dixon, 1992; Chronis et al., 2004; Fabiano, Pelham, Burrows-MacLean, et al., 2006; Northup et al., 1999; Pelham et al., 1993; Pelham, Burrows-MacLean, et al., 2005) or less intensive programs (e.g., DRC, teacher consultation) in regular class settings (e.g., Gittelman et al., 1980; O'Leary & Pelham, 1978; Pelham, Schnedler, et al., 1988). The

effects of the interventions are typically greater with the more intensive programs in special class settings, though they are substantial even with DRCs in classroom settings (DuPaul & Eckert, 1997; Pelham & Fabiano, in press; Pelham, Wheeler, & Chronis, 1998). Effects have been shown in samples from ages 5 to 12 years (e.g., Barkley et al., 2000).

Academic Interventions

The bulk of the studies of classroom interventions for ADHD have focused on deportment rather than academic outcomes. Many of the studies described above have included daily seatwork productivity and accuracy as outcomes, and the impact of the classroom management programs on those variables is well established (DuPaul & Eckert, 1997; Fabiano, Pelham, Coles, et al., 2006; Pelham & Fabiano, in press). However, these studies focus on acute daily functioning rather than on achievement measured over time. In addition, results from single-subject design studies support the short-term effects of academic intervention strategies on the behavior and academic performance of children with ADHD. Specifically, preliminary evidence supports the use of modified task demands (e.g., Zentall, 1989), providing task choices (Dunlap et al., 1994), peer tutoring (e.g., DuPaul, Ervin, Hook, & McGoey, 1998), parent tutoring (Hook & DuPaul, 1999), and computer-assisted instruction (e.g., Ota & DuPaul, 2002) in enhancing on-task behavior and, in some cases, improving achievement. In fact, academic strategies may lead to behavior change that is equivalent in magnitude to contingency management interventions (DuPaul & Eckert, 1997) and are arguably necessary to target the lag in academic achievement that characterizes ADHD. Interventions focused on academic-related behaviors (e.g., taking notes on classroom lectures) also may benefit adolescents (Evans, Pelham, & Grudberg, 1995) and younger elementary school-aged children with ADHD (DuPaul et al., 2005). Beyond the utility of contingency management to improve daily seatwork productivity/accuracy, firm conclusions about the efficacy of academic interventions for this population must be tempered until findings from single-subject design studies are replicated with

larger samples in the context of controlled experimental trials, and academic achievement is employed as an outcome.

Peer Interventions

Interventions focused on peer relationships have been less well studied than parent training and classroom interventions. These interventions focus on teaching social skills, social problem solving, and behavioral competencies (e.g., sports skills) while decreasing aggression and other undesirable behaviors (e.g., bossiness) and are provided in clinic- or school-based weekly social skills groups, after-school or weekend groups (e.g., Frankel et al., 1997), and summer camp settings (e.g., Pelham, Fabiano, et al., 2005). Typically, these programs are not provided as stand-alone programs, but integrate parent training (e.g., Pfiffner & McBurnett, 1997), school-based interventions (e.g., Pelham et al., 1988), or both (Pelham, Fabiano et al., 2005). There is preliminary evidence from a small number of studies that weekly social skills groups might add incrementally to the effects of school-based and home-based interventions (e.g., Pfiffner & McBurnett, 1997). There is considerable evidence that an intensive package delivered in a summer camp setting that includes social skills training, a reward and cost system, group practice, and instruction in sports skills and team membership reliably produces medium to large acute effects (Chronis et al., 2004; Pelham, Burrows-MacLean, et al., 2005; Pelham, Burrows-MacLean, Gnagy, Arnold, et al., 2006; Pelham, Burrows-MacLean, Gnagy, Fabiano, et al., 2005). The MTA study involved parent training, teacher consultation, and a summer camp focused on peer interventions (Wells, Pelham, et al., 2000) and revealed large pre–post improvements that maintained at 1- and 2-year follow up (MTA Cooperative Group, 1999a, 2004a, 2004b, 2006). Studies of these intensive summer interventions have included children ranging from 5 to 14 years of age.

Strength of Evidence for Psychosocial Interventions

Numerous studies summarized in several reviews have shown that effect sizes for psychosocial interventions are in the moderate to large range, depending on the type of study designs. DuPaul and Eckert (1997), Fabiano, Pelham, Coles, et al. (2006), and Pelham and Fabiano (in press) all concluded that the mean effect size in between-group behavioral studies was between .5 and .7 (see also Lundahl, Eisser, & Lovejoy, 2006). The DuPaul and Eckert meta-analysis focused on school-based studies, Lundahl et al. focused on parent training, while Fabiano examined studies across settings, including home, school, and peer/recreational. Effect sizes in crossover designs are computed with a different metric and are rarely included in traditional meta-analyses. When analyzed, they reveal a very large impact of behavioral treatment, yielding considerably larger effect sizes compared with those in between-group studies. Finally, effect sizes in studies with single-subject designs are even larger in meta-analyses that have included them. As discussed below, all of these effects are in the same range as those that have been summarized in reviews of stimulant medication. The only review that has separated the effects of behavior modification by target domain (Fabiano, Pelham, Coles, et al., 2006) has shown that these effect sizes are consistent across multiple functional domains, target behaviors, and assessment methods. When academic achievement has been assessed, there are few studies that have lasted enough time to measure achievement. As with medication, behavioral treatments have had little impact on long-term academic achievement. When acute measures of academic functioning are assessed, effect sizes are in the moderate to large range for seatwork productivity but in the small range for achievement measures.

Limitations of Behavioral Treatments

Although there is considerable evidence that there are effective, behavioral interventions for ADHD, the evidence for them does have limitations. Chief among these are that behavioral

treatments (a) do not work to the same degree for all children and are not sufficient for some; (b) can be relatively more expensive than medication alone in the short run; (c) have far more evidence for acute than for long-term effects; and (d) must be simultaneously implemented across settings and domain—that is, parent training, school interventions, and peer interventions need to be done conjointly to affect three domains. The first, third, and fourth of these limitations apply to stimulant medications as well (see discussion below). Given that both stimulant medications and behavioral treatments have limitations, many professionals believe that combined interventions are most effective and should be routinely employed.

Pharmacological Interventions

Central nervous system stimulant compounds (e.g., methylphenidate, dextroamphetamine, and mixed amphetamine salts) remain the first-choice medications for treatment of ADHD symptoms in children and adolescents (American Academy of Child & Adolescent Psychiatry, 2002; American Academy of Pediatrics, 2001). Recent estimates indicate that approximately 1.5 million children (or greater than 4% of the school-age population) are treated with CNS stimulants in the United States (Safer & Zito, 2000). Stimulant medication use has grown steadily throughout the last two decades, particularly among preschool and secondary school populations (Olfson, Marcus, Weissman, & Jensen, 2002; Robison, Sclar, Skaer, & Galin, 1999). The average duration of medication use is between 2 and 7 years depending upon the age of the child (Safer & Zito, 2000).

Approximately 75% of elementary-school-aged children with ADHD treated with stimulant medications respond positively to one or more doses (e.g., Rapport & Denney, 2000). Numerous empirical studies have documented the short-term behavioral effects of stimulants, including improvements in attention and task completion with concomitant reductions in

impulsivity, disruptive behavior, and, in some cases, aggression (e.g., MTA Cooperative Group, 1999a). Similar behavioral effects have been obtained for adolescents with ADHD; however, the percentage of positive responders is lower (i.e., 50% to 70%) than among elementary school children (Evans et al., 2001; Pelham, Vodde-Hamilton, Murphy, Greenstein, & Vallano, 1991; Smith et al., 1998), especially when measured in home and school settings. Several studies also have documented stimulant-induced, short-term improvements in impulsivity, disruptive behavior, and attention among preschoolers at risk for ADHD (Barkley, 1988; Chacko et al., 2005); however, young children may be at greater risk for adverse side effects of this treatment (see below). Stimulants have no effect on academic achievement in the short-term. No long-term effects have been reliably reported on any outcome measure.

Atomoxetine is a nonstimulant compound that affects norepinephrine. In several controlled trials, this drug reduced ADHD symptoms (e.g., Michelson et al., 2001). However, the number of studies is small, and the dependent measure assessed has typically been parent or clinician symptom ratings, as opposed to the large range of objective measures and hundreds more studies of stimulant effects. The approved label for atomoxetine has recently been modified and carries warnings of potential drug-related problems in aggressive behavior, suicidality, and liver toxicity (U.S. FDA, 2006), though some have disputed these warnings (Barkley & Fischer, 2005). These nonstimulant compounds do not appear to be as effective as stimulants and have comparable (or higher) risk of side effects, and, therefore, are considered second-choice pharmacological treatments (Wigal et al., 2005).

Other nonstimulant compounds evaluated as treatments for ADHD include clonidine, an antihypertensive agent, moderately effective in reducing ADHD symptoms (Connor, Fletcher, & Swanson, 1999) that may ameliorate sleep disturbance associated with the disorder (Prince, Wilens, Biederman, Spencer, & Wozniak, 1996). Guanfacine is an antihypertensive agent that

appears to have similar behavioral effects to clonidine but has not been evaluated extensively with controlled trials (Cohn & Caliendo, 1997).

Studies have investigated various antidepressant medications, including tricyclics (Spencer, Biederman, & Wilens, 1998; Spencer, Biederman, Wilens, Steingard, & Geist, 1993), and bupropion (Casat, Pleasants, Schroeder, & Parker, 1989; Conners et al., 1996). In general, although antidepressants have been effective in reducing some symptoms of ADHD, these compounds are far less well studied, less effective than stimulants, not FDA-approved for treatment of ADHD, and considered second-line treatments, at best, for this disorder.

There is an increasing trend for CNS stimulants to be prescribed in combination with other psychotropic medications (Guevara, Lozano, Wickizer, Mell, & Gephart, 2002), presumably to counteract stimulant side effects and/or to address comorbid disorders. For example, the combination of clonidine and a stimulant is associated with reduced aggression and conduct problems in children with comorbid ADHD and oppositional defiant disorder/conduct disorder (ODD/CD) (Hazell & Stuart, 2003) and comorbid ADHD and Tourette disorder (Kurlan et al., 2002). However, the combination was not more effective than methylphenidate alone on ADHD symptoms in school, and the combination was much less tolerable than methylphenidate or clonidine alone (Palumbo et al., 2005). Although it has been suggested that the combination of atomoxetine and a stimulant also may lead to better symptomatic improvement in children resistant to monotherapy (T. E. Brown, 2004), this combination has not been investigated in any controlled trial to date. Further, there are no data regarding the safety of this combination of medications. There are scant data regarding polypharmacy in general, with this population, despite its widespread use.

Although they are clearly efficacious acutely, medications have limitations, primary among them the lack of long-term demonstrations showing that the medications are safe when taken over long periods of time, that is, years (NIH Consensus Statement, 1998). For all

nonstimulant medications, short-term safety data are also lacking. Second, there is no evidence that stimulants produce long-term benefits—long-term studies have consistently failed to provide positive evidence (e.g., MTA Cooperative Group, 2004a, 2004b, 2006; NIH Consensus Statement, 1998; Volkow & Insel, 2003). In addition, as with behavior therapy, stimulants do not normalize functioning of most children even acutely (e.g., Swanson et al., 2001). Finally, although it is clear that stimulants improve ADHD symptoms, it is less clear that they improve functioning acutely in key domains that are thought to mediate long-term outcomes (e.g., academic functioning, parenting skills, peer relationships).

Strength of Evidence

For the stimulants (primarily methylphenidate), effect sizes for behavior (i.e., ADHD symptoms) based on adult ratings and observations are in the moderate to large range (Conners, 2002). Effect sizes for measures of academic productivity are low to moderate and are in the zero range for academic achievement. The overall effect size for stimulant treatment is in the moderate range, with larger effects associated with teacher and parent ratings than for direct observations and lab measures (Conners, 2002). Effect sizes for atomoxetine are in the moderate to large range on parent/clinician symptom ratings, while the magnitude of effect for other compounds (e.g., antidepressants) typically are lower than for stimulants and are in the low to moderate range overall.

Side Effects

Potential adverse side effects of stimulants include insomnia, appetite reduction, and irritability (Connor & Barkley, 2006), as well as growth suppression (approx. 1 cm per year) with continued use over several years (MTA Cooperative Group 2004b, 2006; Swanson et al., 2006). Growth reductions appear to be greater in young children with ADHD—approximately 1.4

cm/year, or a 20% reduction in growth rate for both height and weight. Acute adverse effects typically diminish with a reduction in dosage; growth suppression can be attenuated with twice-daily vs. t.i.d. dosing and not using the medication during summer and school vacations (Connor & Barkley, 2006). Stimulant medications do not appear to exacerbate tic disorders (Gadow, Sverd, Sprafkin, Nolan, & Ezor, 1995; Kurlan, et al., 2002; Palumbo, Spencer, Lynch, Co-Chien, & Faraone, 2004). Regarding risk for substance abuse, findings have been equivocal, with approximately equal numbers of studies showing no, heightened, and reduced risk (S. L. Anderson, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon, 2002; Barkley, Fischer, Smallish, & Fletcher, 2003; Biederman et al., 1999; Pelham, Molina, et al., 2006).

Nonstimulant compounds are also associated with adverse side effects. For example, atomoxetine can lead to stomach aches, nausea, decreased appetite, and failure to gain weight (Christman, Fermo, Markowitz, 2004). As noted above, the FDA recently issued a warning that atomoxetine may increase the risk of suicidal thinking in children and adolescents with ADHD; this risk is approximately 0.4% (U.S. FDA, 2006). Possible side effects associated with combined medication protocols have not been investigated extensively. However, most side effects of stimulants are dose related. Because many studies have shown that beneficial stimulant effects are maximized at much lower doses in the presence of concurrent behavioral treatment (e.g., Carlson et al., 1992; Pelham et al., 1993, 2005; Pelham, Burrows-MacLean, et al., 2006; Pelham, Gnagy, et al., 2006), a benefit of combined treatments may be lowered risk for such common and dose-related side effects as growth suppression.

Combined Interventions

Studies of combined interventions have the same characteristics as those that have evaluated behavior therapy alone. Thus, interventions have been conducted in controlled

settings such as summer treatment programs and special classroom settings (Abramowitz et al., 1992; Carlson et al., 1992; Pelham et al., 1993; Pelham, Burrows-MacLean, et al. 2003), as well as in regular classroom and home settings (Klein & Abikoff, 1997; MTA Cooperative Group, 1999a; Pelham et al., 1980, 1988). In a prototypic finding in a controlled setting, Carlson and colleagues (Carlson et al., 1992) reported that the effects of a behavioral intervention and 0.3 mg/kg MPH were equivalent and additive on several measures of behavior, such that the combination of the two resulted in behavioral improvement equal to the 0.6 mg/kg dose of MPH alone. Pelham, Burrows-MacLean, et al. (2005; Pelham, Burrows-MacLean, et al., 2006; Pelham, Gnagy, et al, 2006) recently extended this finding to a .15 mg/kg dose of MPH, indicating that *very* low doses of a stimulant plus a behavioral intervention maximize efficacy in a combined treatment regimen. Further, in the most recent study, the .15 mg/kg (per dose) regimen produced *no* side effects. As noted above, this is one of the major benefits of combined interventions for ADHD—better acute efficacy with lower doses and lower side effects. Notably, when high-intensity doses of either medication or behavior therapy are used, there is often little evidence for the value of combined interventions (e.g., Abikoff et al., 2004; Pelham et al., 2000)—not surprising given that a high dose of one effective treatment—regardless of treatment type or modality—often leaves little room for improvement with an additional intervention.

The between-group studies in natural settings also show evidence of combined treatment effects, but the number of studies is smaller, and their effects are somewhat smaller than in controlled settings relative to medication alone. For example, in the MTA (1999a) study, all four treatment groups—study medication, community treatment (mostly medicated by community physicians), behavior therapy, and combined interventions—showed large improvements from baseline to end of treatment, with relatively small differences among them. Further, secondary analyses showed clearly that combined treatment was superior to medication alone on almost every dependent measure, as well as for (a) comorbid children, (b) impairments in multiple domains (vs. *DSM* symptoms of ADHD), (c) parent–child relations, (d)

normalization, and (e) consumer satisfaction with treatment (Conners et al., 2001; Jensen et al., 2001; MTA Cooperative Group, 1999b; Pelham et al., 2006; Swanson et al., 2001; Wells, Epstein, et al., 2000; Wells et al., 2006). Interestingly, at the 10-month follow-up, combined treatment group was superior to behavior therapy only on ADHD and ODD symptoms and not on any other domain of functioning (e.g., social skills, parent–child relationships, academic achievement). This result is because 50% of the apparent incremental value of the medication component of the combined treatment condition had been lost, in part because some subjects stopped taking medication, while the effects of the behavioral intervention had been completely maintained, with only a minority having initiated pharmacotherapy (MTA Cooperative Group, 2004a, 2004b). Another 50% of the medication effect was lost with 1 more year of follow-up, leaving the combined group not different from the behavioral treatment and the medication groups (MTA Cooperative Group, 2006). This outcome is consistent with earlier, smaller studies (Gittelman et al., 1980; Pelham et al., 1988) that showed that when medication is withdrawn from a combined regimen, the medication effect is lost, but the behavioral effect is maintained.

Strength of Evidence

Effect sizes associated with combined stimulant–behavioral interventions are about the same as for stimulants alone (moderate to large) when examining impact on ADHD *symptoms* (MTA Cooperative Group, 1999a). Alternatively, except when ceiling effects are present as discussed, combined stimulant–behavioral treatment protocols lead to larger effects (in the moderate to large range) than for medication alone for a wide range of associated difficulties such as conduct problems, oppositional behavior, social skills, and disruptive behaviors in classroom, home, and recreational/peer settings (Carlson et al., 1992; Conners et al., 2001; Jensen et al., 2001; MTA Cooperative Group, 1999b; Pelham et al., 1993, 2005; Pelham, Burrows-MacLean, et al., 2006; Pelham, Gnagy, et al., 2006; Swanson et al., 2001; Wells, Epstein, et al., 2000; Wells et al., 2006). Combined treatment effects are in the moderate effect

size range for daily measures of academic seatwork productivity (e.g., Carlson et al., 1992; Pelham et al., 2005). As would be expected given the lack of evidence for benefit on long-term achievement of the two components, there is no evidence to date of combined treatment effects on academic achievement.

Diversity Issues

Although the most common treatments for ADHD are stimulant medication (42%) and psychosocial interventions (32%), patterns of use and treatment response may vary as a function of demographic factors (e.g., gender, ethnicity, and age) (Robison, Sclar, Skaer, & Galin, 2004). Most investigations of treatment outcome in the ADHD population have focused on elementary school-aged White males from middle-class backgrounds. Although research focused on girls with ADHD has increased in recent years, only a few studies of gender differences in treatment response are available, and those indicate comparable responsiveness across genders (e.g., Pelham, Walker, Sturges, & Hoza, 1989). The MTA study (1999a, 1999b) did not find gender to be a significant predictor of treatment outcome. Alternatively, at least two studies have found that girls with ADHD are less likely to be treated for their symptoms, particularly with stimulant medication, than are boys with this disorder (Bussing et al., 2005; Robison et al., 2004).

Recent studies indicate that there may be important differences in treatment acceptability and response between racial and ethnic groups, especially in relation to the use of stimulant medication. For example, African American children may experience higher blood pressure with stimulant treatment (R. T. Brown & Sexson, 1987). Several studies have noted lower usage rates of psychotropic medication as a treatment for ADHD among African Americans (e.g., Stevens, Harman, & Kelleher, 2005) and higher dosages of stimulants used with White children (Lipkin, Cozen, Thompson, & Mostofsky, 2005). African American children

with ADHD may be more likely to receive special education services than non-African American children with this disorder (Bussing et al., 2005). This pattern of differential treatment use may be related to racial differences in the acceptability of pharmacological treatment approaches as well as disparities in insurance coverage as a function of socioeconomic status. Finally, the MTA study results indicate a greater need and response to multimodal treatment on some measures among non-White children with ADHD relative to their White peers (A. L. Arnold, Elliott, et al., 2003). On many other measures (e.g., improvement in referred problems, parent satisfaction), treatment effects were independent of ethnicity (Pelham et al., 2006). Other treatment studies have also shown that behavioral treatments are effective independent of ethnicity (e.g., Pelham et al., 1993).

As discussed above, developmental factors may also play a role in treatment. For example, total daily dosages of stimulants (Lipkin et al., 2005) and the use of combined treatment protocols (Robison et al., 2004) increase with the child's age. In recent years, the largest increases in stimulant use are found among adolescents in the 12–18-year-old age range (Olfson, Gameroff, Marcus, & Jensen, 2003). Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

The most important consideration regarding treatment for children with ADHD is an analysis of the risks and benefits associated with the two treatment modalities and whether the relative benefits outweigh the relative risks. Behavioral treatments, pharmacotherapy with CNS stimulants, and combined behavioral and stimulant interventions are all solid evidence-based short-term treatments for ADHD. With medium effect sizes, they improve ADHD symptoms and associated impairments, with stimulants having a larger impact on the former and behavioral treatments on the latter. Both forms of treatment have acute limitations that are addressed in

part in combination therapies, giving rise to the popularity of multimodal treatments. Given that the acute side effects of stimulants are relatively minor and can be controlled by reducing dose or stopping medication, the risk–benefit analysis of the acute effects of stimulants is very favorable. The same is true for behavioral treatments, which have no known risks. Though some have argued that the rewards that are integral to behavior modification may have an iatrogenic effect on intrinsic motivation (Akin-Little, Eckert, Lovett, & Little, 2004), careful analysis of this issue fails to support this alleged side effect (also see discussion below regarding deviancy training in group settings). Because combined treatments yield relatively larger effects with relatively lower doses of medication, a risk–benefit analysis of them compared with medication would be favorable because they produce larger effects with a lower rate of side effects.

Despite the evidence that they are effective in the short-term, there is little evidence documenting long-term effects of any intervention for ADHD, and the risk–benefit analysis is different for long-term use of at least one modality—medication. There is no evidence that stimulants produce effects that maintain over years, generalize after medication is stopped, and/or alter long-term outcomes of treated individuals. There is growing concern that growth suppression may be an iatrogenic effect of stimulants that will reliably accompany long-term use. As discussed above, very little is known about the long-term risks of stimulants in other domains (e.g., potential elevation of risk for substance use). With regard to use over a period of 2 to 3 years, the risk–benefit analysis of stimulant medication does not appear to be favorable because beneficial effects appear to dissipate while side effects (e.g., growth) do not. A long-term risk–benefit analysis of stimulants (e.g., adult outcomes) is not known because, although there are not apparent long-term benefits, long-term *adverse* effects are unstudied. Only a single study has focused on the long-term use of behavioral treatment, and that study (the MTA) showed that the acute benefits of behavioral treatments maintained over time (up to 2 years posttreatment). Thus, the risk–benefit of behavioral treatment over this time period would be

favorable. There are no long-term (e.g., into adulthood) studies of behavioral treatment, so a risk–benefit analysis cannot be conducted. The MTA is also the only study of longer term effects of combined treatment. At the 2-year follow-up, children in combined treatment had the same outcomes as those in behavioral treatment alone, and they had growth suppression, as did the medicated children (albeit less because of lower doses). Thus, the use of combined treatments for 2 to 3 years would not appear to have a favorable risk–benefit ratio. There are no studies of combined treatment into adulthood. For this regimen to have a favorable risk–benefit ratio, it would have to produce incrementally beneficial improvements relative to behavioral treatment alone without a corresponding increase in side effects. There is some indication from a single short-term study that such an outcome might be attainable with very low dosages of stimulants (Pelham, Burrows-MacLean, et al., 2006; Pelham, Gnagy, et al., 2006), but more research is needed.

Despite widespread use, other interventions (e.g., neural feedback, cognitive–behavioral therapy [CBT], antidepressants) have little or no evidence base of support, so a risk–benefit analysis cannot be favorable. This would be particularly true for antidepressants, which have lower efficacy and greater side effects than stimulants.

Future Directions

One key issue that has received very little attention in the empirical literature, despite its importance in clinical practice, is the sequence in which interventions should be implemented for treating ADHD. Should medication be employed as the first-line treatment—the most common practice and the preference of many, if not most, physicians? If so, how long should it be tried and at what doses before—and if—behavioral interventions are added? Alternatively, should behavior modification be employed first, and if so, how should the components (parent training, school intervention, and peer intervention) be sequenced? How long should behavior

modification be tried and at what intensity before medication is added? Might a behavioral-treatment-first sequence result in lower societal use of stimulants or lower doses with fewer side effects when employed? Or should the two major modalities begin simultaneously so that all children receive both modalities? Given that ADHD is recognized as a chronic disorder and treatment needs to be implemented over long periods of time, a relevant question is when, if ever, can treatment be stopped? Which components can be time limited, and how does treatment need to be modified as children move through different developmental stages? Given the minimal impact of medication and psychosocial interventions on academic achievement, particularly over the long-term, what academic interventions are efficacious with this population, and how can these be delivered feasibly along with behavioral strategies in school settings? These are questions practitioners and parents face on a daily basis that beg answers. Studies must directly and systematically investigate these issues.

RATING SYSTEM

Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

ADHD	**ACUTE**		**LONG-TERM (over 12 months)**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION Stimulants	1b Impulsiveness, hyperactivity	1b Classroom task completion, disruptive behavior, noncompliance, aggression 1c Peer interactions/ social skills	1b Impulsiveness, hyperactivity	1 or 2 b Disruptive behavior, aggression, noncompliance 1c Peer interactions/social skills 1d Academic achievement, parent–child relationships, parenting skills	Anorexia Insomnia Growth suppression Potential exacerbation of/risk for substance abuse

		1d Academic achievement, parent–child relationships, parenting skills		1 or 2 d Special education placement, high school graduation, delinquency, vocational adjustment	
Tricyclics	1c Inattention, impulsiveness, hyperactivity	3c	3c	3c	Sedation, increased appetite, risk for cardiac toxicity
Buproprion	2c Inattention, impulsiveness, hyperactivity	No data	No data	No data	Rash, incremental risk for seizures
Clonidine	1c-d Impulsiveness, hyperactivity, inattention	1d Disruptive behavior	No data	No data	Sedation, irritability

Atomoxetine	1c Impulsiveness, hyperactivity, inattention	1d	1a-c Impulsiveness, hyperactivity, inattention	No data	Aggressive behavior Liver toxicity
PSYCHO-SOCIAL	1b Inattention, impulsivity, hyperactivity	1b Classroom task completion, disruptive behavior, noncompliance, aggression 1b Peer interactions/ social skills 1d Academic achievement 1b-c Parent–child relationships 1b-c Parenting skills	2c Inattention, impulsivity, hyperactivity	2c Classroom task completion, disruptive behavior, noncompliance, aggression 2c Peer interactions/social skills 2d Academic achievement 2c Parent–child relationships 2c Parenting skills	None

COMBIN-ATION	1b Inattention, impulsivity, hyperactivity	1b Classroom task completion, disruptive behavior, noncompliance, aggression 1b Peer interactions/ social skills 1d Academic achievement 1b Parent–child relationships 1b Parenting skills	2a Inattention, impulsivity, hyperactivity	2b Classroom task completion, disruptive behavior, noncompliance, aggression 2b Peer interactions/social skills 2d Academic achievement 2b Parent–child relationships 2b Parenting skills	Same as medications alone but reduced in magnitude because doses are lower

Oppositional Defiant Disorder and Conduct Disorder

Children and adolescents with oppositional defiant disorder (ODD) display high levels of noncompliance, defiance, and disruptive behavior (American Psychiatric Association, 2000). Conduct disorder (CD), a more serious disruptive behavior disorder, includes violation of major norms and rules (e.g., stealing) as well as covert and/or overt antisocial behavior (American Psychiatric Association, 2000). Approximately 2%–16% of children in the United States have ODD, and 1%–10% have CD, with males at higher risk for both diagnoses (American Psychiatric Association, 2000). ODD typically begins early in life and can be chronic through adolescence. Alternatively, there are two forms of CD, one beginning in childhood (i.e., during elementary school) and the other beginning in adolescence. Childhood-onset CD is more serious in terms of severity and chronicity of antisocial behavior (e.g., Moffitt, Caspi, Dickson, Silva, & Stanton, 1996). Children and adolescents with ODD or CD are at higher than average risk for ADHD, family and social relationship difficulties, academic underachievement, and delinquency (Frick & Loney, 1999).

Psychosocial Interventions

Psychosocial interventions, the most widely studied treatment approach for children with ODD/CD, include home-based behavior modification (Webster-Stratton, 1994), school-based behavior modification (Walker, Colvin, & Ramsey, 1995), CBT (Lochman & Wells, 2004), combined intervention approaches (Kazdin, Seigel, & Bass, 1992), and residential treatment (Chamberlain, Fisher, & Moore, 2002).

Home-based behavior modification typically involves parents receiving training in both antecedent-based (e.g., giving effective commands) and consequent-based (e.g., token reinforcement, response cost, and time out from positive reinforcement) interventions primarily

targeting child compliance and task completion. Similarly, school-based behavior modification approaches include the use of contingent teacher praise and/or reprimands, token reinforcement, response cost, time out from positive reinforcement, and self-management (e.g., self-monitoring, self-reinforcement) strategies. Most school-based interventions are implemented directly by classroom teachers; however, contingencies can also be delivered by peers (Cunningham & Cunningham, 1998) and/or parents (e.g., Pelham, et al., 1993).

Home- and school-based contingency management interventions are associated with significant improvements in compliance and concomitant reductions in aggression and disruptive behavior (Walker, Colvin, & Ramsey, 1995; Webster-Stratton, 1994), although these effects are less pronounced in adolescents, and generalization of effects across settings and time is limited. Behavioral parent training is associated with a medium effect size for reduction of externalizing behaviors (Maughan, Christiansen, Jenson, Olympia, & Clark, 2005).

Cognitive–behavior therapy (e.g., Lochman & Wells, 2004), multisystemic family treatment (Henggeler, Schoenwald, Rowland, & Cunningham, 2002), and combined contingency management and CBT (e.g., Kazdin, Siegel, & Bass, 1992) have also led to reductions in covert delinquent behavior, aggression, and, possibly, substance use. Multisystemic treatment provides problem-focused treatment within families and also supports family members in managing the interconnected systems of family, peer, neighborhood, and school in order to reduce risks (e.g., interactions with antisocial peers and problematic school performance) associated with delinquency (Tolan & Gorman-Smith, 1997). Various forms of residential treatment have been studied with multidimensional treatment foster care (Chamberlain, Fisher, & Moore, 2002) and the teaching family model (Friman et al., 1996) and have improved academic functioning and reduced arrests, incarceration, and drug use.

Limitations of Psychosocial Interventions

Although psychosocial—more specifically, behavioral—interventions are effective for reducing symptoms of ODD and CD, these treatments have several limitations including the following: (a) effects vary across children and may not be sufficient, (b) costs can be relatively high in terms of resources and time, (c) minimal evidence for maintenance and generalization (i.e., long-term effects) exists, and (d) simultaneous implementation across settings and domain is necessary to achieve optimal effects (Fabiano & Pelham, 2002). Perhaps because behavioral strategies require consistent implementation across time and caregivers, treatment adherence rates typically are under 50% unless ongoing feedback is provided to the adult (i.e., teacher or parent) implementing the treatment (e.g., Sterling-Turner, Watson, & Moore, 2002).

Strength of Evidence

Contingency management interventions implemented at home and school have resulted in moderate to large effect sizes for reduction in conduct problems (DuPaul & Eckert, 1997; Maughan et al., 2005). Cognitive-behavior therapy and multisystemic therapy have also resulted in moderate effect sizes (Brestan & Eyberg, 1998). Thus, the extant literature supports psychosocial interventions for the treatment of ODD (primarily contingency management at home and school) and CD (contingency management, CBT, combined or multisystemic therapy, and, possibly, residential treatment).

Pharmacological Interventions

A variety of psychotropic medications have been used to manage aggression and mood disturbance associated with CD. Although one does not often think of psychostimulants as a treatment for aggression in the context of disruptive behavior disorders, there are several

modest-sized studies attesting to a moderate effect in some children (Aman & Lindsay, 2002). The most elaborate of these showed a sizable effect in children having conduct disorders with and without ADHD (Klein et al., 1997). Several moderate-sized controlled trials have found lithium to reduce aggressive behavior in children and adolescents with CD (Gerardin, Cohen, Mazet, & Flament, 2002; Malone, Delaney, Leubbert, Cater, & Campbell, 2000). Controlled and open trials of classical antipsychotic medications such as haloperidol (e.g., Campbell, Cohen, Small, 1982) have shown significant reductions in aggression and disruptive behavior. However, haloperidol can be associated with significant adverse side effects (e.g., significant extrapyramidal side effects). Janssen Pharmaceutical launched several large-scale trials of risperidone in children with disruptive behavior disorders (DBDs; either CD or ODD). Three acute trials (totaling about 250 children, mostly over a 6-week interval) showed about a 50% reduction in DBD symptoms, as compared with about 20% with placebo (Aman & Lindsay, 2002; Findling et al., 2004; Snyder et al., 2002). There were three long-term trials that followed more than 600 children out to 1 year, with continued suppression of DBD symptoms, but not infrequently with troublesome weight gain. Divalproex sodium has also been found effective in ameliorating CD symptoms. Only one well-controlled study has been conducted to date (Steiner, Petersen, Saxena, Ford, & Matthews, 2003), although there are several small controlled and poorly controlled studies and/or case series attesting to some beneficial effects (see Steiner et al., 2003). For children with comorbid ADHD and ODD/CD, the combination of stimulant medication (e.g., methylphenidate) and clonidine is associated with improvements in symptoms of both disorders (e.g., Hazell & Stuart, 2003).

There is minimal evidence for psychopharmacological treatment of ODD, except in cases where comorbid ADHD is present. The multimodal treatment of ADHD (MTA) study indicated that children with ADHD and ODD responded best to medication treatment (i.e., psychostimulants) with or without the concomitant use of behavioral interventions (Jensen et al.,

2001). Further, as mentioned above, the combination of methylphenidate and clonidine may lead to reduction of both ADHD and ODD symptoms. One controlled study suggests that atomoxetine may also reduce symptoms of both disorders, especially at higher dosages (Newcorn, Spencer, Biederman, Milton, & Michelson, 2005).

Side Effects

All of the medications used to treat aggression and conduct problems are associated with potential adverse side effects that, although rare, can be relatively serious. Side effects of lithium can include polyuria, polydipsia, motor tremor, increase in appetite, dryness of mouth, general muscular weakness, and memory reduction (Henry, 2002; Luby & Singareddy, 2003). Risperidone, haloperidol, and other neuroleptic medications can be associated with serious extrampyramidal side effects (e.g., tardive dyskinesia) as well as headache, nausea, and drowsiness (Edwards, & Pople, 2002; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999). Divalproex sodium can lead to a variety of side effects, including abdominal pain, headache, dizziness, drowsiness, and memory difficulties. Possible side effects of clonidine include sedation, lethargy, dryness of mouth, and low blood pressure (Connor, 2005). Stimulants can be associated with a range of side effects, including loss of appetite, sleep disturbance, headaches, stomach aches, and possibly motor tics (Connor & Barkley, 2006). Atomoxetine can lead to stomach aches, nausea, decreased appetite, and weight loss (Christman, Fermo, & Markowitz, 2004). The FDA recently issued a warning that atomoxetine may increase the risk of suicidal thinking in children and adolescents with ADHD; this risk is approximately 0.4% (U.S. FDA, 2005a). Possible side effects associated with combined medication protocols have not been investigated extensively.

Strength of Evidence

Pharmacological effects on aggression and conduct problems are in the small to moderate range, except for lithium's effects on aggression, which are in the large range. Psychotropic medication (primarily lithium) may reduce aggression and stabilize mood in children and adolescents with CD. Stimulants and the combination of stimulants plus clonidine may address ODD symptoms in children with comorbid ADHD and ODD. In general, however, effect sizes for psychosocial interventions are larger than effect sizes for psychotropic medication with this population.

Combined Interventions

Very few studies have specifically evaluated the effects of combined psychosocial and medication treatment protocols for children with ODD or CD. Kolko, Bukstein, and Barron (1999) examined the separate and incremental effects of two doses of methylphenidate and behavior modification in 16 children with ADHD and either CD or ODD in the context of a partial hospitalization program. Although there were considerable individual differences in treatment response, both treatments were associated with positive effects in isolation and in combination. In similar fashion, the MTA study found that children with comorbid ADHD and ODD/CD showed a positive behavioral response to carefully titrated stimulant medication with or without adjunctive psychosocial intervention. Alternatively, children with ADHD and multiple comorbid disorders (ODD/CD and anxiety disorder) responded optimally to the combined medication and psychosocial treatment protocol (Jensen et al., 2001).

Strength of Evidence

The combination of psychosocial (behavioral) and pharmacological interventions for children with comorbid ADHD and ODD/CD leads to moderate to large effect size reductions for ADHD symptoms. Effect sizes for changes in aggression, oppositional behavior, and conduct problems are in the small to moderate range (MTA Cooperative Group, 1999a, 1999b).

Diversity Issues

Most treatment outcome studies for children and adolescents with ODD/CD have been conducted with White males, with very few studies examining differential treatment response across gender and ethnic groups. There is a higher prevalence of disruptive behavior disorders in boys; however, girls with CD may be at greater risk for comorbid internalizing symptoms (Keenan, Loeber, & Green, 1999). Further, although precursors of CD overlap with boys, some predictor variables may be specific to girls (e.g., emotionality, experience of empathy and guilt), and aggression may be manifested differently (i.e., through indirect or relational aggression rather than physical aggression) (Kann & Hanna, 2000).

Although few studies have specifically examined gender differences in treatment response, investigators have speculated that interventions focused on peer relationships rather than gang involvement may be more effective for girls with CD (Kann & Hanna, 2000). Further, it is possible that family factors (e.g., parenting style) may predict parent training outcomes to a greater degree in girls than in boys (Webster-Stratton, 1996).

Differences in treatment outcome between ethnic and racial groups require further study, although preliminary research examining potential moderators of intervention outcome have not found differences for African American and White children (e.g., Lochman & Wells, 2004). Low socioeconomic status, especially for single-parent families, is associated with lower response to

parent training interventions (Reyno & McGrath, 2006). Lower rates of parental participation and treatment adherence in low SES families may account for negative treatment outcomes. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

No studies have formally analyzed benefits versus risks for pharmacological or psychosocial treatments of ODD/CD. Potentially significant adverse side effects, albeit rare, can occur with psychopharmacological interventions. There are fewer risks associated with behavioral interventions, but these include feasibility and resource concerns, as well as possible social contagion effects of group-based treatments (Dishion & Dodge, 2005). However, the latter have only been found for young adolescents and on some dependent measures, and recent meta-analytic tests have not found overall support for iatrogenic or deviancy training effects in group interventions for children with ODD and CD (Weiss et al., 2005). Given the larger effect sizes associated with psychosocial interventions, these are preferred as first-line treatments over psychotropic medications.

Future Directions

There are several important directions for future investigations of treatments for children with ODD and CD. More effectiveness research studies are necessary to help clinicians implement community-based interventions that have been documented to be effective. In addition, more studies need to examine treatment effects for children and adolescents from diverse backgrounds to identify specific risk factors, treatment predictors, treatment modalities, and outcomes associated with background factors (e.g., gender, race, and ethnicity). Finally, given the complexity and intractability of disruptive behavior disorders, more investigations of

combined treatments need to be conducted to elucidate effective combinations of psychosocial interventions and/or medications across home, school, and community settings.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

ODD CD	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION					
Lithium	2b Aggression				Polyuria, polydipsia, motor tremor, increase in appetite, dryness of mouth, general muscular weakness, memory reduction
Antipsychotics	2b Aggression, disruptive behavior				Sedation, extrapyramidal effects, headache, nausea
Divalproex sodium	2c Aggression				Abdominal pain, headache, drowsiness, dizziness, memory difficulties
MPH and clonidine	2c Aggression				Sedation, appetite reduction, low blood pressure

Atomoxetine	2a ADHD symptoms 2b ODD and ADHD symptoms				Stomach aches, nausea, decreased appetite, and weight loss; possible increase in suicidal thoughts
PSYCHOSOCIAL					
Behavioral	1a-b Compliance, aggression, disruptive behavior	2b Academic functioning 3a Peer relationships	2d Compliance, aggression, disruptive behavior		Possible social contagion effect for group treatment
CBT	3a Covert delinquent behavior Substance abuse	Peer relationships	2-3 a Covert delinquent behavior Substance abuse		Possible social contagion effect for group treatment
Residential	2c Arrests drug use	Academic functioning			Possible social contagion effect for group treatment

COMBINATION MPH and Psychosocial for ODD/CD with ADHD	2b ODD and ADHD symptoms	2d Academic functioning 2c Peer relationships 2c Parent–child relationships	2c ODD and ADHD symptoms	2d Academic functioning 2c Peer relationships	Insomnia, appetite reduction, growth inhibition

Tourette and Tic Disorders

According to the *DSM–IV*, Tourette disorder (TD) requires the presence of multiple motor tics and at least one vocal tic, although not necessarily concurrently, for at least 12 months. Frequent motor or vocal tics, but not both, of at least 12 months' duration warrant a diagnosis of chronic motor or vocal tic disorder. Collectively, these two disorders are referred to as chronic tic disorder (CTD). Transient tic disorder, characterized by mild tics present for at least 1, but not longer than 12, months rarely requires pharmacological intervention and is not considered further in this review. In all cases, tic onset must be before age 18 years. Community prevalence estimates for TD range from 0.1% to 1%, rising to 1% to 2% when including chronic motor or vocal tic disorder as well (Scahill, Sukhodolsky, Williams, & Leckman, 2005). Coprolalia, often portrayed as the defining symptom of TD, is, in fact, relatively rare, occurring in less than 10% of individuals with this diagnosis (APA, 2000).

The clinical course of TD is typically marked at onset by simple motor tics such as eye blinking and facial or head/neck tics at approximately 6–7 years of age, followed by the development of vocal tics and a rostral-caudal progression of increasingly complex motor tics over several years. Tics usually follow a fluctuating course characterized by occasional bouts of increased tic frequency and severity interspersed with periods of relative quiescence. In the majority of cases, CTD follows a fluctuating, yet generally worsening, course, reaching maximum severity in late childhood, followed by a significant decrease in severity throughout adolescence and, in up to 50% of cases, complete remission by adulthood (Leckman et al., 1998). Comorbid ADHD, OCD, anxiety, depression, and/or learning difficulties are common in youngsters with CTD and may account for much of the functional impairment seen in these cases (Freeman et al., 2000).

Psychosocial Interventions

Numerous psychosocial approaches have been reported for the treatment of CTD. including contingency management, massed practice, relaxation training, hypnosis, self-monitoring, awareness training, exposure with response prevention (ERP), and habit reversal training (HRT) (see reviews by Peterson, Campise, & Azrin, 1994; Piacentini & Chang, 2001). Although the medical literature commonly describes psychoeducation and social support as the first-line psychosocial interventions (Leckman, King, Scahill, Findley, Ort, & Cohen, 1999), HRT has received the most empirical attention and support (Peterson, Woods, & Piacentini, 2006). HRT is a multicomponent intervention that first teaches individuals methods to increase awareness of their tics and urges to tic, and then instructs them on employing a competing response (e.g., isometric tensing of muscles opposite to the tic movements) contingent on tic or urge expression (Azrin & Nunn, 1973). Relaxation training/stress management, social support, and contingency management procedures, often paired with HRT, serve to address environmental and intrapersonal tic exacerbating factors and/or enhance treatment motivation and compliance (Azrin & Nunn, 1973).

While HRT has demonstrated durable benefit for youngsters with CTD in a series of single-subject and multiple-baseline design studies and in an as-yet-to-be-published small controlled trial (Piacentini & Chang, 2006), published between-group design data from this age group is very limited. Only two of the six published randomized between-group studies of HRT included children (Azrin & Peterson, 1990; Verdellen, Keijsers, Cath, & Hoogduin, 2004), but neither report provided sufficient detail to examine outcome by age. Of interest, Verdellen et al. (2004) found ERP, most commonly used in the treatment of OCD, to be as effective as HRT for tic reduction in their mixed-age study. Of the remaining psychosocial approaches, only contingency management procedures have generated enough empirical support to warrant consideration of use (Peterson, Woods, & Piacentini, 2006). An NIMH-funded, randomized

controlled, multisite trial comparing a combined HRT plus contingency management approach to psychoeducation plus supportive therapy for childhood CTD (Comprehensive Behavioral Intervention for Tics Study, or CBIT) should significantly enhance the psychosocial treatment evidence base for these disorders when completed in 2007.

Limitations of Psychosocial Interventions

Although a number of single-case, small-case series, and laboratory analogue studies document the benefits of behavior therapy for CTD, data from controlled psychosocial treatment trials, which included children and adolescents, are very limited. Almost all of these studies contain mixed child and adult samples, and findings are rarely broken down by age. Clinical implementation and study of behavioral treatments have also been hampered by resistance to this form of treatment within the medical community and the lack of clinicians trained in these techniques. The psychosocial treatment literature contains insufficient information to ascertain the moderating effects of comorbidity and symptom severity on outcome, which is unfortunate given that these two factors often drive clinic referral. Literature was not found to suggest adverse effects related to HRT.

Strength of Evidence

Overall, the available evidence suggests moderate effect sizes for psychosocial treatment, most notably HRT, of chronic tic disorder in childhood. These effects appear to be fairly durable, with continuing benefits demonstrated out to one year post treatment in some studies. HRT also appears to have a beneficial impact on tic-related functional impairment, although the measure of this variable, the YGTSS Overall Impairment Scale (Leckman et al., 1999) is relatively limited in scope. While less well documented than HRT, exposure (exposure entails having the child withhold tic behavior when the premonitory urge occurs) plus response

prevention and contingency management approaches also appear to be moderately effective for the acute reduction of tic severity.

Pharmacological Interventions

The relatively large number of medications used to treat CTD over the years highlights the difficulty in achieving meaningful symptomatic relief in the absence of significant adverse events (Sandor, 2003). The most well-studied pharmacological agents for childhood CTD include the dopamine receptor blockers (typical neuroleptics), haloperidol and pimozide; the atypical neuroleptics, risperidone and ziprazidone; and the alpha $_2$-adrenergic agonists, clonidine and guanfacine (Cheng-Shannon, McGough, Pataki, & McCracken, 2004; Sandor, 2003; Zinner, 2004). Randomized controlled trials, employing either between-group or crossover designs, have been published for each of these agents (Cummings et al., 2002; Gaffney et al., 2002; Gilbert et al., 2004; Sallee et al., 1997, 2000; Scahill et al., 2001; Shapiro et al., 1989; Singer et al., 1995; The Tourette's Syndrome Study Group, 2002). Although characterized by relatively small sample sizes and brief duration, these studies suggest at least moderate treatment effects for the typical and atypical neuroleptics and guanfacine, with more equivocal support for clonidine. Several other agents, including atomoxetine, a selective noradrenergic reuptake inhibitor, mecamylamine, a nicotinergic receptor antagonist, and botulinum toxin, are being used with some frequency for childhood CTD in spite of both limited empirical support and/or concerns with safety (McCracken et al., 2003; Sandor, 2003; Zinner, 2004). Few controlled data exist regarding the long-term efficacy and safety of psychopharmacological treatments for childhood CTD.

Side Effects

Neuroleptic use is associated with a range of serious adverse effects, including sedation, cognitive dulling, weight gain, extrapyramidal symptoms, ECG findings, akathisia, depression, and anxiety (Cheng-Shannon et al., 2004; Sandor, 2003; Zinner, 2004). While the atypical neuroleptics, risperidone and ziprasidone, are thought to be associated with reduced risk of extrapyramidal symptoms and tardive dyskinesia, risperidone is associated with significant weight gain. Among the typical neuroleptics, Sallee et al. (1997) reported that haloperidol was associated with three times the rate of serious adverse effects as pimozide in youngsters with CTD, although the two treatments did not differ in efficacy. Although many of the controlled child CTD neuroleptic trials reported relatively low rates of serious adverse effects, it must be noted that these trials were generally of insufficient duration, typically no more than 8 weeks, to fully evaluate safety. The adverse effects of long-term treatment with neuroleptic drugs have been well documented (Werry & Aman, 1999), particularly in adult populations, and their therapeutic effects in pediatric populations are of potential concern. Significantly less harmful than that of the neuroleptics, the side effect profile of clonidine and guanfacine includes sedation, headache, irritability, and an increased risk of postural hypotension (Zinner, 2004).

Combined Interventions

Combined interventions for childhood CTD have yet to be systematically studied.

Diversity Issues

The potential moderating effects of gender and race/ethnicity on treatment outcome have not been examined for childhood CTD. The vast majority (85%-95%) of study samples have been White and male, related in some part, at least, to the gender distribution of the

disorder in the community. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

Treatment of tics in children and adolescents has evolved significantly over the past 2 decades. In most cases, the decision to treat a child's tics is not simply based on their presence but rather on the extent to which they are distressing or physically harmful to the child and/or interfere with his or her academic, social, and family functioning. From a psychopharmacological perspective, the level of tic reduction must be balanced with the increased risk of side effects at higher medication doses. Whether these risks also increase with low doses is uncertain. Side-effect-related dosing limitations typically preclude complete eradication of tics by medication alone in favor of a more achievable goal of 40%–50% reduction in tic severity (Scahill, Chappell, King, & Leckman, 2000). Even though clonidine and guanfacine are less consistently effective than the neuroleptics in reducing tic severity, these agents are typically considered as first-line medication treatments for all but the most severe tics because of their increased safety and tolerability.

Renewed attention to psychosocial management strategies for tic control, most notably habit reversal training and contingency management approaches, has the potential to dramatically enhance treatment options for affected youngsters. Although controlled data for childhood CTD are limited, those data that do exist support HRT as a viable treatment option either alone or in combination with medication for youngsters with mild to moderately severe tic disorder. At present, unfortunately, access to treatments for CTD is extremely limited because of a dearth of clinicians, including behavioral psychologists and child psychiatrists, who typically prescribe medications for this disorder. Results from the ongoing NIMH-funded multisite child

CBIT may serve, however, to spur dissemination of HRT throughout the CTD treatment community, with the goal of ultimately establishing this treatment as a front-line intervention.

Future Directions

Although controlled data from children and adolescents is now available for at least six different pharmacological agents and two psychosocial interventions, treatment options for youngsters with CTD remain less than ideal because of the lack of highly efficacious medications, concerns with the safety and tolerability of existing medications, and the lack of clinicians trained in the use of habit-reversal training and other promising behavioral interventions. Given the relatively poor side-effect profiles associated with the most commonly used anti-tic medications, greater attention needs to be placed on developing and testing a fuller range of psychosocial interventions for childhood CTD. Studies examining combined medication/psychosocial treatment approaches, including the identification of treatment sequencing strategies, are also needed. Research documenting the longer term efficacy and safety of existing treatments remains to be conducted, as do studies examining the impact of demographic status (age, gender, race), comorbid psychopathology, and cognitive functioning on outcome. In addition, little is known about the impact of existing treatments on psychosocial functioning, both acutely and over the long-term. Finally, translational studies aimed at elucidating the mechanisms by which behavioral and psychopharmacological treatments operate are also necessary to guide the refinement of existing treatments and spur the development of more effective future interventions.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

Chronic Tic Disorder, incl. Tourette Disorder	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms		
MEDICATION					
Alpha 2 agonists clonidine	2c-d Mild to moderate tics, ADHD	2c-d	No data	No data	Sedation, dry mouth, headache, irritability, dysphoria, postural hypotension. Guanfacine associated with less risk of sedation
Guanfacine	2b-c Tics, ADHD	2c-d	No data	No data	
Neuroleptics haloperidol pimozide	2b tics 2c tics	No data No data	No data No data	No data No data	Sedation, cognitive dulling, akathisia, extrapyramidal symptoms (EPS), ECG effects, risk of tardive dyskinesia, dysphoria. Pimozide associated with less severe sedation and EPS
Atypical neuroleptics	2b tics 2b-c tics	No data	No data	No data	Sedation, weight gain, EPS, galactorrhea, dysphoria, increased risk of hepatoxicity and diabetes mellitus.

risperidone ziprazadone					Ziprasidone less likely to cause weight gain than risperidone.
Atomoxetine	2c tics, ADHD	No data	No data	No data	Stomach aches, nausea, decreased appetite, weight loss, risk of increased suicidal thinking
PSYCHOSOCIAL					
Habit Reversal Training (HRT)	2a-c	2c	No data	No data	May be associated with transient tic increase
Exposure and Response Prevention (ERP)	3b	No data	No data	No data	Attempts to resist tic expression may lead to discomfort
Contingency Management	2c	No data	No data	No data	Potentially time-consuming, questionable generalizability
COMBINATION	No data	No data	No data	No data	

Obsessive–Compulsive Disorder

Obsessive–compulsive disorder (OCD) is generally a chronic and impairing condition with a prevalence of 0.5%–2.0% in children and adolescents (Rapoport et al., 2000). Relatively heterogeneous in terms of presentation, the most common symptoms in childhood include fears of harm or other negative outcomes; concerns with germs, contamination, and illness; and ritualized and/or excessive washing, cleaning, counting, checking, and arranging. The clinical picture and treatment planning is often complicated by the presence of comorbid psychiatric disorders, most commonly other anxiety disorders, depression, ADHD, and tic disorders, which are seen in up to 75% of youngsters with primary OCD (D. A. Geller et al., 2000). Up to 40% of OCD youngsters meet diagnostic criteria for the disorder up to 15 years after initial identification, with another 20% evidencing subclinical disturbance at follow-up (Stewart et al., 2004).

Psychosocial Interventions

The most well-studied cognitive–behavioral treatment for OCD regardless of age is exposure plus response prevention (ERP; Meyer, 1966). From a learning theory perspective, OCD is thought to be maintained by negative reinforcement, wherein performance of the compulsion is reinforced by its ability to alleviate anxiety or distress triggered by an associated obsession. ERP disrupts the negative reinforcement cycle and allows for habituation of associated anxiety by systematically triggering the obsession through in vivo or imaginal exposure while simultaneously encouraging the child to refrain from ritualizing (Foa & Kozac, 1986). Although the contribution of cognitive distortions, including excessive fears of harm and exaggerated responsibility for negative outcomes, is less clear for OCD in children and adolescents than in adults, some form of cognitive intervention has become relatively standard in the treatment of childhood OCD. These techniques are typically aimed at teaching the child to

recognize and relabel his/her obsessive fears as OCD and more accurately evaluate the likelihood of feared consequences. CBT for childhood OCD also typically includes additional treatment components such as psychoeducation, structured parental involvement, and built-in reward systems to enhance motivation and compliance with exposure and foster greater generalization of gains (March & Mulle, 1998; Piacentini & Langley, 2004). In addition to a number of small positive open trials, three randomized controlled trials, two of which compared CBT to medication, have now been published and provide additional support for the efficacy of CBT for childhood OCD (Barrett, Healy-Farrell, & March, 2004; de Haan, Hoogduin, Buitelaar, & Keijsers, 1998; Pediatric OCD Treatment Study Team [POTS], 2004). These studies are more fully described below.

Barrett et al. (2004) found individual and group-format child CBT, each of which also included a family intervention component, both superior to a wait-list control condition. Both CBT conditions led to an approximate 60% decrease in OCD symptom severity, compared with no change for wait-list youngsters. Although this study supports the efficacy of CBT for youngsters with OCD, these findings are tempered by the lack of a primary outcome measure integrating both child- and parent-report information and the fact that the wait-list condition was only 4–6 weeks in duration. Contrary to expectation, treatment-related gains were not observed on any family measures. Observed gains were largely maintained at a 6-month follow-up of the active treatment groups. In the only child OCD trial to date employing psychosocial treatment as a control, individual CBT supplemented with weekly family CBT proved superior to relaxation training plus psychoeducation on some but not all outcome measures (Piacentini et al., 2004). These results are partially consistent with Silverman, Kurtines, Ginsburg, Weems, Lumpkin et al. (1999) and Last, Hansen, and Franco (1998), who failed to find differences in outcome between CBT and psychoeducation/support for non-OCD child anxiety. The results raise questions about the specificity of CBT effects, although not CBT efficacy itself, for these disorders. In the first direct comparison of CBT and medication, CBT proved statistically

superior to clomipramine, a serotonin reuptake inhibitor, in terms of both rate of response to treatment (66.7% vs. 50%) and degree of symptom reduction (59.9% vs. 33.4%) (de Haan et al., 1998). Although controlled data regarding the long-term efficacy of CBT for childhood OCD are limited (e.g., Barrett et al., 2004), findings from open trials (Piacentini, March, & Franklin, 2006) and controlled research with adults (Abramowitz, 1997) suggest that such gains may be durable. In spite of widespread clinical use, the efficacy of psychodynamic, supportive, and family therapy as well as other non-CBT psychosocial approaches have yet to be demonstrated for OCD in individuals of any age (Jenike, 1990; March, Leonard, & Swedo, 1995).

Limitations of Psychosocial Treatment

In spite of a significant expansion in the evidence base supporting the use of CBT for childhood OCD, a number of limitations regarding this form of treatment remain, including the following: (a) many youngsters show less-than-adequate response to CBT, and potential moderators of treatment response remain to be identified; (b) the impact of treatment on functional outcomes remains poorly understood; (c) in spite of theoretical reasons to include family members in treatment, the incremental efficacy of structured family involvement in therapy has yet to be established; and (d) similar to treatment studies of many childhood disorders, treatment studies for childhood OCD are likely to include participants that may not otherwise have sought treatment, which may affect the generalizability of findings to clinical samples.

Strength of Evidence

Multiple controlled trials provide strong evidence regarding the efficacy of exposure-based CBT for treating OCD in children and adolescents, and data from one controlled trial support the durability of benefits up to 6 months posttreatment (Barrett et al., 2004). However, as noted above, sufficient controlled data are not yet available to firmly establish the positive

impact of CBT on psychosocial functioning or the incremental efficacy of adding a systematic family intervention component to individual child treatment.

Pharmacological Interventions

A large number of industry-sponsored randomized clinical trials have demonstrated the efficacy of the SSRIs as well as the serotonin reuptake inhibitor clomipramine for the treatment of childhood OCD (Leonard, Ale, Freeman, Garcia, & Ng, 2005), and fluoxetine, fluvoxamine, sertraline, and clomipramine have all received FDA approval for use in children and adolescents with this disorder. Overall, however, medication efficacy can be considered relatively modest, with active treatment typically yielding an average 30–40% decrease in OCD symptom severity (March & Curry, 1998). A recent meta-analysis of 12 published randomized placebo-controlled medication trials for childhood OCD (1,044 participants) reported an effect size of 0.46, with clomipramine showing superior efficacy to the SSRIs, which did not differ from each other (D. A. Geller et al., 2003). Treatment with SSRIs has been shown to significantly reduce OCD-related functional impairment at least over the short term (D. A. Geller, Biederman, et al., 2001; Liebowitz et al., 2002).

Although a significant proportion of medication responders continue to meet criteria for clinically significant OCD following acute study treatment, longer term data from a 1-year extension trial suggest that treatment gains may continue to accrue over time (Cook et al., 2001). However, these findings are tempered by high rates of sample attrition and the fact that youngsters in the extension trial were allowed to participate in concomitant psychotherapy during this phase of the study. Symptom recurrence following medication discontinuation has not been systematically studied but is expected to be common (Leonard et al., 2005).

Side Effects

As in the non-OCD anxiety trials, children and adolescents with OCD tend to tolerate SSRIs relatively well. The most commonly reported SSRI-related adverse effects include nausea, diarrhea, insomnia, loss of appetite, sedation, tremor, sexual dysfunction, and disinhibition (Leonard et al., 2005). However, these effects are often transient in nature and, in some blinded trials, SSRI-related attrition rates do not differ between the active and placebo treatment groups (March & Curry, 1998). Potential clomipramine-induced cardiotoxicity contraindicates use of this medication as a first- or even second-line treatment (March, Frances, Carpenter, & Kahn, 1997). As noted elsewhere in this report, however, recent FDA findings of an association between antidepressant use and increased risk of suicidality in children and adolescents have dramatically altered the parameters of medication use in this age group.

Strength of Evidence

A number of large-scale controlled trials have demonstrated the efficacy of serotonin reuptake inhibiting medication for treating OCD in children and adolescents. Based on the recent meta-analysis by D. A. Geller et al. (2003), however, the overall efficacy of pharmacotherapy for this disorder can only be described as modest.

Combined Interventions

The recently published POTS trial provides the only controlled data regarding the efficacy of combined (CBT plus medication) treatment for youngsters with OCD. This trial used a multicenter approach to compare CBT, sertraline (SER), and their combination (COMB) to pill placebo (PBO) in 112 OCD youngsters aged 7–17 years (POTS, 2004). Using an intent-to-treat analytic strategy, all three active treatments significantly outperformed pill placebo. In addition, COMB was found superior to both CBT and SER, results of which did not differ from one

another. However, a significant advantage was found for the two CBT conditions using "excellent response" as the outcome (COMB: 54%; CBT: 39%; SER: 21%; PBO: 3%). Study results were tempered by a significant Site x Treatment interaction, where CBT alone was equivalent to COMB at one site but not at the other. Therefore, under certain circumstances, optimal CBT may preclude the need for medication augmentation.

Diversity Issues

Gender and ethnicity have yet to be investigated as potential moderators of treatment response for either psychosocial or psychopharmacological interventions. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

Although the efficacy of both CBT and psychopharmacological approaches are well supported for adults with OCD (e.g., Abramowitz, 1997), sufficient data to evaluate the comparative efficacy and safety of psychosocial and psychopharmacological treatments for OCD in children and adolescents are only now becoming available (Abramowitz, Whiteside, & Deacon, 2005; D. A. Geller et al., 2003). These data support the use of CBT as the first-line treatment of choice, adding medication only if necessary for children and adolescent OCD (POTS, 2004).

Future Directions

In spite of the relatively robust effect sizes noted for CBT and combined treatment, a substantial proportion of children and adolescents in both the CBT and medication trials noted

above demonstrated a less than optimal response. Evidence-based intervention strategies remain to be developed and tested for these youngsters as well as for those whose clinical picture is complicated by higher levels of OCD symptom severity and/or significant diagnostic comorbidity. More data regarding the ability of existing treatments to positively affect psychosocial functioning is also required. In addition, controlled research examining the critical components of CBT for childhood OCD and the mechanisms of action for this treatment has yet to be conducted. For example, while the efficacy of primarily cognitive interventions has garnered some support in the adult literature (e.g. Abramowitz, 1997), this issue remains to be addressed in younger populations. Even though the impact of child OCD on family functioning is relatively well documented (e.g., Piacentini et. al., 2003; Waters & Barrett, 2000), family participation in child treatment has not yet been shown to enhance either child outcomes or family functioning (e.g., Barrett et al., 2004). As a result, additional research is also required to establish the role of the family in child treatment (Barmish & Kendall, 2005).

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

OCD	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION SSRIs and clomipramine	1b-c Obsessions, compulsions	1b General functioning	4b Continued efficacy documented to 12 months of continued use	No data	Can cause agitation, nausea, and suicidality (recent FDA warning). Clomipramine can also cause sedation, fainting, seizures, tremor, weight gain.
PSYCHOSOCIAL Exposure-based CBT	1a Individual obsessions, compulsions 2a for group	1c General functioning 2d	4b Continued efficacy documented to 18 months No data	No data No data	Exposure-triggered anxiety may be uncomfortable for some; intolerable in rare instances (mediator of efficacy)

COMBINATION CBT+SSRI (sertraline)	2a Obsessions, compulsions	No data	No data	No data	Same as monotherapies

Anxiety Disorders

Anxiety disorders are among the most common mental health conditions affecting youth. Epidemiological studies estimate the prevalence of impairing anxiety disorders at greater than 10%, with four of five large surveys estimating prevalence to be 12 to 20% (Achenbach et al., 1995; Costello & Angold, 1995; Pine, 1994; Shaffer et al., 1996). It is recognized that 20% is an unusually high prevalence of anxiety disorders. Although anxiety has been historically considered innocuous and developmentally normative, childhood anxiety disorders are associated with significant impairment; interfere with school performance, family, and social functioning (Benjamin, Costello, & Warren, 1990); and are as impairing in many ways as disruptive behavior disorders (Ialongo et al., 1994). Moreover, anxiety in childhood predicts adult anxiety disorders, major depression, suicide attempts, and psychiatric hospitalization (Ferdinand & Verhulst, 1995; Pine, 1994). Both retrospective and prospective studies confirm that anxiety disorders have an early onset and a chronic and fluctuating course through adolescence and into adulthood (Costello et al., 2003; Eaton, 1995; Kessler et al., 1994).

Most controlled psychosocial and medication trials for childhood anxiety disorder have studied generalized anxiety disorder (GAD), separation anxiety disorder (SAD), and social anxiety disorder (SoAD) collectively, as these three disorders (a) share a common underlying construct of anxiety, (b) are highly comorbid with each other, both cross-sectionally and over time; (c) infrequently occur as isolated conditions; and (d) show similar familial relationships with adult anxiety and depressive disorders (Gurley, Cohen, Pine, & Brook, 1996; P. C. Kendall & Brady, 1995; Last et al., 1991). Studies have found both CBT and pharmacological interventions employing the selective serotonin reuptake inhibitors (SSRIs) to be efficacious for the treatment of children and adolescents with these three disorders in multiple randomized controlled trials. As such, the level of support for these treatments can be considered good to excellent.

Psychosocial Interventions

Several randomized controlled clinical trials have found CBT superior to wait-list control for relieving primary anxiety symptoms associated with GAD, SAD, and SoAD, to the point where a large percentage of treated youngsters were indistinguishable from non-ill peers, and for enhancing social competence in children and adolescents with SoAD (Barrett et al., 1996; P. C. Kendall 1994; P. C. Kendall & Southam-Gerow, 1996; P. C. Kendall et al., 1997; Last et al., 1998). In their systematic review of the CBT literature, Cartwright-Hatton, Roberts, Chitsabesan, Fothergill, and Harrington (2005) identified 10 published trials (comprising 608 youngsters) comparing individual CBT to an inactive control condition for childhood anxiety disorder (excluding trials focusing solely on simple phobia, PTSD, and OCD). Using remission of the primary anxiety diagnosis as the outcome of interest, these authors found pooled remission rates of 56.5% for CBT and 34.8% for wait-list, which yielded a pooled odds ratio of 3.3 (95% CI = 1.9–5.6) in favor of CBT. The long-term durability of positive treatment effects is less well known. Although positive gains have been reported up to 7 years posttreatment (Barrett et al., 2001; Kendall, Safford, Flannery-Schroeder, & Webb, 2004), these data were obtained via single-source telephone interviews in uncontrolled fashion and covered a relatively narrow set of outcome variables.

Like the role of parental involvement in childhood OCD, the role of parental involvement in the treatment of childhood anxiety requires additional research (Barmish & Kendall, 2005; Silverman & Berman, 2001). Although a number of controlled trials have reported the benefits of family involvement in CBT for childhood anxiety versus individual treatment only, findings have not been consistent within or across the different studies (Barrett et al., 1996; Cobham et al., 1998; Nauta et al., 2003; Spence et al., 2000; Wood, 2006). Moreover, the few longitudinal data

available cast doubt on the durability of this benefit (Barrett et al., 2001). In terms of group treatment, Silverman, Kurtines, Ginsburg, Weems, Lumpkin et al. (1999) demonstrated the efficacy of CBT administered in group format (GCBT) for youngsters with social anxiety, overanxious, and/or generalized anxiety disorders (64% of children receiving GCBT no longer met criteria for their primary anxiety disorder vs. only 13% in the wait-list condition), while Beidel, Turner, and Morris (2000) found a group behavioral intervention based on skill enhancement helpful for children with SoAD.

Several small controlled studies have demonstrated the benefits of behavioral treatments (including systematic desensitization, reinforced practice, and participant modeling) in reducing both the subjective fear and avoidance associated with specific phobia (see review by Davis & Ollendick, 2005). Ost, Svensson, Hellstrom, and Lindwall (2001) found an intensive single-session CBT intervention (OST) to be more effective for specific phobia in children than a wait-list condition. In one of the few child CBT trials employing an active comparison condition, Silverman, Kurtines, Ginsburg, Weems, Rabian et al. (1999) found exposure-based contingency management (a behavioral intervention), exposure-based self-control (a cognitive-behavioral intervention), and psychoeducation/supportive therapy to all be equally efficacious for reducing specific phobia in a sample of 81 6–16-year-old youngsters. Of interest, the only other CBT trial to employ psychoeducation/supportive therapy (PST) also found PST and CBT equally effective in this case for reducing school refusal behavior (Last et al., 1998). For children with PTSD, studies have found CBT interventions to be efficacious as compared with wait-list or other non-CBT psychotherapeutic support (Cohen et al., 2004; King et al., 2000; Stein et al., 2003).

Limitations of Psychosocial Interventions

Although the research literature strongly supports the efficacy of CBT for childhood anxiety disorders, certain limitations must be considered when evaluating these data, especially

when comparing CBT findings to those obtained from psychopharmacological trials (Compton, Burns, Egger, & Robertson, 2002). First, most CBT trials have employed wait-list (i.e., no treatment) control conditions, which provide no protection against the confound of therapist attention or positive expectations about treatment. In fact, as noted above, the only two CBT trials employing an active comparison treatment (i.e., psychoeducation/support) found the comparison treatment to perform as well as CBT. Although psychoeducation is an active component of CBT for anxiety, this raises questions regarding the specificity of CBT effects. Second, CBT research for child anxiety has typically limited data analysis to those participants who actually completed treatment (completer analysis) rather than the much more stringent practice of including all randomized individuals regardless of outcome (intent-to-treat analysis). Completer analyses are likely to overstate the actual efficacy of a given treatment because they fail to account for those individuals who dropped out of treatment due to perceived lack of efficacy, dislike of the treatment or therapist, adverse treatment effects, or for other reasons.

Strength of Evidence

Numerous controlled trials have documented the efficacy and durability of CBT and behavioral therapies for the childhood anxiety disorders, whether delivered in individual, group, or family-based format, with effect sizes in the moderate to large range.

Pharmacological Treatments

Although a number of pharmacological agents have been evaluated for the childhood anxiety disorders, the efficacy data strongly favor the SSRIs, at least for the treatment of GAD, SAD, and SoAD. Imipramine, one of the first medications tested for child anxiety, was found to be superior to placebo for children with school avoidance (Gittelman-Klein & Klein, 1973),

though not in children with separation anxiety disorder (Klein et al., 1992). Because of its tolerability profile and risk of cardiotoxicity in overdose and because of the availability of better tolerated medications (for a review, see Werry & Aman, 1999), the use of imipramine has become uncommon. Two small controlled trials failed to demonstrate support for the benzodiazapines clonazepam (Graae, Milner, Rizzotto, & Klein, 1994) and alprazolam (Simeon et al., 1990). In contrast, a recent NIMH-funded multisite, placebo-controlled trial found fluvoxamine highly efficacious and well tolerated in youngsters (ages 6–17 years) with GAD, SAD, and/or SoAD (RUPP Anxiety Study Group, 2001). Subsequent moderator analyses found that lower parent-reported child depression scores at baseline were associated with a more marked advantage of fluvoxamine over placebo. In addition, youngsters with social phobia and greater overall illness severity at baseline were significantly less likely to improve regardless of treatment condition (RUPP Anxiety Study Group, 2001). Similarly, there is evidence from multisite controlled investigations for the efficacy of paroxetine in children and adolescents with social phobia (Wagner et al., 2004); however, the FDA does not currently recommend this medication for use in pediatric populations because of safety concerns (U.S. FDA, 2003). Smaller placebo-controlled trials support the efficacy of fluoxetine and sertraline in children with GAD (Birmaher et al., 2003; Rynn, Siqueland, & Rickels, 2001). Controlled data regarding medication efficacy for PTSD or specific phobia do not exist. However, Black and Uhde (1994) reported mixed findings from a small controlled trial of fluoxetine for selective mutism, a developmental variant of SoAD mostly affecting children under 8 years of age (Bergman, Piacentini, McCracken, 2002). Little data are available regarding the impact of medication on functioning or the durability of observed medication effects. It should be noted that no data exist regarding long-term use of fluoxetine. Fluoxetine has not been approved by the FDA for use with selective mutism.

Side Effects

Similar to results of the OCD trials, in anxiety trials, SSRIs tend to be relatively well tolerated in children and adolescents with anxiety. The most commonly reported SSRI-related adverse effects include nausea, diarrhea, insomnia, loss of appetite, sedation, tremor, sexual dysfunction, and disinhibition (Leonard et al., 2005). However, these effects are often transient in nature and, in some blind trials, SSRI-related attrition rates do not differ between the active and placebo treatment groups (March & Curry, 1998). As noted elsewhere in this report, recent FDA findings of an association between antidepressant use and increased risk of suicidality in children and adolescents have dramatically altered the parameters of medication use in this age group.

Strength of Evidence

Taken in combination, the relative lack of efficacy and adverse safety profiles of the benzodiazapines and tricyclic antidepressants do not support their use in the treatment of children and adolescents with an anxiety disorder. In contrast, data from four controlled SSRI trials document moderate to large positive effects for the acute reduction of the primary symptoms of social anxiety, separation anxiety, and generalized anxiety disorders.

Combined Interventions

Little information is currently available on the relative efficacy of CBT and pharmacotherapy for childhood anxiety as directly compared in the same study. Bernstein et al. (2000) compared CBT monotherapy with the combination of CBT and imipramine for children with school refusal and comorbid depression and found the combination to be superior, while a large NIMH-funded multisite trial, the Child/Adolescent Anxiety Multimodal Treatment Study

(CAMS), is now in progress to directly compare the effects of CBT, sertraline, and their combination in children and adolescents with GAD, SAD, and SoAD. It should be noted that imipramine is associated with a host of adverse effects, including cardiac arythmia, and has even resulted in death (for a review, see Brown & Daly, 2006;). In addition, the efficacy of imipramine is mixed at best with regard to management of anxiety disorders in children.

Diversity Issues

As with most of childhood disorders, the moderating effects of age, gender, and ethnicity on treatment outcome for child anxiety disorders has been poorly studied. In many cases, insufficient sample size, large age ranges, and the relatively homogeneous makeup of many study samples have hampered research on this topic. Barrett et al. (1996) reported a higher response rate for younger children and girls whose parents also completed a 12-session family management program, compared with girls receiving individual treatment only. However, as noted by Silverman and Berman (2001), this finding could be explained by the possible confounding of age with diagnosis (younger children more likely to have separation anxiety disorder that involves higher levels of parental involvement and older children more likely to have comorbid depressive symptoms). With regard to ethnicity, Hispanic/Latino youths have been shown to evidence response rates to CBT similar to those of European American youngsters (Pina et al., 2003). The multisite RUPP fluvoxamine trial did not find child age, gender, race/ethnicity, parental education, or family income to moderate treatment outcome (RUPP Anxiety Study Group, 2001). Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

A substantial body of evidence provides strong support for the efficacy of CBT in reducing the symptoms of childhood anxiety. In addition, data supporting the use of SSRI medication in anxious youngsters have recently emerged from two larger-scale multisite and a two smaller single-site trials. Although currently under study, data examining the efficacy of combined treatment approaches (CBT plus medication) have yet to be published. Unfortunately, studies directly comparing CBT and medication for the (non-OCD) childhood anxiety disorders do not yet exist. Moreover, as noted earlier, comparison of findings from the CBT and psychopharmacological literature is complicated by multiple design differences, including the use of different treatment outcome measures (typically, remission of primary anxiety disorder in the CBT trials and the Clinical Global Impressions–Improvement Scale [CGI-I: Guy, 1976], a single-item clinician rating, in the drug studies) as well as the less common use of active comparison conditions and intent-to-treat analytic strategies by CBT researchers (Compton et al., 2002). In spite of these differences, however, consensus strongly favors CBT as first-line treatment of choice due to the larger database and greater durability of benefit associated with this treatment as well as concerns with medication safety. However, treatment with SSRI medication remains a viable choice for youngsters who are unable to engage in, or are nonresponsive to, CBT as well as those for whom CBT is not readily available. Nonetheless, due to the shortage of child psychiatrists in this country, access to these medications by prescribing providers with knowledge and experience in treating pediatric populations is apt to be quite difficult.

Future Directions

Data from the ongoing NIMH CAMS trial should provide much needed information regarding the comparative efficacy of CBT, SSRI medication, and their combination, as well as guidance regarding which of these treatments works best for which youngsters under which circumstances. However, additional studies are needed to better understand the optimal role of parents and other family members in treatment and to identify potential moderators of treatment response. In light of the fact that the only two CBT trials employing psychoeducation as part of active comparison conditions found surprisingly high response rates to this intervention (Last et al., 1998; Silverman, Kurtines, Ginsburg, Weems, Lumpkin et al., 1999), expanded efforts are also needed to identify the mechanisms of action and critical components of CBT. Finally, although perhaps not alone in this regard, participants in child anxiety research trials have been shown more likely to come from low-income and single-parent families and to have higher rates of externalizing diagnoses and problems than anxious youngsters treated in community settings (Southam-Gerow, Weisz, & Kendall, 2003). In addition, youngsters with other potentially complicating factors (e.g., low IQ, substance use, medical illness) are also typically excluded from clinical trials; as a result, more research is needed to adapt and evaluate current treatments for these complex clinical presentations. Again, there are no data regarding the long-term effects and efficacy of pharmacological treatment for this disorder. In addition, data regarding the percentage of children who actually respond to cognitive therapy and to medication are lacking.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

ANXIETY DISORDERS	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION	1a-c SSRIs decrease anxiety symptoms and avoidance symptoms	1a-c SSRIs improve social functioning	No data	No data	Can cause restlessness and gastrointestinal symptoms. SSRIs associated with increased risk of suicidal behavior
PSYCHOSOCIAL Individual CBT	1a Anxiety symptoms and avoidance symptoms	1a Overall functioning	4a Anxiety symptoms and avoidance symptoms	4a Overall functioning; reduced risk of later substance use	Well-tolerated but limited systematic data

Individual and Parent CBT	1a Anxiety symptoms and avoidance symptoms	1a Overall functioning	4a Inconsistent findings regarding durability of benefit compared to Ind. CBT	4a Overall functioning	
Combination	No data	No data	No data	No data	

Depressive Disorders and Suicidality

Clinical depression, defined to include major depressive disorder and dysthymic disorder, can be identified in children of all ages. Its prevalence rises sharply during adolescence, particularly among girls (e.g., Kessler, Avenevoli, & Merikangas, 2001; Petersen, Compas, Brooks-Gunn, Stemmler, Ey, & Grant, 1993). By age 18, lifetime prevalence rates are approximately 20%, with significantly higher rates among girls (Hankin et al., 1998; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993).

Depressive disorders are associated with substantial social and academic impairment (e.g., Puig-Antich et al., 1993), a wide range of comorbid psychopathology (Kovacs, 1996), increased risk for substance abuse (e.g., Kovacs, Goldston, & Gastonis, 1993), and increased risk of attempted and completed suicide (Marttunen et al., 1991; Rao et al., 1993; Shaffer et al., 1988). These disorders are often persistent, with a high risk of recurrence (DuBois, Felner, Bartels, & Silverman, 1995; Fleming, Boyle, & Offord, 1993; Kovacs, Obrosky, Gatsonis, & Richards, 1997; Lewinsohn, Clarke, Seeley, & Rohde, 1994).

Often associated with depressive disorders, suicidal thoughts and behaviors are reported by a substantial number of youth. In a recent administration of the Youth Risk Behavior Survey to a nationally representative sample, 8.5% of the total sample of high school students self-reported having attempted suicide in the past year (many of these were characterized by a low level of lethality), and 16.9% of the total sample reported having seriously considered making such an attempt (Grunbaum et al., 2004). Although suicidality is not limited to youth with depressive disorders, the majority of adolescents with depressive disorders report significant suicidal ideation, and a significant minority report having made a suicide attempt during the course of their depression (Myers, McCauley, Calderon, & Treder, 1991).

This review excludes psychotic depression because of its relative rarity and because children and adolescents with psychosis are routinely excluded from controlled intervention studies focusing on depression.

Psychosocial Interventions

Depression

Interpersonal psychotherapy for adolescents (IPT-A) and CBT are the only psychosocial interventions for depression in children and adolescents that have been systematically examined. Studies have also begun to examine psychoeducation as a psychosocial intervention for youth with depressive disorders and their families, although this is not considered a primary treatment for depression.

IPT-A. This intervention is a modification of the interpersonal psychotherapy originally developed for depressed adult outpatients by Klerman, Weissman, Rounsaville, and Chevron (1984). It addresses interpersonal issues common during adolescence, such as separation from parents, role transitions, authority conflicts, peer pressure and development of healthy peer relationships, death of a relative or friend, and the challenges associated with single- or step-parent families (Mufson, Moreau, Weissman, & Klerman, 1993). Using a focused, time-limited approach, the IPT therapist helps the adolescent understand and resolve the identified interpersonal issue. Although IPT-A has been recently modified for group settings (Mufson, Gallagher, Dorta, &Young, 2004), published trials have incorporated individual therapy.

Following a promising open clinical trial (Mufson et al., 1994) 1-year follow-up study (Mufson & Fairbanks, 1996), Mufson, Weissman, Moreau, and Garfinkel (1999) conducted a randomized controlled 12-week clinical trial comparing IPT-A to clinical monitoring in a sample of 48 clinic-referred adolescents with major depression. Adolescents who received IPT-A reported a greater reduction in depressive symptoms and greater improvement in social

functioning and problem-solving skills posttreatment. Seventy-five percent of adolescents who received IPT-A met the recovery criterion, compared with 46% of adolescents in the control condition. Despite study limitations, which included substantial attrition from the control condition and a marked difference between IPT-A and control conditions in therapist contact time, findings indicate that IPT-A was beneficial. In a recently published IPT-A effectiveness study, adolescents who met inclusion criteria for depression symptom severity (primarily female, Latina) were randomly assigned to receive either IPT-A or treatment as usual from school-based health clinic clinicians. Adolescents treated with IPT-A showed greater reduction in depressive symptoms and improvement in overall social functioning (Mufson, Gallagher, Dorta, & Young, 2004). Thus, two randomized controlled trials conducted by Mufson and colleagues have demonstrated either the efficacy or the effectiveness of IPT-A.

Cognitive Behavioral Therapy (CBT). Incorporating a variety of techniques, CBT for depression is a present-focused, time-limited, and collaborative approach. It emphasizes the importance of a careful understanding or functional analysis of cognitive and behavioral factors related to presenting symptoms. The CBT therapist generally aims to accomplish one or more of the following: (a) reduce negatively distorted cognitions; (b) improve problem-solving and coping skills; and (c) increase the youth's involvement in healthy, pleasurable activities (e.g., Lewinsohn, Clarke, Hops, & Andrews, 1990). As described in a recent review (Compton et al., 2004), CBT "treatment packages" often consist of required skill-building sessions and optional modular sessions for specific problems. Treatment may also involve parent and family sessions (e.g., Clarke et al., 1999; Lewinsohn et al., 1990). Studies have incorporated variants of CBT, with some placing a greater emphasis on cognitive restructuring (Brent et al., 1997), and others taking a more behavioral and modular skills-training approach (e.g., Adolescent Coping With Depression Course; Lewinsohn & Clarke, 1984; Rohde, Lewinsohn, & Clarke, 2005).

Randomized controlled trials comparing CBT to either no treatment or to relaxation training have generally found CBT to be superior. This has been found whether the studies

provided CBT individually (Wood, Harrington & Moore, 1996) or in group settings (Clarke, Rohde, Lewinsohn, Hops, & Seeley, 1999; Kahn, Kehle, Jenson, & Clark, 1990; Lewinsohn, Clarke, Hops, & Andrews, 1990; Reynolds & Coats, 1986; Stark, Reynolds, & Kaslow, 1987; Weisz, Thurber, Sweeney, Proffitt & LeGagnoux, 1997). One exception is a randomized controlled trial that examined the relative efficacy of social competence training, an attention placebo control, and a no-treatment control for preadolescent children with depressive disorders (Liddle & Spence, 1990). There were no differences found between groups, although the small sample of 31 children suggests extremely limited statistical power, making it difficult to interpret these negative findings.

Other randomized controlled trials, most of which have been conducted more recently, have compared CBT to active control conditions or treatments assumed to be active treatments for depression, including systemic family therapy or nondirective supportive therapy (Brent et al., 1997; Fine, Forth, Gilbert, & Haley, 1991), IPT (Rossello & Bernal, 1999), a life skills/tutoring intervention (Rohde, Clarke, Mace, Jorgensen, & Seeley, 2004), and SSRIs (Treatment of Adolescent Depression Study [TADS], 2004). The TADS study, described in greater detail in the Combination Treatment section, was a large-scale, multisite investigation that sampled moderately to severely depressed adolescents. Twelve-week clinical outcomes for the CBT arm were not found to differ from those of the pill placebo arm. In contrast to these findings, those of Brent et al. (1997) indicated better initial recovery rates for CBT than for systemic family therapy and supportive therapy, although treatment groups did not significantly differ in terms of remission, recovery, relapse, or recurrence across a 24-month follow-up period (Birmaher et al., 2000). Fine et al. (1991) found supportive therapy superior to behaviorally oriented CBT immediately posttreatment, with no differences evident at a 9-month follow-up. Rossello and Bernal (1999) reported no differences in primary outcomes between CBT and IPT treatment groups, and Vostanis, Feehan, Grattan, & Bickerton (1996) demonstrated no difference

between CBT and a nonfocused intervention. Even bibliotherapy (Ackerson et al., 1998) has shown promise as an intervention for adolescent depression but requires further study.

Although relatively small sample sizes make it difficult to draw firm conclusions, overall findings suggest that children and adolescents with depressive disorders respond similarly to differing “active” psychosocial interventions. In fact, a recent comprehensive meta-analysis of psychotherapy for depressed youth shows small (mean effect size of .34) overall effects of weak durability (Weisz, McCarty, & Valeri, 2006). In this meta-analysis, cognitive approaches were no better or worse than noncognitive approaches. It is important to note that results from meta-analyses may be limited by interpretation, as the results may vary in accordance with the decisions regarding the data analyzed.

Psychoeducation. Despite the absence of randomized controlled trials examining the efficacy of psychoeducation as a “stand alone” intervention for the families of children with depressive disorders, it has been used as an adjunct to pharmacological interventions and as a component of many psychotherapeutic interventions for children and adolescents (e.g., Brent, Poling, McKain, & Baugher, 1993; Fristad, Gavazzi, Centolella, & Soldano, 1996; Geist, Heinmaa, Stephens, Davis, & Katzman, 2000; Goldberg-Arnold, Fristad, & Gavazzi, 1999; C. A. King et al., 2006; Rotheram-Borus et al., 1996). In a study that provided a 2-hr psychoeducation session to the parents of 34 depressed adolescents, Brent et al. (1999) found that psychoeducation was feasible, was positively received by families, and it resulted in significant improvements in knowledge. Such psychoeducation has the potential to improve treatment adherence and outcome, particularly given the beneficial effects that have been demonstrated in studies of adult patients with affective disorders (e.g., L. Anderson, 1984). Although additional empirical studies are needed, it would seem ethically responsible to offer patients and their parents psychoeducation concerning (a) depression and its possible impact on functioning, (b) alternative evidence-based treatments available. (c) the potential risks, benefits, and

discontinuation effects of specific recommended treatments, and (d) the importance of close professional monitoring of physical status and safety.

Suicidal Ideation and Behavior

Despite the relatively high prevalence of suicidal behavior among youth, particularly adolescents, and the upsurge in national attention focused on the tragedy of youth suicide (e.g., *Surgeon General's Call to Action to Prevent Suicide*, U.S. Public Health Service, 1999), the availability of evidence-based treatments for suicidal youth is extremely limited. Multisystemic therapy (MST; Henggeler, Schoenwald, Rowland, & Cunningham, 2002) is one of the few psychosocial interventions for suicidal youth to be evaluated in a randomized controlled trial. MST is an intensive, time-limited, family-centered and home-based approach. In a recent study of 156 youths approved for psychiatric hospitalization because of suicidality, psychosis, or other threat of harm to self or others, Huey et al. (2004) found that MST was more effective than emergency hospitalization in decreasing youth-reported (but not parent-reported) suicide attempts. These data are promising despite that the nonequivalency of MST and comparison groups at baseline (31% vs. 19% with histories of suicide attempts, respectively) makes the interpretation of differences in suicide attempts at posttreatment (14% vs. 9%) and 1-year follow-up (4% for both groups) somewhat difficult. MST was not effective in reducing suicidal ideation, hopelessness, or depression severity.

Other randomized controlled trials with suicidal youth have either reported no significant effect for the experimental treatment or significant positive effects for only a subset of adolescents. In their comparison of group therapy (integration of CBT, dialectical behavior therapy [DBT], and psychodynamic approaches) with routine care, Wood and colleagues (2001) found that adolescents in group therapy were less likely to engage in repeated deliberate self-harm (two or more further incidents) prior to a 7-month follow-up. In

a study of a home-based family intervention for youth who had poisoned themselves, Harrington et al. (1998) found no difference between routine care and intervention groups at follow-up. Post hoc analyses, however, indicated that the intervention was linked to reduced suicidal ideation in youth *without* major depression. Cotgrove et al. (1995) investigated the effect of giving suicidal youth a card permitting rehospitalization if needed and requested. They reported a nonsignificant reduction in suicide attempts for the experimental group at a 1-year follow-up (C. A. King et al., 2006) and are studying the efficacy of a social network intervention, the Youth-Nominated Support Team Intervention (YST), for suicidal adolescents who have been psychiatrically hospitalized because of acute suicidality. Although King et al.'s large-scale preliminary study was largely a feasibility trial, findings suggested possible YST-associated improvements in functioning for suicidal adolescent girls. A more rigorous randomized controlled trial, incorporating an extensive risk-management protocol, is currently ongoing to examine the efficacy of a modified version of the intervention.

It is worth noting that DBT (Linehan, Armstrong, Suarez, Allmon & Heard, 1991; Linehan, Heard, & Armstrong, 1993) and cognitive therapy (G. K. Brown et al., 2005) have each shown effectiveness in reducing suicidal behavior in adults. Although randomized controlled trials have not yet been conducted for DBT with adolescents, this strategy has shown some promise in preliminary trials with suicidal adolescents (Katz, Cox, Gunasekara, & Miller, 2004). Similarly, a quasi-experimental study (Rotherham-Borus, Piacentini, Cantwell, Belin, & Song, 2000) found that an emergency room intervention for adolescent girls who had attempted suicide was associated with improved treatment adherence.

Limitations of Psychosocial Interventions

Psychosocial interventions may not appeal to everyone, as they involve the child or adolescent, and often the parent(s), in collaboration with the therapist, and such work requires

significant time and effort. In fact, in a sample of psychiatrically hospitalized adolescents, King, Hovey, Brand, Wilson, and Ghaziuddin (1997) found that youth and families were more likely to adhere with recommended psychopharmacological treatment than with recommended psychotherapy. Nevertheless, most evidence with adults suggests that, when given a choice, patients express a preference for psychosocial interventions over medications (Chilvers et al., 2001; Hall & Robertson, 1998; Jorm, 2000; Paykel, Hart, & Priest, 1998; Priest, Vize, Roberts, Roberts, & Tylee, 1996). There is evidence of similar preferences among depressed youth (Asarnaow et al., 2003, 2005).

The absence of more substantial effect sizes for psychosocial interventions, particularly with suicidal youth and moderately or more severely depressed youth, is also a limitation. These limited effect sizes have been found despite that many of the studies reported did not use intent-to-treat analyses. Furthermore, with few exceptions (e.g., Rohde et al., 2001, 2004), studies have not systematically examined the efficacy of psychosocial treatments for depressive disorders presenting with comorbid conditions such as conduct disorder or alcohol and substance use disorders. The long-term effectiveness of most interventions has also not been established, and a significant proportion of youth remain depressed or only partially recovered after treatment.

The evidence base for the use of these therapies in preadolescents is extremely limited. The effectiveness of IPT-A has not been studied with preadolescents and, in fact, IPT-A was named and modified specifically as a therapy for adolescents. Although CBT is generally conceptualized as a broader therapeutic approach for depression in children and adolescents, most studies of CBT targeting depression have been conducted with adolescents, including the only study of combination treatment. It should be noted that Stark et al. (1987) and Weisz et al. (1997) demonstrated the efficacy of group-based CBT treatment for depression in elementary school-age children. In general, cognitive approaches have shown no advantage over noncognitive approaches in adolescents (Weisz, McCarty, & Valeri, 2006), and it is possible

they will have more limited effectiveness in younger children who may not be developmentally ready to engage in challenging cognitive distortions or related tasks.

Finally, limited resources may present a substantial barrier. It should be noted that access to providers is limited in many geographic regions. In addition, some health care insurance policies offer only limited benefits for psychosocial interventions and, more generally, for the treatment of mental health problems or psychiatric disorders, potentially creating a disincentive to seek treatment.

Strength of Evidence

The specific advantage of one psychosocial intervention over another in randomized controlled intervention trials has usually been small to nonexistent. The specific advantages of psychosocial interventions over wait-list conditions are generally moderate. The specific efficacy advantage of a psychosocial intervention over a placebo (e.g., the TADS study) was nonexistent, but the harm advantage was substantial. Although some psychosocial interventions for suicidal behavior are promising (e.g., MST), there have been methodological challenges and limitations in these intervention studies, and it will be important to replicate initial findings. Studies documenting adverse effects associated with CBT were not found.

Pharmacological Interventions

Depressive Disorders

Roughly 11 million antidepressant prescriptions were written for children and adolescents in the United States during 2002 (Goode, 2004; Rigoni, 2004). Furthermore, approximately 6% of outpatient physician visits for U.S. children ages 5 to 17 involve the prescription, ordering, or provision of antidepressant medication (National Center for Health Statistics, 2004). Meta-analyses have consistently indicated that tricyclics have no significant

pharmacological effect on depression in children (Ambrosini, Bianchi, Rabinovich, & Elia, 1993; Dujovne, Barnard, & Rapoff, 1995; Fisher & Fisher, 1996; Hazell, O'Connell, Heathcote, Robertson, & Henry, 1995; Michael & Crowley, 2002; Sommers-Flanagan & Sommers-Flanagan, 1996). Six of the seven published randomized controlled studies of the efficacy of SSRIs in children and adolescents report significant differences on some measures, suggesting more favorable outcomes for those treated with SSRIs (Emslie et al., 1997, 2002; Keller et al., 2001; Simeon, Dinicola, Ferguson, & Copping, 1990; Wagner et al., 2003; TADS, 2004; Wagner et al., 2004).

Methodological issues and publication biases have made it difficult to accurately determine the efficacy of SSRIs as a treatment for children and adolescents with depressive disorders (Garland, 2004; Whittington et al., 2004). Jureidini et al. (2004) critically reviewed the available published controlled trials of newer antidepressants in children and noted that whereas almost half of the clinician-rated measures favored the study drug, none of the patient-rated or parent-rated outcomes favored the antidepressants over placebo. In addition to questioning the clinical significance of statistically significant results, Jureidini et al. highlighted the methodological weaknesses of these trials, including reliance on last observation carried forward, an emphasis on secondary endpoints, transforming continuous variables into categorical outcomes (e.g., response rates) and thereby inflating small differences, and possible unblinding due to side effects from active medication. An independent analysis by the FDA concluded that only 3 out of 15 randomized controlled trials (including all published and unpublished data sets) of the newer antidepressants found them to be more effective than placebo on primary outcome measures in depressed children (Hammad, Laughren, & Racoosin, 2006), though several of these trials had positive and significant effects on secondary measures.

Suicidality

There are no published studies of psychopharmacological treatment or combined psychosocial and psychopharmacological treatment specifically targeted to suicidal youth. Youth with histories of suicide attempts, recent psychiatric hospitalizations, or substantial suicidal intent have been excluded from psychopharmacology trials, primarily because of safety concerns. A currently ongoing NIMH-sponsored multisite project, the Treatment of Adolescent Suicide Attempters (TASA) study, is collecting feasibility data (e.g., recruitment, safety monitoring, measurement procedures) in preparation for a possible definitive study addressing combination treatments for suicidal youth with depressive disorders.

Side Effects

Based primarily on studies involving adults, the most common side effects of SSRIs in studies of patients with depressive disorders include agitation, sleep disruption, gastrointestinal problems, and sexual problems (Antonuccio et al., 1999). Evidence from animal studies indicates that SSRIs may cause gonadal tissue shrinkage (U.S. Department of Health and Human Services, 2004), and recent case reports in adults suggest the possibility that sexual side effects can persist even after medication is withdrawn in a small minority of cases (Csoka & Shipko, in press). These data, along with case reports on children with growth suppression linked to SSRIs (Weintrob et al., 2002), raise concerns about the possibility that antidepressants could alter the course of pubertal growth and development in adolescents, though this has not been systematically investigated to date.

Side effects and medical risks increase when SSRIs are combined with other medications (Dalfen & Stewart, 2001), as is often the case (Antonuccio et al., 1999). In addition, the withdrawal symptoms of SSRIs are substantial for many, if not most, patients (Coupland, Bell, & Potokar, 1996; Fava, 2002; Rosenbaum, Fava, Hood, Ashcroft, & Krebs, 1998). Increased risk for manic episodes (e.g., Preda, MacLean, Mazure, & Bowers, 2001) and acts of

deliberate self-harm (e.g., Donovan et al., 2000; Healy, 2003) are cause for concern. Although the data are mixed and somewhat controversial, other potential risks that warrant further investigation include the association of antidepressants with breast cancer (e.g., Bahl et al., 2003; Cotterchio et al., 2000; Halbreich et al., 1996; Moorman et al., 2003; Sharpe et al., 2002) and the possibility of irreversible biochemical changes predisposing some susceptible patients to chronic depression (e.g., Ansorge et al., 2004; Baldessarini, 1995; Fava, 1995, 2002). As noted in the Anxiety Disorders section, the only SSRI that is approved by the FDA for use in the pediatric population is fluoxetine.

Strength of Evidence

The FDA identified 15 controlled studies of antidepressants in children, but only 3 found an advantage of the antidepressant over inert placebo. The FDA did not count the additional TADS as a positive study for SSRIs as a singular treatment because of the negative findings for the Children's Depression Rating Scale—Revised, which was the primary depression outcome measure. While the methodology appears sound, the evidence base in support of antidepressants in children is relatively weak. The placebo-related effects account for of the variance in children's outcomes. The FDA black box warning appears as follows:

Suicidality in Children and Adolescents

> Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close

> observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use). (U.S. FDA, 2005b)

Pooled analyses of short-term (4–16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events while on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Combined Interventions

The Treatment of Adolescent Depression Study (TADS Team, 2004) enrolled 439 patients between the ages of 12 and 17 years with sustained (i.e., at least 6 weeks) and moderately severe or severe major depression. These adolescents were randomly assigned to 12 weeks of fluoxetine alone, CBT alone, CBT combined with fluoxetine, or placebo. The variant of CBT used in this study consisted of individual therapy, psychoeducation, and conjoint parent–adolescent sessions. Combining various cognitive and behavioral strategies was more comprehensive and modular, with less time spent on cognitive restructuring, than the CBT used in the Brent et al. (1997) study. On the primary depression endpoint (Children's Depression Rating Scale—Revised), combination treatment was superior to other treatment conditions, whereas neither fluoxetine alone nor CBT alone separated from placebo. Response rates on a global improvement measure were 71% for the combination treatment, 61% for fluoxetine alone, 43% for CBT alone, and 35% for placebo, with the two fluoxetine-containing conditions superior to CBT and to placebo but also resulting in twice as many harm-related adverse events. The

pattern of findings suggested that CBT has a small protective effect on suicidality, with CBT alone resulting in the lowest rate of harm-related events (4.5%), fluoxetine alone having the highest (11.9%), and the combination in the middle (8.4%). This may reflect the benefit of learning coping skills in the CBT conditions. A conservative treatment strategy designed to minimize risk might involve a sequential approach that uses psychosocial interventions initially, close monitoring, and the addition of fluoxetine for nonresponders whose parents are fully informed of the potential risks and benefits.

It will be extremely important to examine longer term follow-up findings in terms of safety issues and the differential (and combination) efficacy of CBT and fluoxetine. This is particularly critical given that the most suicidal youth were excluded from TADS (i.e., those with suicidal intent, a suicide attempt requiring medical attention within the past 6 months, or suicidal ideation with disorganized family). There is a lack of safety data concerning the use of antidepressants with a more fully representative sample of depressed adolescents. It will be important to examine the possible long-term protective effect of CBT. Studies have found that adults treated to remission with CBT are significantly less likely to relapse following treatment termination than are adults treated to remission with medications (Hollon, Thase, & Markowitz, 2002; Hollon et al., 2005), although studies with children have not demonstrated this to date (Birmaher et al., 2000; Brent, Kolko, Birmaher, Baugher, & Bridge, 1999).

Diversity Issues

Depression treatment studies have not generally examined the extent to which age, gender, race, and ethnicity moderate the efficacy of psychosocial interventions and pharmacotherapy for children and adolescents with depressive disorders.[1] In fact, this has not

[1] Such moderator analyses are being conducted at the present time for TADS.

even been a possibility in most studies because of small sample sizes or samples that lack sufficient variability for such analyses. For instance, many studies on depression include samples that are predominantly female (e.g., Rossello & Bernal, 1999), raising questions about the generalizability of results to males. Most studies have limited recruitment to either preadolescents (e.g., Stark et al., 1987; Weisz et al., 1997) or adolescents (e.g., Lewinsohn et al., 1990; Reynolds & Coats, 1986; TADS, 2004), making it impossible to examine whether age group (preadolescent, adolescent) moderates treatment efficacy.

Finally, most depression treatment studies have sampled primarily White or, in the case of IPT, Latino, populations, and no depression treatment studies have reported efficacy for specific racial or ethnic groups. This is the case despite evidence that drug adherence and metabolism are affected by ethnocultural issues (Lin et al., 1993; Munoz & Hilgenberg, 2005; Munoz et al., 1994) and that minorities are much less likely to seek mental health treatment than nonminorities (Munoz et al., 2005). Thus, existing knowledge of evidence-based treatments is of a general sort, much like the broad brush strokes across a canvas. Further research examining treatment effects and outcomes by diversity variables is necessary. It will be important to (a) learn about treatments that are efficacious for specific populations of youth and (b) train providers to implement these treatments in a culturally and linguistically competent manner so that minorities may have access to a broader range of options than just psychopharmacological treatments.

Risk–Benefit Analysis

The acceptability of the risk–benefit profile with fluoxetine, the only antidepressant to show consistent evidence of some benefit in depressed children and the only SSRI approved by the FDA for use with children and adolescents, involves value judgments as to the cost of harm-related and psychiatric-related adverse events. While the risk of increased suicidality appears to be relatively low (i.e., 2 extra suicidal patients for every 100 treated with an SSRI compared with

a placebo) and no patients actually completed suicide in the FDA database of controlled trials, the stakes are clearly high. Furthermore, because randomized trials involving antidepressants have excluded suicidal patients, data concerning potential risk are limited. The question might be asked, How many children should benefit from an antidepressant to justify one extra child harmed by an antidepressant?

Whittington et al. (2004) reviewed all of the available data (published and unpublished) from controlled trials of SSRIs in youth with depressive disorders. This meta-analysis concluded that the risk–benefit profile (number needed to treat to benefit one extra patient [NNTB] vs. number needed to treat to cause a serious adverse harm event in one extra patient [NNTH]) was favorable for fluoxetine but was unfavorable for paroxetine, sertraline, citalopram, and venlafaxine because of poor efficacy and increased risk of harm-related behaviors. TADS (2004), which was conducted more recently than the studies included in the Whittington et al. review, offers the only data pertinent to the short-term relative risks of offering patients psychotherapy alone, medication alone, the combination, or a placebo. Despite that suicidality decreased across all four arms of this study, fluoxetine was associated with a significantly higher rate of harm-related adverse events (such as suicidal ideation), physiological side effects (diarrhea, insomnia, and sedation), and psychiatric adverse events (irritability, mania, and fatigue) compared with placebo or CBT alone. Using the global response rate outcome from the TADS study, the NNTB is about 3 in the combined condition, 5 for fluoxetine alone, and 12 for CBT alone, all compared to placebo. In terms of harm-related adverse events, the NNTH is approximately 20 in the fluoxetine-containing conditions compared with the nonmedication conditions. Considering psychiatric-related adverse events, the NNTH is approximately 10 in the fluoxetine-alone condition compared with placebo and only about 5 compared with CBT alone. It is trade-offs like these that have led regulatory bodies in Europe, Britain, Canada, Australia, and the United States to issue stern warnings or outright contraindications for the use of

antidepressants in children. When risk of harm is considered in a cost–benefit analysis together with medical cost offset (Hunsley, 2003), relapse, and side effects, psychological interventions can be very cost-effective, particularly in a group format (Antonuccio, Thomas, & Danton, 1997). Finally, although these drugs have modest adverse effects in the short-term, future research must demonstrate their long-term effects on the central nervous system of children and adolescents.

Future Directions

Clinical depression has an indisputably adverse impact on the developmental trajectories of youth. Despite this well-established fact and the recent increase in treatment of depression, the evidence for a singular treatment approach involving antidepressant medication or CBT suggests only modest positive effects achieved with a substantial investment of resources. The specific advantages over placebo for either treatment alone have been modest in many studies and nonexistent in some studies. One large-scale study does, however, suggest that combination treatment may be more effective in the short-term (TADS, 2004). Clearly, we have only moved part way toward our goal of developing evidence-based interventions that reduce depression severity and its associated functional impairment and that ultimately enable children and adolescents to achieve sustained recovery from depression. Additional research is needed to improve the efficacy and safety of existing psychopharmacological and psychosocial interventions, to replicate findings concerning the efficacy of IPT with independent teams of investigators, to consider other theoretically based interventions, and to continue to examine the potential benefit of combination treatments. Additional research efforts are needed to investigate the long-term safety and efficacy for children and adolescents.

Studies of the comparative efficacy of psychosocial and pharmacological interventions are less common in children than in adults, and available evidence leaves open the question of whether their short-term efficacy differs in a clinically meaningful way. TADS (2004) found no

differences between singular treatments on the primary depression outcome measure; however, there was greater improvement with SSRI treatment on a secondary measure. In contrast, available evidence appears to suggest a short-term risk advantage for psychosocial interventions, though harm has only recently been systematically and carefully evaluated. In summary, the benefits and risks of various treatment options or combination treatments must be weighed against the benefits and risks of providing no treatment or inadequate treatment for depression, a condition that is associated with substantial morbidity and mortality (Brent, 2004).

It is striking how little is known about even some of the most basic issues. Additional studies are needed to determine the efficacy of these treatments in younger children, the active ingredients in CBT and IPT psychotherapies, the long-term benefits and risks of individual and combination treatments, the safest and most efficacious sequencing of psychosocial and psychopharmacological treatments, the potential differential efficacy of treatments for boys and girls and differing racial/ethnic groups, and the extent to which treatments are efficacious in depressed youth with comorbid psychiatric disorders. It is particularly striking that almost all available data from randomized controlled clinical trials pertain to adolescents.

It is ironic that the specific advantages of available treatments, whether psychosocial or psychopharmacological, for depressed youth are small compared with the “nonspecific” effects of placebo and other supportive comparison treatments. It could be argued that more resources are warranted to investigate and train practitioners in the “nonspecifics” of the therapeutic alliance, support, exposure, and problem-solving skills that seem to cut across many treatments. It could also be argued that “watchful waiting” may be appropriate for some youth who present with milder symptoms of depression.

Data to guide the treatment of suicidal youth are even more limited. In addition to highlighting the importance of additional focused research in this area, studies conducted thus far suggest that multilayered or sequenced interventions may be needed to intervene effectively with suicidal youth (C. A. King et al., 2006). It will be important to address the diagnostic

heterogeneity that characterizes these youth and to target the chronic psychopathology and psychosocial difficulties that are often present.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group but not clinical trial; 4 = no control group

DEPRESSIVE DISORDERS AND SUICIDALITY	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION					
Fluoxetine	1c Depressive symptoms	1d	No data	No data	Agitation, irritability, insomnia, sedation, GI problems; suicidality
Other SSRIs	1d	1d	No data	No data	As above
PSYCHOSOCIAL					
IPT	1c Depressive symptoms; selected population	1c Overall functioning; selected population	No data	No data	

CBT MST	1c Depressive symptoms, suicidal ideation 2c-d Suicide attempts		1-2c Depressive symptoms		
Combination Fluoxetine + CBT	2a Depressive symptoms 2c Suicidal ideation				Insomnia, fatigue, gastrointestinal problems

Bipolar Disorder

The diagnosis of bipolar disorder (BPD) in children has been controversial. In particular, the core symptoms necessary for diagnosis, the necessity of discrete episodes, and the definitions of cycling have been debated, and their application varies across studies (Kowatch & Fristad, 2006). While classic Bipolar I disorder is not common in youth, bipolar spectrum disorders (Bipolar I, mania plus depression; Bipolar II, hypomania plus depression; cyclothymia, hypomania plus “hypodepression” [i.e., subsyndromal depression]; and bipolar–not otherwise specified [BP-NOS]) are not uncommon (Kowatch & Fristad, 2006). When BP-NOS is diagnosed, it is important to state clearly the reason for this diagnosis (e.g., one symptom below threshold, duration less than 7 days). In all cases, careful observation of children and receipt of information from multiple informants are important.

Diagnostic criteria of the *DSM–IV–TR* for a manic episode require “a distinct period of persistently elevated, expansive, or irritable mood” (American Psychiatric Association, 2000). However, as irritability is ubiquitous in childhood disorders, some clinical researchers have required hallmark criteria of expansive/elated mood or grandiosity to diagnose mania in children (cf. B. Geller et al., 2000, 2001, 2002, 2004). Additionally, many children meet symptom criteria for mania, with the exception of the duration criteria. These children may have intense rapid mood swings and are often diagnosed with BP-NOS.

It is important when diagnosing BPD to keep developmental considerations in mind. Because cognitive maturation influences children’s experience of and expression of emotional states, children may be less able to express symptoms such as hopelessness, and their limited ability to compare and evaluate themselves against others makes low self-esteem more difficult to assess (Klaus & Fristad, in press). In addition, the expression of manic symptoms such as grandiosity increase in goal-directed activity, and excessive involvement in pleasurable activities varies based on age and must be differentiated from typical childhood behaviors. Use of "FIND"

(frequency, intensity, number, and duration of symptoms) criteria (Kowatch et al., 2005) can assist the clinician in determining when a behavior is a symptom and not merely a manifestation of ordinary developmental differences.

Recently, with phenomenological studies shedding light on course of illness (B. Geller, 2000, 2001, 2002, 2004), empirical guidelines for the diagnosis of BPD-Type I have improved, although less examination of the diagnostic boundaries for BPD-Type II, BPD-NOS, and cyclothymia has occurred (Kowatch et al., 2005). NIMH has recently funded a four-site study, the Longitudinal Assessment of Manic Symptoms, that should clarify the diagnostic parameters for these bipolar spectrum disorders. Diagnoses can be made in preschool children (Tumuluru et al., 2003; Wilens et al., 2003), although they require additional caution.

As with depression, earlier age of onset appears to be associated with a stronger genetic loading and a more pernicious course, although data on preschool children with BPD are quite limited (Kowatch & Fristad, 2006). Relatively little is known about prevalence rates. Lewinsohn and colleagues (1995) reported lifetime prevalence rates of 1.0% for the diagnosis of BPD, with an additional 5.7% reporting subthreshold symptoms. These adolescents experienced functional impairments similar to the BPD group into young adulthood. However, this study was based solely on interviews with adolescents, and more recent research has emphasized the importance of including parent report in diagnosing BPD (Youngstrom et al., 2004). It is important when diagnosing BPD in youth to pay particular attention to issues of differential diagnosis and comorbidity, as the overlap of symptoms found in ADHD, PTSD, and BPD is significant. Empirical knowledge regarding treatment of BPD in youth is summarized below.

Psychosocial Interventions

Three research groups have tested psychosocial interventions. All, or the majority, of these participants in psychosocial treatment studies for BPD were on concomitant medication, consistent with current treatment guidelines (Kowatch et al., 2005). Pavuluri and colleagues (2004) reported that 34 youth aged 5–18 years who were nonrandomly assigned to the RAINBOW psychosocial program and care in a specialty medication clinic fared better at follow-up than those managed with standard clinic care. Miklowitz and colleagues (2004) provided adjunctive family-focused psychoeducational treatment for adolescents to 20 youth aged 13–18 years in an open trial and noted improvement in depressive, manic, and behavioral symptoms over a 1-year follow-up. Miklowitz and colleagues are piloting a randomized clinical trial for adolescents with BPD, but results have not yet been published (Miklowitz, 2005). Fristad and colleagues have conducted three randomized clinical trials, two with multifamily psychoeducation groups and one with individual family psychoeducation; all three trials indicate that children aged 8–12 and their families demonstrated improvement across a variety of symptom and functional outcome measures following brief, structured intervention (Fristad, Gavazzi, & Mackinaw-Koons, 2003; Fristad, Goldberg-Arnold, & Gavazzi, 2002, 2003).

Limitations of Psychosocial Intervention

The number of published studies is severely limited. Only four randomized clinical trials have been conducted; of these, two are nearing completion, and two are completed. Three of the four trials are pilot studies with small sample sizes. Only one study is with adolescents; three are with children aged 8–12.

Strength of Evidence

Despite limited data, the interventions used by the various investigators described above have more similarities than differences in their content, and results across studies are comparable, lending support to the concept that psychoeducationally oriented interventions are effective adjunctive treatments in the comprehensive care of youth with BPD.

Pharmacological Interventions

Few randomized double-blind psychopharmacological studies have been conducted (Kowatch et al., 2005). Treatment guidelines based on combining available evidence with expert opinion have recently been published (Kowatch et al., 2005). These guidelines reviewed evidence for the treatment of BPD-I with psychosis, BPD-I without psychosis, and BPD-Depressed episode. A review was conducted to determine if any articles had been published since the guidelines went into press; 10 additional articles were found, but none added incremental evidence.

Strength of Evidence

Lithium is the best studied medication, with evidence supporting its use, although even the randomized controlled trials have some limitations, such as small sample size and methodologic issues, including crossover designs, which are less than ideal for a cyclic disorder (Kowatch et al., 2005). Open trials also support its use (Kafantaris, Coletti, Dicker, Paula & Kane, 2001, 2003). Quetiapine has demonstrated efficacy in a double-blind, placebo-control trial as an adjunct to valproate (DelBello, Schwiers, Rosenberg, & Strawkowski, 2002). An NIMH funded multicenter trial is currently under way to determine the efficacy of lithium in children with Bipolar I (NIMH, 2006). Another study of lithium pharmacokinetics, efficacy, safety, and effectiveness is being started under a contract by the National Institute of Child Health and

Human Development (NICHD). A large, multisite trial funded by NIMH is in progress to compare the relative effectiveness of lithium, valproate, and risperidone in children aged 8–14 with Bipolar I.

Open trials, which have methodologic limitations, also support the use of divalproex (Kowatch et al., 2000; Papatheodorou & Kutcher, 1993; Papatheodorou, Kutcher, Katic, & Szalai, 1995, West et al., 1994, 1995); clozapine (Kowatch et al., 1995), carbamazepine (Kowatch et al., 2000), olanzapine (Frazier et al., 2001), and topirimate as an adjunctive intervention (DelBello et al., 2002), and there is retrospective evidence for the efficacy of risperidone (Frazier et al., 1999). Very limited studies are available for BPD-Depressed episode. No randomized controlled trials have been conducted with youth. Open trials, retrospective chart reviews, and case reports suggest that divalproex (Kowatch et al., 2000), lamotrigine (Kusumaker & Yatham, 1997), and SSRIs (Biederman et al., 2002) are beneficial, although SSRIs have also been reported to be mood destabilizing.

Side Effects

Side effects associated with psychotropic medication for BPD are common and range from nuisance to more severe toxicities. Some medications, such as atypical antipsychotics, can induce weight gain that can result in a series of general metabolic disorders, including type 2 (non-insulin-dependent) diabetes mellitus, lipid level changes, and transaminase elevation (Kowatch et al., 2005). The American Diabetes Association, in conjunction with the American Psychiatric Association, recently published a monitoring protocol for all individuals receiving atypical antipsychotic medications (American Diabetes Association & American Psychiatric Association, 2004). There are anecdotal reports of cognitive side effects from essentially all medications used for mood stabilization, including problems with word retrieval, working memory, and cognitive dulling. Polycystic ovarian syndrome (PCOS) is related to use of

divalproex in females; current guidelines suggest monitoring menstrual patterns as well as weight gain in females for whom divalproex has been prescribed (Kowatch et al., 2005).

Other uncommon but problematic side effects associated with various medications that warrant careful monitoring include the following: lithium—hypothyroidism; antipsychotics—abnormal involuntary movements, prolactin elevation; divalproex—pancreatitis; ziprasidone—intracardiac conduction effects; clozapine—hematologic and neurologic adverse events, neuroleptic malignant syndrome.

Combined Interventions

Strength of Evidence

Essentially no psychosocial trials have occurred in the absence of concomitant pharmacotherapy, and no medication studies for BPD have tested the adjunctive benefit of psychosocial intervention. Studies that include both medication and therapy have not used a dismantling methodology to determine the unique contribution of each treatment. Thus, no empirical guidelines regarding the incremental benefit of concomitant medication and therapy exist.

Diversity Issues

Treatment studies to date have been too small in size to make meaningful comparisons between treatment response for males versus females, or minority versus majority racial or ethnic groups. Biederman and colleagues (2004) examined 74 females and 224 males from their outpatient clinic setting, all of whom fulfilled *DSM–III–R* criteria for BPD. They found no meaningful differences in symptom expression, types of treatment received, severity of educational deficits, severity of family and interpersonal functioning, or patterns of comorbidity

between males and females. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

There are few long-term safety studies conducted with many medications used to treat BPD, and of those available, most have studied adults. It is critical for clinicians, youth, and parents to conjointly consider a cost–benefit analysis when determining what medications to try in the treatment of BPD. Psychosocial interventions appear to confer benefit with no risk reported to their delivery; thus, psychosocial treatment of BPD is advised. Unfortunately, psychotropic agents used to treat BPD are not without significant risk, although they are considered first-line treatment in all published treatment guidelines (Kowatch et al., 2005). Many more clinical trials in children are needed to exam the efficacy, as well as the safety, of these medications. Finally, the development of safe and effective psychotropic agents to manage BPD in children is sorely needed.

Future Directions

Nonpharmacological physiologic interventions have not been conducted in children and adolescents with bipolar spectrum disorders. However, a rationale for testing several interventions has been provided via adult studies, including vagus nerve stimulation and transcranial magnetic stimulation (Hirshberg, Chiu & Frazier, 2005).

While two recent consensus statements emphasize the need for pharmacological and psychosocial management of BPD (Coyle et al., 2003; Kowatch et al., 2005), studies designed to test the relative contribution of both treatment components have not been conducted. There is growing agreement over the diagnosis of BPD-I in youth, but there is less clarity regarding the clinical profiles of youth with bipolar spectrum disorders (BPD-II, cyclothymia, and BP-NOS). A multisite research study to address this has commenced. Unfortunately, there is a paucity of

research on both pharmacological and psychosocial interventions for BPD, and empirical guidelines are lacking for their combination. Currently, clinical guidelines exist for the assessment and treatment of BPD in youth (Kowatch et al., 2005); it is anticipated these will be modified as new research is completed.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

BIPOLAR DISORDER	ACUTE	LONG-TERM	ADVERSE OUTCOMES
MEDICATION			
Lithium	2d (YMRS)	--	Weight gain, polydipsia, polyuria, headache, tremor, gastrointestinal pain, nausea, vomiting, anorexia, diarrhea, hypothyroidism
Carbamazepine	2d (YMRS)	--	Nausea, but majority of side effects were mild to moderate and tolerated by most subjects; risk for neutropenia, agranulocytopenia, thrombocytopenia
Divalproex sodium	2d (YMRS)	--	Risk for liver toxicity, liver failure, pancreatitis, weight gain, polycystic ovary syndrome

Topiramate	4d (CGAS score, overall CGI-S score, and mania CGI-S score)	--	Headache, nausea, vomiting, diarrhea, and somnolence
Olanzapine	4d (YMRS)	--	Cognitive disturbance, dysphoria, gastrointestinal disturbances, tremors, sedation, and blurry vision
Risperidone	4d (mania CGI severity score)	--	I Increased appetite, somnolence, abdominal pain, weight gain, and sedation
PSYCHOSOCIAL			
CFF-CBT	4d (CGI-BP)	--	None reported
FFT	4c (K-SADS Depression subscales) 4c (K-SADS Mania subscales) 4d (CBCL)	--	None reported
MFPG	2d (UMDQ)	--	None reported

IFP	2c (mood)	--	None reported
Combination			
Lithium + adjunctive psychotic	4d (YMRS)	--	None listed
Divalproex sodium + Risperidone	2d (YMRS)	--	Weight gain, sedation, nausea, increased appetite, stomach pain, tremors, cognitive dulling, akathisia, and galactorrhea
Lithium + Risperidone	2d (YMRS)	--	Weight gain, sedation, nausea, increased appetite, stomach pain, tremors, cognitive dulling, akathisia, polyuria, and buccolingual movements
	4d (YMRS)		Emesis, enuresis, stomach pain, tremor, increased thirst, headache, nausea, sedation, increased appetite, diarrhea, decreased appetite, respiratory

Lithium + Divalproex sodium			congestion, fever with flu symptoms, dizziness, and body ache

Note: YMRS = Youth Mania Rating Scale; CGI-BP = Clinical Global Impression Scales for Bipolar Disorder; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; CBCL = Child Behavior Checklist; UMDQ = Understanding Mood Disorders Questionnaire.

Schizophrenia Spectrum Disorders

Psychosis can occur across a range of disorders appearing in childhood. For example, when psychotic or psychotic-like symptoms occur during the severe manifestation of OCD, PTSD, MDD, or BPD, they are considered evidence of the severity of that condition rather than an indicator of a separate diagnostic condition. Schizophrenia spectrum conditions, per se, are rare in childhood, although diagnostic procedures are well defined for children age 8 and older (Asarnow, Tompson, & McGrath, 2004). Thomsen (1996) examined all youth hospitalized for schizophrenia over a 13-year period in Denmark. Of 312 patients, only 1% had onset prior to age 13, and only 9% prior to age 15. Boys are twice as likely as girls to be diagnosed before age 18 (McClellan, Werry, & the Work Group on Quality Issues, 2001). Early onset is associated with poorer outcome and higher rates of negative symptoms in adulthood (McClellan et al., 2001).

Premorbid abnormalities are common and include social withdrawal, isolation, disruptive behavior disorders, academic difficulties, speech/language problems, and developmental delays (McClellan et al., 2001). Symptoms tend to shift from positive (i.e., hallucinations, delusions, disorganized speech and behavior) to negative (i.e., flat affect, anergia, social withdrawal) over time (McClellan et al., 2001). Ten to twenty percent have IQs in the borderline range or below (McClellan et al., 2001).

A majority of youth presenting with schizophrenia spectrum disorders maintain these diagnoses over time (Asarnow et al., 2004). Variable functional outcome has been reported. Werry and colleagues (1991) reported the worst findings, with only 17% of their sample in school or employed full-time from 1 to 16 years (5 years, on average) after study entry. In a longer follow-up (6–40 years, with 16 years on average), Eggers and colleagues (2002) reported that only 7% of their sample were in stable partnerships, although 73% were involved in some type of employment. Asarnow and Tompson (1999) followed a cohort of youth 3–7

years of age following diagnosis and reported 56% had improvement in functioning, with 28% reporting relatively good psychosocial adjustment (GAF scores $\geq$ 60).

Because of the low-prevalence rate, little is known about schizophrenia spectrum disorders in youth. Most of what is known about psychosocial and psychopharmacological treatment comes from studies of adults. This seems hardly satisfactory considering the vast physiologic and psychological differences between adults and youth.

Psychosocial Interventions

Meta-analyses of adult studies indicate that family psychoeducation and CBT can help reduce relapse, although support is less strong for social skills training, and there is no evidence of efficacy for cognitive remediation (Asarnow, Tompson, & McGrath, 2004). A recent review of studies examining psychosocial treatment for first-episode psychosis comes to similar conclusions (Penn, Waldheter, Perkins, Mueser & Lieberman, 2005). Of note, while four recently conducted comprehensive studies were reviewed, few participants in these studies were under age 18. Three of the four studies included participants under age 18; however, the majority of participants in each study were over age 18. This is consistent with data indicating that schizophrenia-onset typically is seen in individuals ranging in age from 16 to 30 years (Mueser & McGurk, 2004). One study examined 12 adolescents with schizophrenia treated over a 2-year period with a comprehensive treatment program that included hospitalization that ranged from several months to one year and an intensive outpatient psychoeducational program that commenced upon discharge. These 12 were compared with 12 historical controls from the same setting who received an unspecified combination of individual psychotherapy, neuroleptic medication, and milieu therapy while hospitalized. The experimental group was less likely than the control group to experience two or more hospitalizations, and their degree of improvement in

psychosocial functioning was greater. Additionally, their cost of care was lower in the 2-year period than that of the control group.

Family involvement in treatment may be particularly important in treating children, who are more dependent developmentally on family members. In particular, the role of expressed emotion (EE: an interaction style characterized by critical, hostile, intrusive interchanges) appears important for treatment. In Butzlaff and Hooley's (1998) meta-analysis of studies examining EE in adults, they reported that 65% of patients returning to homes characterized as high in EE relapsed within one year, compared with 35% who returned to homes low in EE. The case study of a 9-year-old with schizoaffective disorder describes improved functioning following an eight-session multifamily psychoeducational group intervention for children with mood disorders (Klaus, Fristad, Malkin, & Koons, 2005). A randomized study of 97 families having a family member aged 16–26 with schizophrenia indicates that those receiving family intervention in addition to standard intervention spent an average of 10 months less in institutional care at a 5-year follow-up (Lenior, Dingemans, Linszen, Dehaan, & Schene, 2001). Community-based maintenance is clearly associated with improved functional outcome for adults (Simmonds, Coid, Joseph, Marriott, & Tyler, 2001), with similar results reported for children with serious emotional disturbance, not all of whom had a diagnoses of psychosis (Henggeler, Schoenwald, Rowland, & Cunningham, 2002).

Limitations of Psychosocial Interventions

There are no clinical trials of psychosocial interventions on children to report. There is one historical control study of adolescents that suggests that psychoeducationlly oriented comprehensive care is beneficial. Adult studies and case reports suggest that psychosocial intervention is an important adjunct in the treatment of schizophrenia spectrum disorders.

Pharmacological Interventions

In adults, antipsychotic medication is considered the sine qua non of treatment (Mueser & McGurk, 2004). A study conducted by Harrigan, McGorry, and Hrstev (2003) indicates that the duration of untreated psychosis is an independent predictor of poor outcome in adults, suggesting the importance of rapid intervention when psychotic symptoms emerge.

In both adults and children, traditional neuroleptics and atypical antipsychotic agents are considered first-line agents (Mueser & McGurk, 2004; McClellan, Werry, & Work Group on Quality Issues, 2001). Randomized double-blind studies are limited to haloperidol, clozapine, risperidone, and olanzapine. In the largest trial, 50 youth aged 8–19 with prominent psychotic symptoms were treated in an 8-week randomized double-blind parallel comparison of haloperidol, risperidone, and olanzapine. Treatment response was 53%, 74%, and 88%, respectively (Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004). Over 15 studies indicate the efficacy of clozapine in children and adolescents, but serious adverse events occur at a higher rate than in adults (for a review, see Remschmidt, Hennionghausen, Clement, Heiser, & Schultz, 2000). Case studies suggest ziprasidone is beneficial in the treatment of psychosis (Meighen, Shelton, & McDougle, 2004). A large-scale, multicenter trial, Treatment of Early Onset Schizophrenia Spectrum Disorders, is currently under way, and it should shed more light on pharmacological intervention. In this four-site study, 165 youth aged 8–19 years are being randomized to risperidone, olanzapine, or molindone for 8 weeks, with 2 or more weeks at a predetermined maximal dose. Those with a positive response continue under masked conditions for an additional 44 weeks. Findings have not been published but should provide information on safety and efficacy of three antipsychotic medications.

Side Effects

All currently available medications carry the risk of serious adverse side effects and must be monitored closely (McClellan et al., 2001). A serious yet common side effect of atypical antipsychotic medications is weight gain that can result in a series of general metabolic disorders, including type 2 (non-insulin-dependent) diabetes mellitus, lipid level changes, and transaminase elevation (Kowatch et al., 2005). The American Diabetes Association, in conjunction with the American Psychiatric Association, recently published a monitoring protocol for all individuals receiving atypical antipsychotic medications (ADA and APA, 2004). There are anecdotal reports of cognitive side effects, including problems with word retrieval, working memory, and cognitive dulling (Kowatch et al., 2005). Neuroleptics may be associated with a shortened life span (Joukamaa et al., 2006). Other uncommon but problematic side effects associated with various medications that warrant careful monitoring include the following: antipsychotics—abnormal involuntary movements, prolactin elevation; ziprasidone—intracardiac conduction effects; clozapine—hematologic and neurologic adverse events and neuroleptic malignant syndrome.

Strength of Evidence

Many studies treat youth with psychotic symptoms, not necessarily schizophrenia spectrum disorders. Almost no studies include children under the age of 13. The number of studies is quite limited and deal only with acute outcomes, with the exception of one 2-year follow-up study of a comprehensive treatment program that used an historical control group who received an undocumented assortment of interventions.

Combined Interventions

Strength of Evidence

While a combination of psychopharmacological and psychosocial treatment is recommended (Asarnow, Tompson, & McGrath, 2004; McClellan, Werry, & Work Group on Quality Issues, 2001), the dearth of research in each respective area has resulted in no studies designed to specifically determine the relative efficacy of each treatment component in combination care. Promising initial findings have been presented by McGorry and colleagues (2002). They provided combination low-dose risperidone and CBT to 31 participants aged 14-28 (average age = 20) with subthreshold symptoms and compared their results to 28 controls who received needs-based intervention (supportive psychotherapy and case management). McGorry and colleagues reported that this combination treatment reduces the risk of early transition to psychosis, although the relative contributions of each intervention could not be determined.

Diversity Issues

Given the small number of studies conducted on relatively small sample sizes, no meaningful comparisons have been made between treatment response for males versus females, or minority versus majority racial or ethnic groups. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

The symptoms of schizophrenia spectrum disorders carry with them significant morbidity and mortality. Thus, adverse events associated with treatment must be weighed in light of the benefit they provide. Given this, there is support for utilizing pharmacological agents in well-monitored trials. There is no known risk of psychosocial interventions designed to aid the child

and family in coping with psychotic symptoms; in fact, some evidence suggests psychosocial intervention can provide benefit.

Future Directions

Schizophrenia spectrum disorders are rare in childhood and uncommon in adolescents. Almost no empirical studies have examined psychosocial interventions, and few have tested psychopharmacological agents in this population. On the basis of the extant literature, psychosocial interventions that are psychoeducational, family-based, and cognitive–behavioral are suggested. Newer pharmacological agents hold promise for the future, although all carry the risk of adverse side effects. Much more research is needed to develop optimal treatment guidelines for youth with schizophrenia-related disorders.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

SCHIZOPHRENIA SPECTRUM DISORDER	ACUTE	LONG-TERM	ADVERSE OUTCOMES
MEDICATION			
Haloperidol	2c (BPRS-C)	--	Mild to moderate sedation, extraphramidal symptoms, and weight gain
Clozapine	2d (BPRS)	--	Mild to moderate sedation, extraphramidal symptoms, and weight gain
Risperidone	2d (BPRS-C) 4d (BPRS)	--	Mild somnolence, acute dystonic reactions, Parkinsonian syndrome, mild orofacial dyskinesia, blurred vision, impaired concentration, and weight gain

Olanzapine	4d (BPRS) 4c (BPRS) 2d (BPRS-C)	--	Weight gain, increased appetite, constipation, nausea/vomiting, headache, somnolence, insomnia, difficulty concentrating, sustained tachycardia, transient elevation of liver transaminase levels.
Psychosocial MFPG	Case Study	--	
COMBINATION Lithium + adjunctive psychotic	4d (YMRS)	--	None listed

Note. BPRS = Brief Psychiatric Rating Scale; BPRS-C = Brief Psychiatric Rating Scale for Children; YMRS = Youth Mania rating Scale.

Autism Spectrum Disorders

Autism spectrum disorders (ASD) and intellectual disabilities (mental retardation) usually become apparent in the first 2–3 years of life and are characterized by major deficits in cognitive abilities and communication, resulting in life-long functional impairment. Most children with ASD also have general cognitive deficits consistent with mental retardation (MR). Based on the most recent estimates, the prevalence of autistic disorder is about 22 per 10,000 ; the prevalence of ASD (a broader category that includes autistic disorder) is about 60 per 10,000 (Chakrabarti & Fombonne 2005; Yeargin-Allsopp et al. 2003). The prevalence of MR is estimated to range between 1% and 3% (Volkmar & Dykens, 2002).

Psychosocial Interventions

Therapeutic interventions for children with ASD and MR can be divided into two categories: (a) comprehensive treatment programs aimed at correcting the core deficits of ASD and improving communication and interpersonal behavior and (b) ad hoc interventions to address specific behavioral problems, such as aggression, self-injury, stereotypes, and compulsions. While there is currently no curative intervention that can fully correct the deficits of these disorders, treatment can nevertheless substantially improve the functioning of these children (Bryson et al., 2003; Koegel et al., 2003; Lovaas & Smith, 2003; National Research Council, 2001).

A number of comprehensive treatment programs are currently in use for children with ASD (Koegel & Koegel, 1995; Lovaas, 1987; National Research Council, 2001; Rogers & Lewis, 1989; Schopler & Mesibov, 1995). Although different in their theoretical foundation, these programs have common characteristics, such as targeting multiple skill domains, intensive direct instruction (20–40 hr/week), involvement of the parents in delivering the intervention,

structured teaching settings, emphasis on early intervention (in preschool years), and long duration (at least 2 years). These interventions include both psychotherapy and educational elements, and a distinction between educational and psychotherapeutic components is practically impossible.

Specific psychosocial interventions, mainly based on the principles of behavior therapy, are of benefit in decreasing target symptoms, such as aggression, self-injury, and compulsive behaviors, and improving functioning (Eikeseth et al., 2002; Kahng et al., 2002; Smith et al., 2000).

Limitations of Psychosocial Interventions

Even though these interventions can lead to major improvements, especially in the domains of communication and general behavior, complete remediation of the core deficits of autism has not been achieved. Moreover, comprehensive treatments are rather expensive and require highly trained staff and substantial commitment from the family in order to be carried out. While some treatments have suggested improvement, these programs are quite costly. Even so, the cost of these therapies may far outweigh the adverse effects of pharmacological treatments and deserve careful attention in the literature.

Strength of Evidence

Overall, the evidence for the efficacy of psychosocial interventions in ASD and MR in decreasing symptoms and improving functioning is good but is not as well documented through controlled clinical trials for conditions such as ADHD. There are, in fact, only a few, relatively small, controlled clinical trials (Lovaas, 1987; Smith et al., 2000), and the evidence comes primarily from quasi-experimental designs and single-case studies. Therefore, computation of effect sizes as compared with a control condition is not possible at this time; however, researchers believe that these interventions can result in marked improvement. It should be

noted that there are a myriad of single-subject designs demonstrating improvement in behaviors with operant techniques. The incorporation of these techniques into controlled clinical trials is an area that will be important for future research to explore. Although psychosocial interventions constitute the mainstay of treatment for children with ADS, it is generally recognized that larger and more representative controlled studies to test their efficacy are needed (Lord et al., 2005).

Pharmacological Interventions

Pharmacotherapy is currently an ancillary intervention to control problematic behaviors, such as aggression, self-injury, tantrums, impulsiveness, and stereotypic-compulsive behavior, rather than one that corrects the core deficits of the disorder. These behaviors, common among children with ASD and/or MR, cause substantial impairment. Attempts to develop pharmacological interventions to correct the core communication deficits of ASD have not been successful, as shown in the examples of fenfluramine, naltrexone, and secretin (Campbell et al., 1988; Sandler et al., 1999; Sturmey, 2005). Ongoing research on the pathogenesis of autism and related disorders may indicate more promising targets for future drug development.

Despite their ancillary role, psychotropic medications are commonly used in the treatment of children with ASD and MR. In fact, epidemiological community surveys indicate that 33% to 47% of children with ASD receive at least one psychotropic medication during a 1-year period (Aman, Lam, & Collier-Crespin, 2003; Aman, Lam, & Van Bourgondien, 2005; Witwer & Lecavalier, 2006). The most commonly used psychotropic medications in ASD are antidepressants, antipsychotics, stimulants, and the alpha-agonist clonidine. Also used are mood stabilizers, such as lithium and divalproex sodium. The strength of the evidence for the efficacy of these medications is variable, ranging from placebo-controlled clinical trials to open-label case reports.

Stimulants are used to control symptoms of hyperactivity, impulsiveness, and inattention, which are commonly encountered among children with ASD and MR, despite that the current *DSM–IV* nosological perspective does not permit a formal diagnosis of ADHD in the context of a pervasive developmental disorder. A recently completed, publicly funded, multisite controlled clinical trial has provided evidence that methylphenidate was efficacious in relieving ADHD symptoms in children with ASD, but its efficacy and tolerability were more variable than in children with ADHD who have no developmental disorder (Research Units on Pediatric Psychopharmacology Autism Network, 2005a). Approximately 50% of the children with ASD had a positive response to methylphenidate, and about 18% had adverse events, some of which were highly disruptive, although short-lived.

A 4-week placebo-controlled within-subject study compared methylphenidate, administered at different doses, with placebo. Of the 72 children who entered the study, 18% interrupted treatment because of adverse events, and only 48% showed clinically significant improvement. These rates contrast with a discontinuation rate due to adverse events of less than 5% and an improvement rate of more than 70% in hyperactive children without pervasive developmental disorders (Greenhill et al., 2001).

Antipsychotic medications, antidopaminergic agents marketed for the treatment of psychosis in adults, are commonly used off label to treat behavioral problems such as aggression and severe tantrums in children. Typical antipsychotics have been used for decades to control behavioral problems in children with MR and ASD. In particular, placebo-controlled studies document the efficacy of haloperidol in autism (L. T. Anderson et al., 1989). In more recent years, atypical antipsychotics, such as risperidone, have gradually replaced the typical antipsychotics. Evidence from a multisite controlled, publicly funded clinical trial shows that risperidone is efficacious in decreasing severe behavioral disturbances in 5–17-year-old children with autism (Research Units on Pediatric Psychopharmacology Autism Network, 2002). About two thirds of children treated with risperidone improved, as compared with 12% on

placebo at the end of the 8-week trial. Shea et al. (2004) essentially replicated these findings in a group of children with autism, PDD-NOS, or Asperger's syndrome who were not selected for extremely disruptive behavior. The beneficial effect seen by the Research Units on Pediatric Psychopharmacology Autism Network (2005b) was sustained up to the 6 months of treatment, but when the medication was discontinued, the behavioral problems usually recurred. This long-term effect was recently replicated by an independent group of researchers (Troost et al., 2005). Thus, risperidone is efficacious but noncurative and is associated with weight gain, which can make long-term treatment problematic. The efficacy of other antipsychotics has been less well investigated and is currently limited to uncontrolled studies.

Selective serotonin reuptake inhibitors such as clomipramine, fluoxetine, and fluvoxamine have been used in the treatment of compulsive repetitive behaviors. There is limited evidence from small controlled trials that clomipramine and fluoxetine are efficacious in children with autism for managing perseverative behaviors, such as compulsions, stereotypes, and self injury (Gordon, State, Nelson, Hamburger, & Rapoport, 1993, Hollander et al., 2005). Fluoxetine has a more favorable tolerability profile than clomipramine, but there is some uncertainty whether children and adolescents respond as well as adults (Aman et al., 1999). Further controlled investigations are ongoing as to the efficacy of SSRIs in reducing repetitive behaviors and improving the general functioning of children with ASD.

Clonidine and the pharmacologically related guanfacine are alpha agonists that are marketed for the treatment of hypertension in adults but are also used off label to treat hyperactivity in children. These drugs are often used in children with ASD in an attempt to control behavioral problems such as hyperactivity, aggression, and severe tantrums. At this time, their efficacy is supported only by open-label, uncontrolled reports (Posey & McDougle 2001).

Mood stabilizers, such as lithium and divalproate, are also used in children with ASD and MR for the control of explosive aggression and severe tantrums. These medications are

effective treatments for adults with bipolar disorders, but in spite of their use in children with ASD and MR, conclusive evidence for their efficacy in these patients does not exist. In particular, their efficacy is not supported by any randomized controlled trials in children and adolescents with ASD and/or MR. A few small trials in adults provide preliminary support for their efficacy.

Side Effects

The medications used in the management of children with ASD or MR have distinctive adverse events that relate to the pharmacological activities of these agents. In some cases, there is evidence that the risk–benefit ratio of these medications is less favorable in the case of children with ASD than in non-ASD children. For instance, adverse events, primarily agitation, irritability, and insomnia, led to discontinuation of methylphenidate in 18% of children with ASD aged 5–14 years (RUPP Autism Network, 2005), a rate that is substantially higher than that reported in non-ASD children with ADHD (less than 2%). In general, children with ASD and MR can be considered at increased risk for drug-induced adverse events, because their brains are likely to be more sensitive to pharmacological intervention due to the underlying developmental disturbance, and also because their deficits in communication can impair or delay recognition of drug toxicities. For the medications with best evidence for efficacy (i.e., antipsychotics), two types of adverse events are noteworthy: neurological toxicities for typical antipsychotics (i.e., dystonias, dyskinesias, tremor, Parkinsonism, and akathisia) and weight gain for commonly used atypical antipsychotics such as risperidone and olanzapine. The latter drugs may also increase the risk for metabolic disturbances such as diabetes and hyperlipidemia (American Diabetes Association et al., 2004).

Strength of Evidence

Randomized controlled studies strongly support the efficacy of antipsychotics and stimulants in decreasing symptoms of disruptive behavior in children (age 5 and older) and adolescents. The effect of antipsychotics is large (i.e., Cohen's effect size > 0.8), while that of stimulants is more modest (effect sizes between 0.2 and 0.5). Less clear is the impact of these agents on functioning. In a randomized trial, treatment with risperidone resulted in improvement in the restricted and repetitive patterns of behavior but did not change the deficits in communication and social interactions that are typical of autism (McDougle et al., 2005).

Combined Interventions

Psychosocial and psychopharmacological interventions are often used conjunctively, but little is currently known on the interactions between these two treatment modalities. For instance, it is not known whether medications enhance the efficacy of psychosocial treatment, or whether psychosocial treatment allows medication eventually to be discontinued without recurrence of symptoms.

Diversity Issues

Data do not currently exist on the impact of treatment by subjects subgroups. In general, studies have been too small in size to be able to detect subgroup differences. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

The balance between risk and benefit clearly favors psychosocial interventions and is also generally favorable for selected medications, such as antipsychotics and stimulants, when used in the short-term (2–6 months), but data on longer term use are lacking. Psychopharmacological interventions are often less favorable for children with ASD and/or MR than for nondevelopmentally impaired peers. For instance, stimulants and SSRIs are generally less well tolerated by ASD children, compared with non-ASD peers with ADHD or anxiety disorders.

It should be noted that there is a corpus of research in the field of ASD and MR related to behavior therapy in these two patient populations. While there are not many controlled clinical trials comparing behavior therapy to no treatment, studies in the field of applied behavior

analysis that have employed ABA designs have yielded impressive data with regard to the efficacy of operant techniques with these populations, particularly in targeting specific symptoms that are associated with these disorders. Although a complete discussion of this impressive literature is not within the scope of this report, interested readers are referred to a number of sources (e.g., Baumeister & Baumeister, 1995; Harris, 1995; Kobe & Mulick, 1995).

The determination of risk–benefit for psychotropic use in children with ASD and MR must be made at the level of the individual child and take into consideration the medication side-effect profile as well as the severity of the symptoms, level of dysfunction, response to alternative, nonpharmacological treatment, and current medical condition (e.g., risperidone may not be appropriate for an obese child).

Future Directions

There is a need for further research on the effectiveness of existing comprehensive interventions, specifically the extent of the improvement these interventions can provide, the identification of subgroups of children more likely to benefit from them, the relationship between the intensity of treatment and treatment outcome, and the overall cost–benefit analyses (Lord et al., 2005). In addition, it is necessary to apply neuroscience findings to the development of novel treatments, both psychosocial/educational and pharmacological, to better address the core symptoms of ASD and MR.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

Autism Spectrum Disorders	**ACUTE**		**LONG-TERM (over 12 months)**		**ADVERSE OUTCOMES (see risk–benefit discussion)**
	Primary Symptoms	Functional Outcomes	Primary Symptoms	Functional Outcomes	
MEDICATION					
Stimulants	1c Inattention, hyperactivity, impulsiveness	4d	No data	No data	More adverse side effects (irritability, social withdrawal, affective blunting, insomnia) than with non-ASD
Antipsychotics	1a Self-injurious behavior, severe tantrum, stereotypes	1a General functioning by decreasing aggression	No data	No data	Neurological adverse events Weight gain, sedation, increased risk for diabetes

PSYCHOSOCIAL	1a Self-injurious behavior, severe tantrum, stereotypes, language and communication social skills	1a Improved functioning in interpersonal, academic, and other adaptive behaviors	3c For targeted symptoms, self-injurious behavior, severe tantrum, stereotypes, language and communication social skills	3c Improved functioning in interpersonal, academic, and other adaptive behaviors	Usually well-tolerated, but limited data available
COMBINATION	No data	No data	No data	No data	No data

Anorexia Nervosa and Bulimia Nervosa

Anorexia nervosa may arise in children as young as 8 years of age, whereas bulimia nervosa rarely appears before the age of 12 (Gowers & Bryant-Waugh, 2004). More common than full-blown eating disorders are clinically significant symptoms that may include a significant preoccupation with food, weight, or shape and some sort of disordered eating. The prevalence of anorexia nervosa in girls appears to be between .3% and 1%, peaking during the ages of 15–19, with a female-to-male ratio of about 11 to 1 (W. G. Johnson, Tosh, & Varnado, 1996; Van Hoeken, Seidell, & Hoek, 2003). The prevalence of bulimia nervosa appears to be between 1% and 3%, with a female-to-male ratio of about 30 to 1 (Gowers & Bryant-Waugh, 2004; W. G. Johnson et al., 1996).

Depression is commonly associated with eating disorders. Approximately 45% of individuals with anorexia nervosa and up to 88% of those with bulimia nervosa have a lifetime history of mood disorder (Pike & Striegel-Moore, 1997). Depressive symptoms do not appear to influence outcome (Gowers & Bryant-Waugh, 2004). On the other hand, OCD and residual OCD symptoms are associated with poorer outcome (Gowers & Bryant-Waugh, 2004). Comorbid anxiety disorders appear to be at least as common as depression, with two thirds of all individuals who are diagnosed as having an eating disorder also meeting criteria for one or more lifetime anxiety disorders, most commonly OCD or social phobia (Kaye et al., 2004).

Psychosocial Interventions

The evidence base for treatment efficacy of anorexia nervosa across all age groups is weak; there are very few randomized controlled trials (Gowers & Bryant-Waugh, 2004; Treasure & Schmidt, 2003). Only a few, small controlled studies have been reported in adolescents with anorexia nervosa. Russell et al. (1987) compared 13 sessions of whole family therapy to

individual therapy in 21 youths (mean age = 17 years); the improvement rate was 90% with family therapy versus 18% with individual therapy. Another study involving 37 youths (mean age = 14 years) found an improvement rate of 81% with family therapy versus 66% with individual therapy (Robin et al., 1995). A study of 40 youths (mean age = 15 years) compared whole family therapy with separate family therapy and found no difference in response rate between the two (Eisler et al., 2000).

Based on existing, limited evidence, it appears that behavioral family therapy may be considered a reasonable first-line approach to anorexia nervosa in adolescence. In those few controlled studies that do exist, clinicians are forced to extrapolate from data that include adults to design an evidence-based treatment for children. A recent review (Treasure & Schmidt, 2003) showed limited evidence from one randomized controlled trial that focal therapy, cognitive–analytic therapy, and family therapy were more effective than treatment-as-usual in adults. Another small randomized controlled trial showed outpatient treatment was as effective as inpatient treatment in those adolescents and adults who did not need emergency medical treatment. Another 10 randomized controlled trials did not find differences between various psychotherapies or psychotherapy and dietary advice (Treasure & Schmidt, 2003). A very recent randomized controlled trial (McIntosh et al., 2005), in a mostly adult sample that included women with anorexia nervosa as young as 17 years old, found nonspecific supportive clinical management to be superior to either CBT or IPT.

Several systematic reviews of bulimia nervosa treatments are available, but no randomized controlled trials involving adolescents have been published (Gowers & Bryant-Waugh, 2004). These reviews have found that CBT is an effective intervention for the purging and eating behaviors of bulimia nervosa and associated symptoms such as depression. CBT usually involves psychoeducation, self-monitoring, application of behavioral strategies to establish more regular eating habits (e.g., self-reward for three meals plus two snacks at regular times of the day), eliminating rigid dieting, and strategies to decrease bingeing and purging.

Treatment may include stimulus control strategies to help the patient avoid or change situations that typically trigger a binge or purge. Treatment may also involve addressing cognitive distortions (e.g., certain foods are “good or bad”) and using exposure techniques for avoided food or anxiety-evoking situations. Interpersonal therapy, though also beneficial, has resulted in more modest effects.

Limitations of Psychosocial Interventions

In some cases, because of concerns about physical safety, patients may need to be hospitalized until treatment has been determined to be efficacious and there are no longer dangers to individual health and well-being. Also, it is fairly common for treated patients to continue to experience persistent subthreshold symptoms (e.g., Jager et al., 2004). It should also be noted that psychosocial interventions may be a limited resource in some communities.

Strength of Evidence

The evidence for psychosocial interventions for anorexia nervosa is weak, as it is based primarily on case series or other uncontrolled reports. There are only a few randomized controlled trials targeting children and few outcome studies of any kind on anorexics. The evidence for psychosocial interventions in bulimia nervosa is much stronger, though there are no studies targeting children specifically, forcing clinicians to extrapolate from adult data. The effects sizes of psychosocial interventions in the acute treatment of bulimia nervosa are moderate. There are not enough data to make conclusions about long term follow-up.

Pharmacological Interventions

Ten studies of controlled drug trials (usually tricyclic antidepressants or SSRIs) with anorexics failed to document efficacy in terms of physical and psychological outcome (Treasure & Schmidt, 2003). Results from a placebo-controlled study found that fluoxetine reduced the risk of relapse after weight restoration in adults with anorexia nervosa (Kaye et al., 2004). However, an observational, 2-year longitudinal follow-up of adults with anorexia nervosa did not show any benefit of antidepressant treatment for relapse (Strober et al., 1997). Atypical antipsychotics, especially olanzapine, have been tried in open-label, nonrandomized single-case studies, some of which involved adolescents (Barbarich et al., 2004, Mehler, 2001). Results from these studies

suggest a possible benefit of olanzapine in increasing weight and decreasing weight obsession. In bulimia nervosa and binge-eating disorder, an early review (W. G. Johnson et al., 1996) concluded that antidepressants reduce bingeing and purging, although this result appears independent of any antidepressant effect. CBT also reduces bingeing and purging, and direct comparisons with medication alone favor CBT, particularly when longer term follow-up is considered (W. G. Johnson et al., 1996). More recent reviews of antidepressant trials (Bacaltchuk et al., 2000; Whittal et al., 1999) found short-term improvements in bulimic symptoms and a small improvement in depressive symptoms. Tricyclic antidepressants, SSRIs, and monoamine oxidase inhibitors had comparable efficacy and tolerability (Bacaltchuk et al., 2000).

Side Effects

The side effects of antidepressants are delineated in the Depressive Disorders and Suicidality section of this report. Side effects in patients with depression are not expected to be demonstrably different than in patients with eating disorders. It is important to note that the black box warnings about increased risk of suicidality apply to the use of all antidepressants in children, whether the antidepressants are used to treat depression or eating disorders. Based on adult studies (Lieberman et al., 2005), up to 70% of patients who take atypical antipsychotics like olanzapine experience moderate to severe adverse events, including insomnia (16%), sleepiness (30%), urinary hesitancy, dry mouth or constipation (24%), sexual problems (27%), menstrual irregularities (36%), and orthostatic faintness (9%). Up to 30% of patients taking olanzapine experience a weight gain more than 7%, raising risk for diabetes and other weight-related problems (Lieberman et al., 2005)

Strength of Evidence

The evidence for psychopharmacological interventions for anorexia nervosa is weak to nonexistent. There are no randomized controlled trials targeting children and few outcome studies of any kind in anorexic patients. The evidence for psychopharmacological interventions in bulimia nervosa is much stronger, though there are no studies targeting children specifically. The effects sizes for psychopharmacological interventions in the acute treatment of bulimia nervosa are moderate. There are not enough data to make conclusions about longer term follow-up.

Combined Interventions

No studies have systematically evaluated the efficacy of combining psychosocial and pharmacological interventions for anorexia nervosa. Bacaltchuk et al. (2000) found evidence for the superiority of combining psychotherapy and antidepressants over antidepressants alone for bulimia nervosa in terms of remission rate and mood symptoms, but not in reducing binge frequency. Given the preponderance of the evidence, CBT would appear to be the treatment of first choice for bulimia nervosa in children and adolescents, typically resulting in a recovery rate of 40% to 50% (D. A. Anderson & Maloney, 2001), compared with a recovery rate of only about 19% with antidepressants alone (Bacaltchuk et al., 2000).

Diversity Issues

Minimal data on the role of ethnicity or racial background for children and adolescents with eating disorders exist. Some data show that ethnic minority women who seek treatment for anorexia nervosa have lower admission weights than White women, suggesting that anorexia nervosa may go undetected or untreated longer in ethnic minority women (Pike & Striegel-Moore, 1997). Typically a disorder of White, affluent Western cultures, bulimia nervosa appears to be increasing among non-White groups, including African Americans and women in developing non-Western cultures (Pike & Striegel-Moore, 1997).

Although not addressed in this review, African American and Latina girls and adolescents are also at increased risk for obesity, with approximately 20% of African American girls, 25% of African American adolescent girls, and 20% of Latina girls and adolescents at or above the 95th percentile for body mass index (CDC, 2000). Subgroups of the population such as gymnasts, models, and dancers may be more at risk for developing bulimia nervosa because of cultural pressure to conform to a certain body image (Pike & Striegel-Moore, 1997). Better

prognosis in bulimia nervosa has been associated with shorter duration of the disorder, less severe symptoms, higher social class, younger onset, family history of alcoholism, high self-esteem, and lower perfectionism (Gowers & Bryant-Waugh, 2004). Efforts should be made to include boys in treatment outcome studies of eating disorders. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

In the treatment of anorexia nervosa, there is a lack of controlled data, perhaps because of the practical challenges of doing such research, forcing clinicians to rely on expert opinion. Based on reviews of the treatment outcome literature, to achieve recovery in bulimia nervosa, compared with placebo, the NNTB for CBT appears to be about 3, and for antidepressants, about 9; there are not enough data to calculate an NNTB figure for combination treatment. Compared with placebo, the NNTH for antidepressants in terms of treatment discontinuation due to an adverse event appears to be about 19 (Bacaltchuk et al., 2000). There are not comparable data to allow an NNTH calculation for psychosocial treatment, though adverse medical events are expected to be lower than those for antidepressants.

Future Directions

Future research needs to precisely determine the effectiveness of specific forms of family therapy in anorexia nervosa and the value of SSRI medication in decreasing risk for recurrence in patients who have reached remission. Promising results of guided self-help interventions for bulimia nervosa, usually CBT based, should be further pursued (Hay et al., 2003). Research should also examine ethnic and cultural influences on eating disorders in general and in response to treatment in particular. Randomized controlled trials for the

treatment of anorexia nervosa are especially needed to examine the relative efficacy of medication or psychosocial interventions alone and in combination. It is noteworthy that in September 2005, NIMH funded a cooperative agreement to conduct a multisite clinical trial of a specific form of family behavioral therapy (the “Maudsley approach”) involving more than 200 adolescents with anorexia nervosa. The expected duration of this study is 5 years.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

ANOREXIA NERVOSA BULIMIA NERVOSA	**ACUTE** **Primary Functional**		**LONG-TERM** **Primary Functional**		**ADVERSE OUTCOMES**
MEDICATION	4d Anorexia nervosa 2b Bulimia nervosa	4d Anorexia nervosa 2b Bulimia nervosa	No data 2b Bulimia nervosa	No data	
PSYCHOSOCIAL	2c Anorexia nervosa 2b Bulimia nervosa	2c Anorexia nervosa 2b Bulimia nervosa	No data 2b Bulimia nervosa	No data	

COMBINATION	Anorexia nervosa no data 2b Bulimia nervosa	Anorexia nervosa no data 2b Bulimia nervosa	No data	No data	

Elimination Disorders

Elimination disorders include nocturnal enuresis and encopresis. Nocturnal enuresis is defined as repeated urination into bed or clothes, which occurs at least twice per week for at least 3 consecutive months in a child who is at least 5 years of age and where the condition is not due to either an adverse side effect of a drug or to a medical condition (American Psychiatric Association, 2000). Nocturnal enuresis is especially common during early childhood years. Approximately 15%–20% of 5-year-olds and 7%–15% of 7-year-olds are enuretic at least once per month. About 7% of 7-year-old boys and 3% of 7-year-old girls are enuretic weekly (Ondersma & Walker, 1998). In addition, 3% of children with enuresis remain incontinent well into adulthood (Mellon & Houts, 1998). Diurnal enuresis is much less frequent than nocturnal enuresis, with nocturnal enuresis being more common among girls and occurring in approximately 1% of 6–12-year-olds.

Encopresis is defecation in inappropriate places over a given time span, occurring at least once per month for at least 3 months (American Psychiatric Association, 2000). The child must be at least 4 years of age, and the behavior must not be exclusively due to the adverse effects of medications or physical problems other than constipation. Finally, the diagnosis of encopresis requires a determination of whether the soiling is due to constipation (American Psychiatric Association, 2000). It has been estimated that 1% of 5-year-olds have encopresis, and the disorder is five to six times more prevalent among males. Referrals for encopresis account for approximately 3% of pediatric outpatient referrals and 5% of referrals to psychiatric clinics (Franklin & Johnson, 2003). Frequency of encopresis decreases with age, with a spontaneous remission rate of about 28% per year (Franklin & Johnson, 2003).

Psychosocial Interventions

Given the potential for some type of organic etiology for both enuresis and encopresis, a practitioner should partner with a pediatrician when assessing and managing enuresis and encopresis. Research has shown operant techniques to be successful in the management of both enuresis and encopresis. A number of reviews and numerous well-controlled clinical trials have clearly documented the importance and efficacy of the basic urine alarm as an important treatment modality for enuresis in combination with “dry-bed-training,” which is a basic operant approach to the management of enuresis (for a review, see Mellon & McGrath, 2000). Full spectrum home training is one multicomponent treatment approach that includes the urine alarm and other components, including retention and control training with monetary rewards, cleanliness training, self-monitoring of wet/dry nights, and a graduated overlearning procedure. These approaches are manualized, and an advantage of this multicomponent treatment approach over the basic urine alarm treatment alone is the inclusion of components designed to reduce relapse after successful therapy (for a review, see, Mellon & McGrath, 2000). Approaches focusing on enhancing compliance that include a cognitive approach (e.g., hypnotic interventions) clearly warrant further investigation.

Well-established interventions for encopresis have not been documented to date, although the literature has identified several probable efficacious therapies and three promising interventions. Two specific medical interventions (one with a fiber recommendation and one without) with positive reinforcement are likely efficacious treatments for encopresis. Biofeedback in combination with medical interventions has shown particular promise in the management of constipation with abnormal defecation. Other promising interventions for encopresis include correction of paradoxical contraction, positive reinforcement, dietary education, goal setting, and skills-building focused on relaxation during defecation.

Limitations of Psychosocial Interventions

The efficacy of the urine alarm in the management of nocturnal enuresis is well documented in a number of compelling literature reviews (Dooleys, 1977; Houts, Berman, & Abramson, 1994; S. B. Johnson, 1980; Mellon & McGrath, 2000; Moffatt, 1997). However, patient characteristics predicting best-treatment outcome for the alarm remain unclear. Further, it is unclear whether other components of treatment add to the effectiveness of the urine alarm. Finally, the interaction of enuresis and the frequently occurring comorbid physical conditions, including maturational delays in central nervous system development, of children with enuresis in the context of learning theory remains unknown (Mellon & McGrath, 2000).

Limitations of psychosocial interventions for encopresis include the failure of clinical trials to delineate specific symptoms (e.g., incontinence, constipation, abnormal defecation) that are especially responsive to specific behavioral interventions. In addition, the role of adherence on the part of families is unclear, particularly as this may predict treatment outcome or failure. Given that disease management has been associated with familial functioning, the role of the family in predicting treatment outcome is of utmost importance. Finally, there is little research that has provided information with regard to severity and duration of encopresis and how this is influenced by behavioral approaches.

Strength of Evidence

The basic urine alarm alone is considered to be necessary in the treatment of enuresis; evidence-based research has demonstrated that the urine alarm in combination with dry-bed training is an effective treatment. Further, full spectrum home training has been demonstrated to improve outcome for children with enuresis, but it is classified only as probably efficacious because other studies have not replicated the data from the full spectrum home training behavioral intervention. Other approaches that focus on improving compliance with treatment or

incorporate a cognitive focus warrant further investigation, although no information can be provided with regard to their strength of evidence.

By contrast to the enuresis literature, in the management of constipation and encopresis, no well-established investigations are available in the extant literature. Specifically, medical interventions that include positive reinforcement and interventions that include biofeedback have been concluded to be probably efficacious (McGrath, Mellon, & Murphy, 2000).

The behavioral approaches in the management of enuresis and encopresis have demonstrated the most success relative to other therapies, including pharmacotherapy, in the immediate management of symptoms as well as in ensuring durability once therapy has ceased.

Pharmacological Interventions

There are no available pharmacotherapies that specifically target encopresis except of those agents that manage constipation. Imipramine was one of the first pharmacotherapies successfully used for the pharmacological management of enuresis. Nonetheless, due to the adverse effects, including cardiac toxicity and other known toxicities associated with tricyclic antidepressants, synthetic vasopressin (DDAVP) soon replaced imipramine as the pharmacotherapy of choice for the management of enuresis. Because the synthesis of this medication was especially costly in oral tablet form (a great deal of the compound would be needed for the purpose of achieving adequate blood levels), the route of administration was soon developed to be administered by means of nasal spray. Clearly, while DDAVP has been shown to be efficacious in the management of enuresis (there are no data to indicate the number of respondents), once the medication is withdrawn, the child almost always reverts to wetting (Moffatt, Harlos, Kirshen, & Burd, 1993). Thus, durability is clearly in the short-term, with no generalization or hope of durability in the long-term.

There are no available studies examining the combination of either imipramine or DDAVP, the two basic pharmacotherapies demonstrated to be efficacious in the management of enuresis, in combination with operant approaches. Although medical interventions designed to reduce constipation are frequently used simultaneously with behavioral approaches and biofeedback to manage encopresis, no specific pharmacological agent has been studied with behavioral approaches for the purpose of managing encopresis. For this reason, behavioral therapy is necessary even if it is employed as an adjunct to pharmacotherapy.

Side Effects and Other Limitations of Pharmacological Interventions

Limitations in the pharmacotherapy of enuresis (i.e., imipramine or DDAVP) include the high cost of treatment, the fact that the pharmacotherapies rarely stop bedwetting, and that upon cessation of pharmacotherapy, the child experiences complete relapse (Moffatt, Harlos, Kirshen, & Burd, 1993).

Strength of Evidence

The strength of evidence with regard to the use of pharmacotherapy in the short-term management of enuresis is that pharmacotherapy is an effective treatment only for enuresis; there are no known psychotropic medications for encopresis.

Combined Interventions

As Mellon and McGrath (2000) have observed, the combination of the urine alarm with desmopressin offers significant promise and may push the already high success rates of conditioning approaches to nearly 100%. In support of this conclusion, Woo and Park (2004) examined the efficacy of a urine alarm for the management of enuresis as a second-line therapeutic approach for those children who failed to respond to pharmacotherapy. Findings revealed that after using the urine alarm for those children who failed a trial of pharmacotherapy, over 90% of partial responders became full responders. These findings support the observations of Mellon and McGrath (2000) of the high success rates of behavioral treatments for the management of enuresis.

Strength of Evidence

No conclusions can be made with regard to strength of evidence of combined psychosocial and psychopharmacological treatments because of the dearth of multimodal studies.

Diversity Issues

With the exception of the literature that has focused on the difference in the prevalence of enuresis and encopresis among boys and girls (Franklin & Johnson, 2003; Ondersma & Walker, 1998), no studies have focused specifically on pharmacotherapies or on nonpharmacological therapies as they are associated with gender, ethnicity, or race. Treatment response has also not been studied as a function of gender, race, or ethnicity. Further research examining treatment effects and outcomes by diversity variables is necessary.

Risk–Benefit Analysis

Given the strength of evidence associated with behavioral approaches for the management of enuresis and the limited adverse effects of these therapies documented in the extant literature, behavioral approaches are concluded to be of high benefit and of little risk in the management of enuresis and encopresis in pediatric populations. In both the short- and long-term, a number of risks have been associated with imipramine therapy, a tricyclic antidepressant medication that had been used to manage enuresis that could result in problems with cardiac conduction or death. More recently, because of the concerns pertaining to cardiac toxicity associated with imipramine, DDAVP has been used as a pharmacotherapy for enuresis and has been demonstrated to be efficacious in the short-term, although there is limited investigation with regard to the safety of this agent in either the short- or the long-term. Thus, the benefit of behavior therapy appears to be especially high for both enuresis and encopresis,

while the benefit of pharmacotherapy for enuresis is not especially high. No psychopharmacotherapy has been demonstrated to be efficacious in the management of encopresis.

Future Directions

Behavioral techniques in the management of both enuresis and encopresis have high benefit and low risk and are efficacious in the management of enuresis and probably efficacious in the management of encopresis. The use of pharmacotherapy is efficacious in the management of enuresis, but not without risk. Clearly, controlled trials are needed to address both the combined and comparative efficacy of DDAVP and behavior management for children with enuresis. Until such data are forthcoming, little can be said about their efficacy.

RATING SYSTEM
Effect Size a = .81 +, large evidence; b = .51 to .80, medium evidence; c = .21 to .50, small evidence; d = .20 or less, no evidence
Quality 1 = replicated clinical or large-body single-subject study; 2 = controlled clinical trial or replicated single-subject study; 3 = comparison group, but not clinical trial; 4 = no control group

Elimination Disorders	**ACUTE**		**LONG-TERM**		**ADVERSE OUTCOMES**
MEDICATION	**Enuresis** **Encopresis**	2b Imipramine 2b DDAVP			Cardiac conduction disturbances, orthostatic hypotension
PSYCHO-SOCIAL	**Enuresis** **Encopresis**	1a Urine Alarm 1a Dry Bed Training 1b Full Spectrum Home Training 2b Positive reinforcement			

		2b Biofeedback 3c Correction of paradoxical contraction 4c Dietary education 4c Goal setting 4c Skill building			
COMBINA-TION	**Enuresis** **Encopresis**	4a Urine alarm in combination with DDAVP			

CONCLUSIONS

Empirical evidence and clinical experience support the therapeutic benefit of a number of psychosocial and pharmacological interventions for the treatment of children and adolescents with mental disorders. A considerable and recent increase in research has advanced the knowledge base regarding treatment of the most common childhood disorders, providing better guidance to clinicians and improving the ability of clinicians and patients to make better informed treatment decisions. For many of these interventions, the short-term efficacy for decreasing symptoms is fairly well demonstrated. In contrast, evidence supporting the acute impact of treatment on daily life functioning and the long-term impact on both symptoms and other outcomes is less well documented. In particular, safety concerns remain for a number of psychopharmacological interventions.

An important question—touched on briefly in several sections in this report—is which treatment should be used first. The answer to this question is critical in determining, for example, how many children need and receive a particular intervention when two exist. Moreover, given that many caregivers have definite preferences about treatments for their children, sequences in which treatments are initiated are of paramount importance to families.

Algorithms recommending particular treatment sequences abound (American Academy of Child & Adolescent Psychiatry, 2002; American Academy of Pediatrics, 2001). For example, the American Academy of Child and Adolescent Psychiatry (2000) guideline on treatment of BPD suggests that medication and psychosocial interventions both be used simultaneously. The American Academy of Pediatrics (2001) guidelines for ADHD states that treatment for ADHD should involve medication, behavior therapy, or their combination, without a sequence specified. However, it is worth noting that none of these algorithms for treatment sequencing is evidenced-based—a result of the fact that to our knowledge, there are not yet any published studies in

which different sequences or simultaneous implementation of multiple modalities have been systematically compared. Existing recommendations for treatment sequencing are thus based entirely on expert consensus.

It is the opinion of this working group that in the absence of empirical evidence, the decision about which treatment to use first (i.e., which treatment is the most favorable to the child) should be guided by the balance between anticipated benefits and possible harms of treatment choices (including absence of treatment). By this we mean that the safest treatments with demonstrated efficacy should be considered first before considering other treatments with less favorable profiles. For most of the disorders reviewed herein, there are psychosocial treatments that are solidly grounded in empirical support as stand-alone treatments. Moreover, the preponderance of available evidence indicates that psychosocial treatments are safer than psychoactive medications. Thus, it is our recommendation that in most cases, psychosocial interventions be considered first. The acute and long-term safety and efficacy data that are available for each disorder will be central to this determination.

It also should be acknowledged that there are cultural and individual differences about how to weigh safety and efficacy data, and consumers (i.e., families) might weigh them differently. Ultimately, it is the families' decision about which treatments to use and in which order. A clinician's role is to provide the family with the most up-to-date evidence, as it becomes available, regarding short- and long-term risks and benefits of the treatments. As our evidence base continues to grow, the ultimate goal will be to provide information that will allow families to apply their own preferences about how to weigh safety and efficacy in order to make an informed choice on behalf of their child.

Traditionally, psychosocial and pharmacological interventions have been examined in separate studies with distinct differences in methods and designs, making it difficult to compare the relative efficacy and safety of these two different treatment modalities. This is a major limitation of the field, since treatment guidelines need to integrate all effective interventions,

including both psychological and psychopharmacological, and the standards applied to these two modalities need to be comparable. As one step in this direction, a number of recent federally funded initiatives have directly compared the relative effectiveness of psychosocial and psychopharmacological interventions, alone and in combination (MTA, TADS, POTS, CAMS). These studies have their own limitations, but they offer additional perspectives on comparing treatments for children and adolescents.

A few general trends emerged from the literature reviewed for this report. Most notably, the evidence base for treatment efficacy is somewhat uneven across disorders, with most of the research focusing on childhood ADHD, adolescent depression, and, more recently, the anxiety disorders. It is notable that some of the most severe mental health conditions of childhood, including BPD and schizophrenia, have received proportionally less attention from treatment researchers. The use of psychosocial treatments as first-line interventions is supported for a certain number of conditions, including ADHD, ODD, CD, autism, anorexia nervosa and bulimia nervosa, OCD, PTSD, other anxiety disorders, and depression. Finally, there are a number of disorders whereby psychosocial, psychopharmacological, or their combination have been demonstrated to be effective, at least acutely. These include ADHD and depression.

Despite recent advances in treatment research, significant knowledge gaps remain. Most of the evidence for efficacy is limited to acute symptomatic improvement, with only limited attention paid to functional outcomes and long-term effects. In addition, few studies have been conducted in practice settings, and with the possible exception of ADHD and CD, where much research has been conducted in school settings, little is known about the therapeutic benefits of intervention under usual, or real-life, conditions. Furthermore, whereas the benefits of some behavioral treatments have been well documented through numerous single-subject design studies and group crossover designs, there is a relative dearth of well-controlled randomized clinical trials supporting their effectiveness. The interpretation of study findings for a number of disorders is also limited by certain design features, including inadequate statistical power,

choice of control group, and lack of an intent-to-treat analytical strategy. Few studies have addressed the sequencing and integration of different interventions—that is, which of the treatment alternatives should be first line—and little empirical evidence is available to guide the management of initial treatment nonresponders. Moreover, in spite of the high rates of diagnostic comorbidity in childhood, few studies have addressed the treatment of youngsters with multiple disorders or other complex presentations.

For the purposes of this report, the premise of “evidence-based practice” is defined as set forth in the Institute of Medicine (IOM) report in 2001: practice that “involves the integration of best research evidence with clinical expertise and patient values." The working group recognizes that this is a narrow definition of evidence-based practice, but we believe it was necessary to employ this narrower definition in order to meet the charge of conducting a consistent, comparative analysis of psychotropic medications relative to psychosocial interventions. The working group believes it is in concert with the *APA Policy Statement on Evidence-Based Practice in Psychology* (American Psychological Association, 2005). This report relies on the best available evidence in the scientific literature and reports the best evidence available for each major class of child and adolescent disorder.

A notable advance in the field has been the attempt to develop evidence-based clinical practice guidelines for a number of disorders, including ADHD, depression, OCD, BPD, and schizophrenia. Although these guidelines represent an important step in translating research findings into practice, this effort has been hampered by the current limitations in the knowledge base and by differences in the standards that are used to develop guidelines (e.g., summaries of evidence, expert consensus, guild consensus). In summary, although great strides have been made in the development of beneficial treatments for child and adolescent mental health disorders, significant gaps remain to be addressed.

RECOMMENDATIONS

Research and Funding

The development and dissemination of evidence-based treatments for child and adolescent psychopathology is a national priority (American Psychological Association, 2005; U.S. Public Health Service, 2000). As described in this report, however, there are several notable gaps in the knowledge base at this time. The evidence base for treatments is uneven across disorders, age groups, and other defining characteristics (e.g., race, ethnicity, and socioeconomic status). Furthermore, data are lacking concerning the long-term effects of the majority of treatments as well as their effects on functional outcomes (e.g., academic achievement, peer relationships). The failure to make all pharmaceutical data available to the public has also been a barrier to the understanding of efficacious treatments and possible associated adverse events.

To advance knowledge in the field and improve the lives of children and adolescents and their families, it is recommended that researchers, research-funding organizations, and other stakeholder, including those who establish funding priorities, work together to strengthen the evidence base for the treatment of child and adolescent psychopathology.

Research Priorities

- Conduct longitudinal investigations of treatment efficacy and effectiveness, examining outcomes in terms of targeted symptoms, functional impairments, adaptive functioning, safety, and quality of life.

- Conduct investigations of treatment efficacy, effectiveness, dissemination, safety, and impact across groups from diverse backgrounds.

- Conduct investigations of treatment efficacy, effectiveness, and safety for children and adolescents with comorbid disorders and complex presentations.

- Conduct more research on understudied age groups for each type of disorder where necessary (e.g., prepubertal depression; preschool and adolescent ADHD, adolescent autism).

- Determine the optimal sequencing of multimodal treatment components that maximizes efficacy, including functional outcomes, and minimizes side effects and adverse events.

- Determine optimal doses, intensities, compositions, and duration of psychosocial and psychopharmacological treatments.

- Increase research on the role of schools and primary care providers in the development and delivery of mental health services for child and adolescent disorders.

- Conduct research to elucidate the moderators and mediators of treatment effects in order to refine treatments and develop novel and more effective interventions.

- Conduct research to understand factors (e.g., child, adolescent attitudes, parent preference, external barriers to treatment, medication side effects) associated with treatment adherence.

- Determine optimal strategies for encouraging providers to use evidence-based treatments, and identify factors that facilitate or inhibit the implementation of these treatments.

- Examine the differential contributions (both benefits and risks) of individual components in multicomponent treatments (e.g., combined psychosocial and psychopharmacological treatments, and polypharmacy).

- Conduct research on the impact of systems-level factors (e.g., organization and financing) on the use of evidence-based treatments for child and adolescent disorders.

- Increase research on the cost effectiveness of mental health services, focusing on contrasting evidence-based practices of different modalities, doses, and types.

- Conduct research on how factors of diversity, including race/ethnicity, gender, sexual orientation, and disability, contribute to beliefs and attitudes about psychotropic drug use.

- Investigate prescribing practice variability based on socioeconomic class and racial/ethnic backgrounds.

- Increase research related to how disabilities, both physical and comorbid psychiatric, moderate and mediate all types of treatment modalities for various child and adolescent mental health diagnoses.

Policy

- Recommend increased collaboration across federal funding agencies involved in child treatment research (e.g., NIMH, NICHD, National Institute of Neurological Disorders and Stroke [NINDS], Agency for Healthcare Research and Quality [AHRQ], CDC, Substance Abuse and Mental Health Services Administration [SAMHSA], and Institution of Education Science [IES]).

- Advocate to require public disclosure of all efficacy and safety data emanating from both psychosocial and psychopharmacological treatment research on child and adolescent disorders.

- Advocate for federal monitoring agencies (e.g., FDA) to be fully independent of political and economic influences.

- Advocate for the establishment of a governmental entity analogous to the FDA that monitors the development and marketing of psychosocial treatments.

- Encourage the creation of sustained partnerships between private, professional, and public organizations to facilitate research funding and the dissemination of outcomes.

- Encourage ongoing communication among researchers, professional providers, and families to facilitate the use of evidence-based practice in real-world settings.

- Create a standing workgroup within APA to monitor progress in child and adolescent treatment research and communicate the status of this research to the professional community and the public.

- Advocate for increased federal funding for child and adolescent treatment research.

Professional Education

Within child and adolescent psychology, the importance of contemporary training in evidence-based interventions at the predoctoral, postdoctoral, and continuing education levels is essential. It is recommended that evidence-based treatments, including psychosocial and psychopharmacological interventions, for the various disorders of childhood be taught to all applied psychologists working with children and families. Regardless of discipline, a working knowledge of current psychopharmacology and psychosocial therapies is of paramount importance for all professionals involved in the treatment of child and adolescent disorders. In addition, it is recommended that cultural competence training be included in all pre-service and in-service settings.

Predoctoral Level

To become familiar with psychological interventions and develop skills in the implementation of psychosocial interventions for a variety of disorders, it is recommended that the predoctoral training of professional psychologists include a

broad-based education in the various evidence-based treatments discussed in this review. Specifically, it is recommended that:

- Predoctoral students are required to be proficient in the critical review of treatment literature to ensure the ongoing review of and familiarity with the changes that undoubtedly will occur in the field during their practice lifetimes.

- Predoctoral casework include training in principles of clinical psychopharmacology as well as knowledge of current literature on pharmacological treatment efficacy in predoctoral coursework.

- Coursework, training practica, and internships include skill development in the procedures and instruments that are evidence based for monitoring client/patient outcomes in both clinical practice and clinical trials, including symptom change, functional outcomes, both positive and negative, and adverse side effects, in coursework, training practica, and internships.

- Trainees are familiar with the broad array of evidence-based psychosocial interventions and support emerging proficiency in their implementation with their patients.

Postdoctoral Level

It is recommended that training at the postdoctoral level further the development of skills in the implementation of evidence-based psychosocial interventions and general knowledge of evidence-based psychopharmacological and psychosocial treatments,

consistent with current training guidelines for postdoctoral fellowships for child and adolescent psychology.

- Encourage postdoctoral students to continue the breadth and further increase the depth of training in evidence-based interventions for postdoctoral students.

Continuing Education

It is recommended that continuing education for child and adolescent practitioners and training faculty emphasize contemporary evidence-based strategies in the treatment and management of childhood disorders.

- Encourage the American Psychological Association, as well as each of its divisions related to child practice, to support continuing education activities in the evidence-based psychosocial interventions, as well as in psychopharmacology.

- Teach practitioners systematic methods for monitoring medication and psychosocial treatment efficacy, as well as the evaluation of potential adverse effects and functional outcomes.

- Establish procedures with the APA Continuing Education Accreditation Committee to ensure that the CE approval program is consistent with APA's Guidelines for Evidence-Based Practice.

- Develop programs to teach practitioners to monitor medication and psychosocial treatment efficacy, as well as to evaluate potential adverse effects.

- Ensure that board certification in clinical child and adolescent psychology, as well as in school psychology, indicates a high degree of knowledge and proficiency in evidence-based interventions.

- Train providers to collaborate with other members of the child or adolescent's treatment team, including physicians, school personnel, caregivers, and others involved in the comprehensive care of youth (e.g., tutors, parole officers, case managers).

- Teach providers to develop treatment plans and discuss risk–benefit analyses collaboratively with parents, adolescents, and sometimes children to facilitate informed decision-making when formulating treatment plans.

Public Education

A tremendous amount of information regarding childhood psychopathology and treatment is easily accessible from different sources, most notably the Internet. However, the quality of this information is highly variable and potentially misleading to consumers. In addition, media portrayals of mental illness in childhood and its treatment are at times inaccurate and misleading. Parents, caregivers, and other stakeholders must be provided with accurate information about childhood mental health disorders and their efficacious treatment.

To improve recognition and understanding of childhood mental illness and its treatment, it is recommended that professional organizations, the medical community, federal agencies, foundations, private industry, health care organizations, accrediting bodies, and other stakeholders commit to educating the public about these disorders and appropriate treatments that have been empirically demonstrated to be both safe and effective.

- Assist parents and other stakeholders in accessing accurate information about evidence-based treatments for child and adolescent mental health disorders so that they may be informed consumers of services.

- Provide caregivers, educators, and other stakeholders with information on the benefits and risks of various psychosocial and psychotropic treatments and their influence on the functional problems for which the patients are being treated and long-term outcomes.

- Educate and encourage the media in accurately portraying children and adolescents with mental health disorders and the evidence-based treatments they receive.

- Establish mechanisms to inform the public and professionals about which treatments do NOT work in order to minimize naïve consumer exposure to professionals that make false or unsubstantiated claims about treatment effectiveness.

Service Delivery

Although this report did not address access and service delivery issues, it cannot be concluded without acknowledgement of these important concerns, which have a clear impact on the ability to obtain safe, evidence-based, and effective treatments. Of youth identified with mental health disorders, 60% do not receive care, and many of those who do receive care see providers with limited or no expertise in pediatric mental health (U.S. Public Health Service, 2000).

The limited availability of providers trained in evidence-based treatments for child and adolescent mental health disorders underscores the critical importance of addressing the issues previously discussed, including the development of an appropriately trained workforce and the dissemination of evidence-based treatments as the knowledge base continues to develop. New challenges must be addressed—for example, the need for continuing caution in the use of new medications, especially in light of the fact that 20% of new medications receive black box warnings or are removed from the market (Lasser et al., 2002).

For youth and their families, the barriers to care may be many, including poor to no health insurance reimbursement for treatment, transportation issues, and the challenges brought about by location of residence (i.e. urban/rural characteristics). Disparities in the use of mental health services by children and adolescents have also been noted along the lines of race/ethnicity, socioeconomic status, gender, geographic location, provider type, and the presence or absence of a physical disability (U.S. Public Health Service, 2000).

Systematic reimbursement for evidence-based psychosocial and psychopharmacological treatments must be established. Current funding and administrative mechanisms often encourage the use of medication or non-evidence-based psychosocial treatments over empirically based psychosocial treatments. Finally, mental health services for youth are provided across a number of different service sectors, either simultaneously or

sequentially, and collaborative care is often hampered by cost, discipline, and administrative barriers.

It is recommended that policymakers, professional organizations, educational and training institutions, and providers develop policy and implement practices ensuring that youth with mental health disorders are identified and have access to empirically validated, safe, reimbursable treatments.

Policy

- Facilitate the implementation of the evidence-based interventions reviewed in this report in public practice in mental health, primary care, and educational settings.

- Establish an ongoing mechanism to disseminate scientifically proven information on the benefits and risks of psychosocial and psychopharmacological interventions as the knowledge base continues to develop.

- Promote the timely availability of combined psychosocial and psychopharmacological treatments for disorders in which combination treatment has shown superior efficacy and/or safety to either treatment alone.

- Advocate for improved postmarketing surveillance of psychotropic medications, perhaps inviting consumer feedback with each refill, as risks that are relatively rare may not be fully appreciated until a treatment has been in wide use after marketing.

- Advocate for the establishment of partnerships between and among government funding agencies at the federal, state, and local levels, large insurers/managed care organizations, and regulatory bodies to allow private and public mental health agencies to develop a workforce of providers trained in evidence-based practice.

- Facilitate the development of interdisciplinary partnerships among physicians, mental health practitioners, educators/schools, community leaders, government agencies, and families to ensure adaptation, dissemination, and implementation of evidence-based treatments in usual-care settings.

- Support partnerships between clinicians and researchers that creatively adapt evidence-based treatments to usual-care settings.

- Teach health and mental health providers and agencies to use evidence-based practice to monitor treatment effects in their cases and evaluate the benefits, risks, and cost effectiveness of their service provision.

- Advocate for the monitoring of access to and coordination of quality mental health care services at the local, state, and national levels and by sociodemographics. Where data suggest that youth are receiving substandard or more risky care because of access-related issues, work to change the health and mental health care delivery systems.

- Advocate for collaborative care models, both fiscally and administratively, that provide mental health services for youth in a variety of settings through a number of public and

private mechanisms, including, but not limited to, subspecialty mental health, primary care, schools, child welfare/child protective services, juvenile justice, and others.

- Advocate for the establishment of procedures within government funding agencies at the federal, state, and local levels to encourage local mental health agencies to implement evidence-based practices.

- Advocate for the establishment of procedures within government funding agencies at the federal, state, and local levels to encourage Medicaid mental health agencies to implement evidence-based practices.

Practice

- Promote collaborative decision making among providers, parents, and youth (as developmentally appropriate), involving a careful risk–benefit analysis and informed treatment decision-making.

- Deliver care in a family-focused, culturally competent manner that encompasses child and family preferences and values in treatment decision-making.

- Develop treatment manuals in diverse languages and adapted for diverse cultures and age groups.

- Given the potential harm of psychotropic drugs, the lack of data on safety of drug combinations and the lack of long-term data on safety, encourage practitioners to treat

youth with drugs only when necessary and then only with the lowest dose of the fewest medications for the shortest possible time period.

- Support clinicians in their role as advocates for improved and effective mental health care for youth and their families.

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