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Unanswered Questions Regarding Atypical Antipsychotic Use in Aggressive Children and Adolescents

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ABSTRACT

The aim of this paper was to discuss the arguments for and against the use of atypical antipsychotics in children and adolescents with aggression, and provide recommendations for future research. A MEDLINE search (1985–2004) was performed to identify key literature. Search terms included, but were not limited to, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, children, and adolescents. The search was limited to English-language literature and randomized controlled trials. The use of atypical antipsychotics in children and adolescents has increased significantly over the past few years. Atypical antipsychotics are associated with a more favorable side-effect profile, and growing evidence supports their efficacy for aggression in this population. However, the long-term effects of these agents are unknown. No head-to-head evidence exists to suggest whether pharmacological or nonpharmacological treatments are superior for managing aggression associated with childhood and adolescent psychiatric and behavioral conditions. Future research of atypical antipsychotics in children and adolescents needs to evaluate not only the efficacy but also the effectiveness. Examination of treatment mediators and moderators may help to optimize treatment regimens and improve patient outcomes. Finally, effective interventions require the development and implementation of evidence-based treatment strategies using a multidisciplinary approach.

INTRODUCTION

The use of antipsychotic medications in children and adolescents has seen a dramatic increase over the past decade. From 1991 to 1996, prevalence rates for antipsychotic use in a mid-Atlantic Medicaid state nearly doubled (Zito et al. 2003). During the latter part of the decade, and after the introduction of newer atypical antipsychotics to the market, prevalence rates of overall antipsychotic use and newer atypical antipsychotic use increased by 160% and 494%, respectively, in children and adolescents enrolled in the Texas Medicaid system (Patel et al. 2002). Additionally, antipsychotics are commonly used for children and adolescents in the inpatient setting. In a study by Pappadopulos et al., atypical antipsychotics accounted for

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27.8%, and typical antipsychotics accounted for 10.0%, of psychotropic medication prescriptions at discharge from New York child and adolescent public inpatient psychiatric facilities (Pappadopulos et al. 2002).

Several possible explanations exist for the increase in the use of atypical antipsychotics in children and adolescents. Firstly, growing evidence supports the efficacy of atypical antipsychotics in the treatment of aggression, for which these agents are most commonly prescribed (Gracious and Findling 2001). Secondly, a shift may be occurring in who is actually prescribing antipsychotics. Studies have demonstrated that antipsychotics are commonly prescribed by physicians other than child and adolescent psychiatrists (Goodwin et al. 2001; Jensen et al. 1999; Kaplan et al. 1994). Goodwin et al. found that pediatricians and general practitioners may prescribe antipsychotic medications to children and adolescents more frequently than psychiatrists (Goodwin et al. 2001). Plausible explanations regarding this shift to "primary-care mental health" include a shortage of child and adolescent psychiatrists in the United States and the emphasis on managed care. Currently, approximately 6300 child and adolescent psychiatrists practice in the United States. The U.S. Bureau of Health Professions predicts a 30% increase in the number of practicing child and adolescent psychiatrists to 8312. However, these numbers fall well short of the estimated 30,000 child and adolescent psychiatrists predicted to meet the need of an increased prevalence of mental disorders and consumer demands (American Academy of Child and Adolescent Psychiatry (AACAP) 2001). Furthermore, the growing emphasis on managed care in Medicaid systems may encourage parents to seek initial mental health care with primary-care physicians (Rohland et al. 1999). In an epidemiological study of child and adolescent psychosocial problems in primary care, community-based pediatricians and family practitioners reported that 18.7% of the children they treated in 1996 had mental health problems, compared to 6.8% in 1979. Significant increases over the 17-year period were seen in children and adolescents with attention-deficit/hyperactivity disorder (7.8%) and behavioral and conduct problems (6.5%) (Kelleher et al. 2000). Given the growing prevalence of childhood mental disorders and problems with the continuity of care between primary and specialty mental health-care providers, primary-care physicians may have limited options other than to treat these disorders themselves. Other factors, including the reluctance of families to seek psychiatric help, stigma associated with psychiatric disorders, and systemic barriers to access, may contribute to the treatment of pediatric psychiatric and behavioral disorders by primary-care providers, and perhaps to increased medication use (Mitka 2000).

Given the increased prevalence of antipsychotic use in children and concerns expressed regarding the increased use of all psychotropic medications in children, this paper presents the arguments and evidence for and against atypical antipsychotic use in children and adolescents with aggressive behavior. Furthermore, this paper will address unanswered questions and provide recommendations for the future.

Arguments supporting the use of atypical antipsychotics in aggressive children and adolescents

Favorable side-effect profiles of atypical antipsychotics. Atypical antipsychotics were developed as a result of typical antipsychotics having unfavorable side-effect profiles, especially the occurrence of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), and lacking efficacy for some patients, particularly those with negative symptoms of schizophrenia (Worrel et al. 2000). Over the past 12 years, 6 atypical antipsychotics, which include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, have been introduced to the market.

The presence of EPS during the course of treatment in children and adolescents can be problematic and debilitating to the patient. Emergence of such symptoms can lead to decreased medication adherence, decreased patient self-esteem, and poor patient outcomes (Findling et al. 1998). Prevention and management of EPS may be extremely important in youths, as they may be more susceptible to the development of EPS, especially dystonic reactions (Keepers et al. 1983). Atypical antipsychotics

may be associated with a decreased propensity to cause EPS and TD in children and adolescents, compared to typical antipsychotics (McConville and Sorter 2004; Worrel et al. 2000).

Hyperprolactinemia is another abnormal finding seen less during treatment with atypical antipsychotics, with the exception of risperidone, compared to typical antipsychotics. Increased prolactin serum concentrations in females can result in breast enlargement, galactorrhea, and dysmenorrhea; in males, hyperprolactinemia can lead to gynecomastia and sexual dysfunction (Compton and Miller 2002). Although hyperprolactinemia is believed to account for less than 10% of drug discontinuations, this is poorly studied, and more research is necessary to examine the course and impact of this side effect (Findling et al. 1998).

Although placebo-controlled trials with risperidone suggest side-effect advantages, head-to-head, short- and long-term comparisons of atypical and typical antipsychotics in children and adolescents are needed to clearly establish their relative side-effect profiles.

Efficacy of atypical antipsychotics for aggressive behaviors. Much of the efficacy data for atypical antipsychotics have come from randomized, controlled trials in the adult population. Evidence suggests that these agents not only improve the collection of symptoms associated with schizophrenia and other psychotic disorders, but also improve patient outcomes, such as relapse, rehospitalization, and quality of life (Csernansky et al. 2002; Glick et al. 2001; Rabinowitz et al. 2001; Weiden et al. 1996; Worrel et al. 2000). For children and adolescents, evidence from controlled clinical trials supporting the efficacy of atypical antipsychotics is growing, especially for the treatment of disruptive behavioral disorders and aggression (Table 1). Of the atypical antipsychotics, the most data suggesting efficacy for aggressive behaviors across different psychiatric conditions in children and adolescents are available for risperidone.

In a 10-week, randomized, double-blind, placebo-controlled study, 20 youths, 6–14 years of age, with conduct disorder (CD), aggressive behavior, and average intellectual functioning were randomized to receive either risperidone or placebo. As measured by the Rating of Aggression Against People and/or Property Scale (RAAPP), low-dose risperidone (mean dose, 0.028 mg/kg per day) was more efficacious than placebo in reducing aggression during the last 4 weeks of the study. Large effect sizes for RAAPP scores for weeks 7–10, and at week 10, were determined (1.28 and 1.05, respectively) (Findling et al. 2000).

In children and adolescents with subaverage intellectual functioning, risperidone has been shown to be efficacious in reducing aggressive behaviors. In a 4-week, randomized, controlled trial of 13 children and adolescents (6–14 years of age) with behavioral problems and borderline intellectual functioning, risperidone (mean dose, 1.2 mg/day) was superior to placebo in reducing scores on the Aberrant Behavior Checklist (ABC), Clinical Global Impressions (CGI) scale, and the Visual Analog Scale (VAS) (Van Bellinghen and De Troch 2001). In another small sample of 38 hospitalized adolescents (mean age, 14.0 years) with severe aggression and subaverage levels of intelligence, Buitelaar et al. demonstrated that treatment with risperidone (mean dose, 2.9 mg/day) was associated with significant improvements on the CGI-Severity scale (CGI-S), modified Overt Aggression Scale (OAS-M), and the ABC (Buitelaar et al. 2001). Medium effect sizes for these measures were reported (risperidone versus placebo, 0.6–0.9).

Aman et al. conducted a 6-week, randomized, double-blind, placebo-controlled study of risperidone in 118 children and adolescents, 5–12 years of age, with disruptive behavior disorders and subaverage intelligence (Aman et al. 2002). Patients receiving risperidone (mean dose, 1.16 mg/day) had significantly greater improvements on the conduct-problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF), compared to those receiving placebo (effect size over 0.64). Additionally, the risperidone group showed improvements on other behavioral measures, including subscales of the ABC and Behavior Problems Inventory (BPI), and the VAS. Similarly, Snyder et al. demonstrated risperidone's efficacy for the treatment of disruptive behaviors in 110 children (5–12 years of age) with subaverage intelligence (Snyder et al. 2002). In a 6-week, randomized, double-blind, placebo-controlled trial, risperidone (mean dose, 0.98 mg/day) was superior to placebo in reducing

TABLE 1. RANDOMIZED CONTROLLED TRIALS OF RISPERIDONE IN CHILDREN AND ADOLESCENTS WITH AGGRESSION

Study design	*N*	*Diagnoses*	*Rating instruments*	*Results*	*Untoward effects*	*Reference*
R, DB, PC; 10 weeks	20	CD	RAAPP	RAAPP: RIS > PBO ($p = 0.008$)	Increased appetite, sedation, insomnia, restlessness, irritability, enuresis, nausea/emesis	Findling et al. 2000
R, DB, PC; 4 weeks	13	SA-IQ, BEHAV	ABC, CGI, VAS	ABC: RIS > PBO ($p < 0.05$ for irritation and hyperactivity); CGI: RIS > PBO ($p < 0.05$); VAS: RIS > PBO ($p < 0.001$)	Somnolence, increased appetite, weight gain	Van Bellinghen and De Troch 2001
R, DB, PC; 6 weeks	38	CD, ODD, ADHD, SA-IQ, AGGR	CGI-S	CGI-S: RIS > PBO ($p < 0.05$)	Tiredness, sialorrhea, nausea, weight gain	Buitelaar et al. 2001
R, DB, PC; 6 weeks	118	CD, ODD, DBD, SA-IQ	Conduct problem subscale of N-CBRF	N-CBRF: RIS > PBO ($p \leq 0.01$)	Somnolence, headache, vomiting, dyspepsia, weight increase, elevated serum prolactin, increased appetite, rhinitis	Aman et al. 2002
R, DB, PC; 7 weeks	110	CD, ODD, DBD, SA-IQ	Conduct problem subscale of N-CBRF	N-CBRF: RIS > PBO ($p < 0.001$)	Somnolence, appetite increase, dyspepsia, abnormal crying, headaches, urinary incontinence, hyperprolactinemia, weight increase	Snyder et al. 2002
R, DB, PC; 8 weeks	101	AD	Irritability subscale on ABC, CGI-I	ABC: RIS > PBO ($p < 0.001$); CGI-I: RIS > PBO ($p < 0.001$)	Increased appetite, fatigue, drowsiness, dizziness, drooling	McCracken et al. 2002

DB, double-blind; PC, placebo-controlled; R, randomized; AD, autistic disorder; ADHD, attention-deficit/hyperactivity disorder; AGGR, aggression; BEHAV, behavioral problems; CD, conduct disorder; DBD, disruptive behavioral disorders; ODD, oppositional-defiant disorder; SA-IQ, subaverage intelligence; ABC, Aberrant Behavior Checklist; CGI, Clinical Global Impressions Scale; CGI-I, Clinical Global Impressions Scale—Improvement; CGI-S, Clinical Global Impressions Scale—Severity; NCBRF, Nisonger Child Behavior Rating Form; RAAPP, Rating of Aggression Against People and/or Property Scale; VAS, Visual Analog Scale; NS, not significant; PBO, placebo.

scores on the conduct subscale of the N-CBRF, as well as the ABC, BPI, CGI-Improvement (CGI-I), and VAS.

In an 8-week, randomized, double-blind, controlled trial, 101 children, between the ages of 5 and 17 years and with autistic disorder and behavioral problems, were assigned to receive risperidone or placebo (McCracken et al. 2002). Treatment with risperidone (mean dose, 1.8 mg/day) resulted in significant improvements in behavioral disturbances, as indicated by the scores on the ABC irritability subscale and CGI-I, compared to placebo. For ABC irritability subscale scores, a large effect size of 1.2 was reported.

Several details regarding the evidence suggesting efficacy for aggression need further emphasis. Firstly, consistent measures were used across studies to evaluate aggressive behavior. The ABC, CGI, and N-CBRF are widely used instruments that have been shown to be reliable and valid (Aman et al. 1985a; Aman et al. 1985b; Aman et al. 1996; National Institute of Mental Health 1985). Secondly, the treatment effects associated with risperidone were fairly large compared to placebo, suggesting specific pharmacological benefit with this agent (range of effect sizes: 0.6–1.28). These effects were also consistently seen in children of varying ages, from 5 to 17 years of age. Thirdly, the onset of efficacy of risperidone was rapid, with significant separation from placebo occurring during the 1st week and sustaining throughout the study duration. Finally, risperidone administration was well tolerated. Risperidone was comparable to placebo with regard to extrapyramidal symptoms. Elevated prolactin serum concentrations were seen with low-dose risperidone, but no clinical sequelae were reported (Aman et al. 2002; Snyder et al. 2002). The availability of such evidence is important, as the prevalence of aggressive behavior is increasing across the spectrum of childhood disorders, and aggression may account for most of the antipsychotic prescribing in children and adolescents (Gracious and Findling 2001; AACAP 2002). Additionally, the availability of these data is reflected in the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY), as well as a recent international consensus statement on attention-deficit/hyperactivity disorder and disruptive behavioral disorders (Kutcher et al. 2004; Pappadopulos et al. 2003).

It is important to note, however, that these data supporting risperidone for the treatment of aggression are from short-term studies. Long-term studies are necessary to fully determine whether the clinical benefits of risperidone seen short term extend beyond the studied treatment periods. In a 48-week, open-label extension study, low-dose risperidone (mean dose, 1.5 mg/day) showed therapeutic effectiveness in children with disruptive behavioral disorders and subaverage intelligence (Findling et al. 2004). Subjects who received risperidone during the 6-week, double-blind trial maintained improvement, while those who received placebo improved with risperidone treatment, as demonstrated by significant reductions in scores on the conduct problem subscale of the N-CBRF.

Because of the lower frequency of side effects when dosed appropriately, atypical antipsychotics may be preferred by clinicians for use in aggressive children and adolescents when antipsychotic treatment is considered appropriate. Although the use of these agents for the treatment of aggression remains off-label, the body of supporting evidence from randomized, controlled trials represents an evidence-based treatment approach.

Arguments against the use of atypical antipsychotics in aggressive children and adolescents

Lack of indications in children and adolescents. Typical antipsychotics are approved for the treatment of severe behavioral problems (chlorpromazine) and for the treatment of tics and vocal utterances of Tourette syndrome (haloperidol and pimozide). Currently, the U.S. Food and Drug Administration (FDA) has not approved indications for atypical antipsychotics in the treatment of psychiatric or behavioral problems in children and adolescents. Although evidence exists to support the efficacy and safety of risperidone for aggressive behavior in children, it is unclear whether this is sufficient to receive a FDA-approved indica-

tion for a specific disorder. The evidence supporting atypical antipsychotic use for aggression also lacks consistency in the patient populations studied. With the exception of studies conducted by Aman et al. and Snyder et al., data supporting the efficacy of risperidone for aggression originate from controlled trials evaluating different patient populations (Aman et al. 2002; Buitelaar et al. 2001; Findling et al. 2000; McCracken et al. 2002; Snyder et al. 2002; Van Bellinghen and De Troch 2001). Firstly, most available data supporting risperidone use for aggression originate from patients of subaverage intelligence or with developmental disorders (Aman et al. 2002; McCracken et al. 2002; Snyder et al. 2002). Five of the six controlled studies reported subject intelligence levels, and of these studies, only the McCracken study included a small percentage (5%) of subjects with average or above-average intelligence. It is unclear how these findings translate to patients of normal intelligence or those seen in routine clinical practice. Secondly, inclusion criteria regarding the severity of aggression differed across the studies, possibly resulting in heterogeneity of psychopathology. In the studies by Aman et al. and Snyder et al., subjects were required to have a rating of 24 or more on the conduct problem subscale of the N-CBRF (Aman et al. 2002; Snyder et al. 2002). An Aggression subscale T-score two standard deviations or more above the mean on the Child Behavior Checklist was required in the Findling study, and persistent, overt aggression (score of at least 1 on the OAS-M) was required for inclusion in the study by Buitelaar et al. (Buitelaar et al. 2001; Findling et al. 2000). Less-specific inclusion criteria related to the severity of aggressive behaviors were reported in the studies by Van Bellinghen and De Troch, and McCracken et al. (McCracken et al. 2002; Van Bellinghen and De Troch 2001). While it may be argued that the generalizability of the results may increase owing to the heterogeneity of patient populations, it is difficult to evaluate the reproducibility of these studies for specific populations. Additionally, some psychiatric disorders and nonsyndromal states may also be characterized by aggressive behaviors, for which safety and efficacy data are lacking. Other possibilities explaining why no pediatric indications for the treatment of aggressive behaviors exist for atypical antipsychotics may be the lack of financial initiative for drug manufacturers, philosophical concerns from regulatory agencies regarding the use of antipsychotics in children and aggression as a discrete disorder, and political pressure from groups opposed to the use of medication intervention for the treatment of psychiatric and behavioral problems.

Potential adverse and long-term effects of atypical antipsychotics. Although low in incidence, serious side effects, such as EPS, TD, and neuroleptic malignant syndrome, have been reported with atypical antipsychotic use (Feeney and Klyklyo 1996; Raitasuo et al. 1994; Sikich 2001). As certain subgroups of youths, such as those with developmental disorders or mental retardation, may be more sensitive to the development of drug-induced movement disorders, treatment with atypical antipsychotics may result in EPS or TD (Connor et al. 2001).

Other side effects of concern associated with these agents include weight gain, hyperglycemia, new-onset diabetes, hyperlipidemia, cardiovascular abnormalities, and hyperprolactinemia (Schur et al. 2003). The development of metabolic and cardiovascular side effects may increase the risk of morbidity and mortality in this population. Weight gain may be especially problematic in children and adolescents, as they may be subject to problems with self-esteem, social functioning, and medication adherence. Compared to adults, weight gain associated with atypical antipsychotic treatment may be greater in this population, as younger-aged children are generally more sensitive to adverse events (McConville and Sorter 2004). Six-month data of risperidone in youths with autism showed weight gain greater than developmentally expected norms (Martin et al. 2004). Obese children are also at high risk of developing impaired glucose tolerance or type 2 diabetes (Young et al. 2000). Given that the overall incidence of type 2 diabetes is increasing in children and adolescents, particularly among minorities, treatment with some atypical antipsychotics may precipitate or exacerbate abnormal glucose-blood concentrations and associated clinical se-

quelae (Brosnan et al. 2001; Macaluso et al. 2002). Among the atypical antipsychotics, risperidone is most frequently associated with hyperprolactinemia, particularly at higher doses (Frazier et al. 1999; Sikich et al. 2001). In short-term studies of risperidone for the treatment of aggressive behaviors, hyperprolactinemia was seen with low doses, but no adverse events related to prolactin levels were reported (Aman et al. 2002; Buitelaar et al. 2001; Snyder et al. 2002). In two 48-week, open-label trials, administration of low-dose risperidone in children and adolescents also resulted in asymptomatic increases in prolactin-serum concentrations (Findling et al. 2004; Turgay et al. 2002). The issue of long-term elevated prolactin-serum concentrations, and its clinical ramifications, has yet to be fully determined, particularly in younger populations.

Long-term implications of atypical antipsychotic use in children and adolescents have yet to be thoroughly determined. Although associated with cognitive benefits in adults with schizophrenia, the cognitive effects of these agents in children and adolescents have not been systematically evaluated (Pandina et al. 2003). A 6-week trial comparing risperidone and placebo in 118 children and adolescents with disruptive behavioral disorders evaluated memory, using the Modified Verbal Learning Test—Children's Version (MVLT-CV), and attention and vigilance using the Continuous Performance Test (CPT) (Pandina et al. 2003). Both the risperidone and placebo groups showed significant improvements in memory from baseline to endpoint, with no significant differences between groups. No significant within- or between-group differences were reported in CPT scores, suggesting risperidone treatment did not affect cognitive performance. Data from a long-term, open-label study of risperidone in youths with disruptive-behavioral disorders and subaverage intelligence also suggest that treatment with risperidone does not affect cognition and may result in cognitive improvement (Findling et al. 2004). Similarly, data regarding atypical antipsychotic effects on growth and development have yet to be published. A study by Dunbar et al. analyzed pooled data from five multicenter trials of risperidone in children and adolescents with disruptive behavioral disorders to retrospectively examine the effects on growth and sexual maturation over a 12-month period (Dunbar et al. 2003). Results showed no significant correlations between prolactin-serum concentrations and growth or sexual maturation. Patients receiving risperidone had a mean height increase of 1.2 centimeters (cm) greater than the reference population, but this deviation from expected growth was normally distributed. Sexual maturation occurred more rapidly in patients receiving risperidone than in the reference population, as described by a mean of 0.12 Tanner Stages. Additional data are necessary to fully elucidate the effects of risperidone on cognition and growth in children and adolescents with aggressive behavior across diagnoses.

Pharmacological versus nonpharmacological treatments. One of the most important issues is the question of whether pharmacological intervention is the best modality for treatment of behavioral problems. Because antipsychotics are frequently used for nonpsychotic disorders, such as aggression, closer scrutiny of this issue is necessary. Nonpharmacological treatments, such as behavioral therapy and psychoeducation, may provide alternative treatment modalities, but are often underutilized in "real-world" clinical settings (Brestan and Eyberg 1998). Substantial evidence supports psychotherapeutic approaches for the treatment of aggression, particularly in children and adolescents with developmental disorders (Alpert and Spillmann 1997; Beail 1998). Parent-management training (PMT), problem-solving skills training (PSST), and multisystemic therapy (MST) are psychosocial treatments shown to be efficacious for aggressive youth, with parent-management training being the most widely evaluated (Kazdin 2000). Studies have addressed the efficacy and effectiveness of parent training in young children, demonstrating medium to large effect sizes. The effectiveness of parent training in children and adolescents between 9 and 18 years of age has yet to be fully determined, although several models for younger children exist (Webster-Stratton and Hammond 1997, 1999; Webster-Stratton and Herbert 1994).

Kazdin et al. evaluated the relative effects of PMT, PSST, and a combination of both treatments

in a randomized, controlled trial of 97 children, between 7 and 13 years of age, who were referred to an outpatient child conduct clinic (Kazdin et al. 1992). PMT consisted of 25 weekly sessions, while PSST consisted of 16 sessions. All three groups demonstrated improvement, with the combination group having the largest percentage of patients who were normalized on the Child Behavior Checklist (CBCL) by posttreatment. At the 1-year follow-up, the combination group showed continued improvement in child behavior and parent stress, and the PSST group further improved in child behavior. Although the combination treatment resulted in improved short- and long-term child behavior, effect sizes related to CBCL total scores were modest when compared to the other treatments (combination versus PSST, 0.45; combination versus PMT, 0.39).

In a 24-week randomized, controlled trial of 92 children, 4–7 years of age with oppositional-defiant disorder (ODD) or CD, Webster-Stratton and Hammond examined the effects of adding child training (CT) to parent training (PT) (Webster-Stratton and Hammond 1997). Children were randomized to receive CT, PT, CT + PT, or control. At posttreatment, 80.8% of the PT group and 70% of the CT + PT group were normalized according to parent-rated CBCL scores. Thirty-seven percent of the CT group and 27.3% of the controls were considered normal. Effect sizes for CBCL total scores were largest for PT when compared to controls, followed by CT + PT and CT (1.27, 1.25, and 0.49, respectively).

To determine the effectiveness in the typical service setting, Taylor et al. conducted a randomized, controlled trial comparing Webster-Stratton's Parents and Children Series (PACS) to eclectic typical treatment in 110 families of children 3–8 years of age with conduct problems (Taylor et al. 1998). PACS consisted of group therapy, and eclectic treatment was comprised of individual and family therapy. Compared to wait-list (WL) controls, PACS and eclectic treatment showed greater improvement for total problems, as measured by the Eyberg Child Behavior Inventory (ECBI), CBCL, and the Parent Daily Report (PDR). Medium effect sizes were reported for ECBI scores (PACS versus WL, 0.57; eclectic versus WL, 0.43; PACS versus eclectic, 0.49).

In published studies, effect sizes are often quite large with pharmacological treatment, while those related to behavioral management for aggression have typically been modest. In addition, a few long-term follow-up studies of up to 4 years have been conducted in aggressive, delinquent youths who have received an intensive home-based therapy (MST) (Borduin et al. 1995; Henggeler et al. 2002). However, no evidence is available to suggest whether pharmacological treatment or nonpharmacological treatment is superior with this population. Furthermore, it is unclear whether, and when, children may benefit most from the combination of both interventions. Head-to-head comparisons, using the same inclusion and exclusion criteria and standardized measures across both types of interventions, are vital in defining the role of both pharmacological and nonpharmacological interventions. Evidence supporting the long-term efficacy and safety of atypical antipsychotics in children and adolescents is also necessary. Existing studies need to be replicated to see whether the beneficial effects of atypical antipsychotic treatment hold across patient populations and service settings. Although atypical antipsychotics may be superior to typical antipsychotics in some ways, these agents still have the potential to cause harmful side effects when used inappropriately. More data are needed on side effects that may negatively impact the outcomes of children and adolescents receiving atypical antipsychotic treatments.

Unanswered questions and directions for the future

Treatment guidelines for childhood and adolescent disorders. Aggression may occur with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), ODD, CD, and bipolar disorder. According to TRAAY, treatment for the primary psychiatric or behavioral disorder should be initiated following psychosocial and educational interventions (Pappadopulos et al. 2003). If these treatments fail to manage severe and persistent aggression, clinicians should consider treatment with an atypical antipsychotic, using a conservative dosing approach and routine assessment of

treatment effects and medication side effects. Psychosocial interventions should be continued and emphasized after the initiation of antipsychotic treatment.

Consensus recommendations, such as those by Pappadapulos et al., are useful in providing clinicians with guidance regarding the use of antipsychotics to treat aggression in youths (Pappadopulos et al. 2003). However, the recommendations are limited by the amount of available data to support evidence-based recommendations, such as the availability of controlled trial data being only available on 1 agent (risperidone) of the 6 atypical antipsychotics. Therefore, treatment guidelines in this area should be viewed cautiously by clinicians. While atypical antipsychotics may play a role in the treatment of childhood and adolescent psychiatric disorders, more information is necessary before one can make definitive conclusions about these agents as a class. However, the growing body of evidence for risperidone may allow for specific evidence-based recommendations regarding the use of this particular agent for the treatment of aggression across a spectrum of psychiatric disorders in children and adolescents. For example, experts have recommended the use of risperidone as a first-line agent in the treatment of aggression and impulsivity in children and adolescents (Kutcher et al. 2004).

Disorder-targeted versus symptom-targeted treatment. A question exists regarding whether disorder-targeted pharmacological treatment or symptom-targeted pharmacological treatment is more appropriate in children and adolescents. Arguments for disorder-targeted treatment over symptom-targeted treatment include greater evidence of efficacy based upon diagnosis and, possibly, less potential for polypharmacy. The use of polypharmacy in children and adolescents is of concern because it leads to greater risk of drug-drug interactions, a higher probability of adverse events, a potential increase in treatment nonadherence, and increased cost. On the other hand, disorder-targeted treatment requires an accurate diagnosis, which can be extremely difficult in children. For example, much debate exists regarding the diagnoses of ADHD and bipolar disorder, as significant overlap in symptoms occurs with these disorders, and questions exist regarding the most appropriate diagnostic criteria for bipolar disorder in prepubescent children (Giedd 2000). Symptom-targeted treatment may allow for short-term administration of medications until symptom resolution, as may be the case for aggression. However, this method of treatment can result in polypharmacy and place the child or adolescent at risk for adverse events. Additionally, improvement in symptoms may be viewed as a justification for long-term treatment, and the evidence to support a rationale for this decision is frequently limited.

Given the merits of basing treatment on a particular diagnosis, the field of psychopharmacology may be shifting toward disorder-targeted treatment. However, this may not be the case for the treatment of aggression, which is seen across a number of child and adolescent psychiatric disorders. Studies evaluating the effects of risperidone on aggressive behaviors have utilized diverse patient populations, including those with a diagnosis of disruptive behavior disorders, subaverage intelligence, or autistic disorder. In addition, studies of behavioral treatments have targeted children with aggressive symptoms, regardless of diagnosis. Because aggressive behaviors are so widespread across diagnoses, it is possible that pharmacological and nonpharmacological treatment for these children will focus on symptom resolution, at least in the foreseeable future.

To put this in perspective, fever can be examined as an analogy. Fever results from multiple etiologies, infectious and inflammatory processes are examples. Regardless of the cause, antipyretics typically have efficacy in lowering body temperature. However, antipyretics do not address the underlying condition creating the hyperthermia. If antipyretics are used without addressing the underlying etiology, then the underlying disease process may progress. However, when used in combination with interventions to address the underlying disorder, antipyretics are extremely useful pharmacological agents, as they reduce symptoms and make the patient more comfortable. When applying this analogy to the treatment of aggression, atypical antipsychotics can be useful in

patient management, as they decrease symptoms and assist in minimizing the possibility that patients will harm themselves or others. However, unlike fever, a threshold severity level of aggression serving as an index to initiate atypical antipsychotic treatment has not been established, and the decision to treat with an atypical antipsychotic relies primarily on clinical judgment, or as an option to be pursued when other strategies (behavioral treatments, or first-line treatments for a primary disorder) have proven insufficient (Pappadopulos et al. 2003). It is critical that the underlying disorder be identified, treated, and attempts made to improve the individual's adaptive functioning over the long term. Unlike many other areas of medicine, the pathophysiolgic etiology of most mental disorders is unknown. From the perspective of discrete biological targets, the current phenomenological approach to diagnosis may or may not be a more accurate approach to pharmacological intervention than using target symptoms, such as aggression. Thus, from a biological perspective, it is unclear whether symptom-focused or syndromal-based treatment approaches are more appropriate.

"Real-world" effectiveness of atypical antipsychotics in children and adolescents. The gap between scientific evidence and clinical practice seems to be widening. Not only is it difficult to implement evidence-based practices in routine clinical care, little is actually known about how well atypical antipsychotics work in the "real-world" setting. Although randomized, controlled trials (RCTs) are considered the gold standard in establishing treatment efficacy and remain a necessity in the child and adolescent population, future research should also aim at providing evidence of treatment effectiveness. While RCTs offer strong evidence of efficacy, the results are generated under conditions in which the external validity may be compromised. Effectiveness trials are subject to a number of threats to internal validity, as patients under study are more likely to be heterogeneous, and there is less control over extraneous variables, such as treatment setting, frequency of visits, medication adherence, and evaluation of treatment effects. Albeit, these factors, effectiveness trials may provide more complete answers to the question of how well an agent works or does not work in the "real-world" setting.

Mediators and moderators of treatment effects. Closer examination of moderators of treatment effects would provide a better ability to optimize treatment for a child or adolescent and, hopefully, improve patient outcomes. Patient, clinician, or setting characteristics may provide plausible explanations for treatment response or nonresponse. For example, in the National Institute of Mental Health (NIMH) Multimodal Treatment of Children with ADHD (MTA) Study, only subjects with comorbid anxiety and disruptive behavioral disorders experienced greater improvements with behavioral treatment plus methylphenidate, compared with methylphenidate alone (Jensen et al. 2001). More recently, in a study evaluating the effects of fluvoxamine in children and adolescents with anxiety disorders, lower baseline depression scores were associated with greater improvement, while subjects with social phobia were less likely to improve (Walkup et al. 2003). Closer examination of the mediators of treatment effects will provide a better ability to make treatments more efficient and effective. Treatment adherence (or nonadherence) is one of many factors that may account for treatment response (or nonresponse), as it did in both of the above trials (Jensen et al. 2001; Walkup et al. 2003). More specifically related to aggressive behaviors, certain subtypes of aggression ("explosive" aggression) may respond more favorably to pharmacological treatment, compared to other subtypes ("predatory" aggression) (Pappadopulos et al. 2003). Other factors which may determine the effectiveness of atypical antipsychotics outside of the ideal research setting include family acceptance, concern of stigmatization, provider and/or organizational choice, dosage optimization, and frequency of clinic visits.

The development and deployment of effective interventions. A conceptual model developed by the Workgroup on Child and Adolescent Mental Health Intervention Development and Deployment describes the required processes for the development and deployment of effective

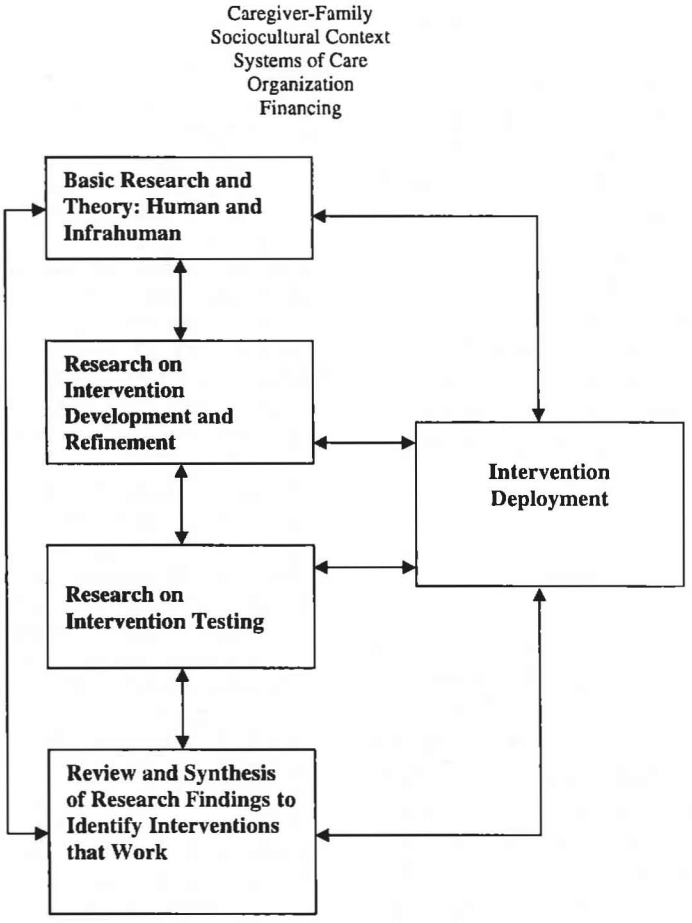

FIG. 1. A model for intervention development and deployment (National Advisory Mental Health Council 2001).

interventions for children and adolescents (Fig. 1) (National Advisory Mental Health Council 2001). The first step in the model occurs at the basic-sciences level. Evidence-based theories regarding etiology and pathophysiology of child and adolescent psychiatric and behavioral problems need to be established and tested, so that clinicians have a better basis for what they are actually treating. Based upon these studies, biological targets for drug action are identified, and compounds are subsequently developed that modify these biological processes (Scolnick 2003). Medications developed in such a manner are then studied for their efficacy in the treatment of child and adolescent psychiatric and behavioral disorders. Identification of factors influencing treatment effects is necessary during this step to better tailor treatment strategies according to a child's personal, familial, and environmental and societal characteristics. Thirdly, evidence-based treatment strategies need to be evaluated in the clinical setting for their effectiveness. For example, effectiveness studies examining pharmacotherapy versus different psychosocial treatments versus multimodal approaches need to be studied in different types of aggression. These strategies are refined and prepared prior to testing at this stage. Interventions that are shown to be effective are then implemented, using multidisciplinary approaches that have been shown to be effective in implementing and diffusing evidence-based practices into routine care (Hoagwood and Olin 2002; Rosenheck 2001; Torrey et al. 2001).

Currently, biological targets based upon pathophysiological evidence do not exist to support the use of atypical antipsychotics in the treatment of aggression or, for that matter, in the treatment of any mental disorder. As additional research evidence evolves regarding brain function and the pathophysiology of mental disorders, future treatments should be developed based upon biological molecular targets (Scolnick 2003). In other respects, the remainder of these principles can, and should, be applied to the development and acceptance of treatment modalities in psychiatry, including the use of atypical antipsychotics for the management of aggression in children.

CONCLUSIONS

Concern over the growing use of atypical antipsychotics in children and adolescents exists for a number of reasons. Although both basic and clinical research supporting the rationale, efficacy, and safety of these agents in the management of aggressive behaviors is limited, the use of atypical antipsychotics in children and adolescents is growing. In many respects, this may be a reflection of the need and demand for effective treatments in these complex disorders. Clinicians choosing to prescribe atypical antipsychotics should do so after considering the issues at hand and carefully evaluating the patient and his or her surroundings. In general, antipsychotics should only be used in combination with behavioral and other psychosocial interventions that have proven benefit, and attempts should be made to limit the duration of treatment. Future research is necessary to shed light on what, how, and when the best treatments can be provided to children and adolescents.

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