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Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY), Part I: A Review

Objectives: To review the evidence for the safety and efficacy of nonpharmacological and pharmacological treatments for aggression in children and adolescents. **Method:** *Medline* and *PsycINFO* searches (1990–present) were conducted for double-blind, placebo-controlled studies of atypical antipsychotics for aggression and for literature on the use of other pharmacological agents and psychosocial interventions for aggression. Case reports and adult literature regarding the safety of atypical antipsychotics were used where controlled data for youth were lacking. **Results:** Controlled data on the treatment of aggression in youth is scarce. Psychosocial interventions may be effective alone or in combination with pharmacological treatments. Psychotropic agents (e.g., stimulants, mood stabilizers, β-blockers) have also been shown to have limited efficacy in reducing aggression. Antipsychotics, particularly the atypical antipsychotics, show substantial efficacy in the treatment of aggression in selected pediatric populations. Atypical antipsychotics are generally associated with fewer extrapyramidal symptoms than are typical antipsychotics. **Conclusions:** Psychosocial interventions and atypical antipsychotics are promising treatments for aggression in youth. Double-blind studies should examine the safety and efficacy of atypical antipsychotics compared to each other and to medications from other classes, the efficacy of specific medications for different subtypes of aggression, combining various psychotropic medications, optimal dosages, and long-term safety.

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Although psychotropic medications have been used to treat aggression in children and adolescents for many years (Pappadopulos et al., 2002), there has been limited research to support this practice. A number of methodological problems exist that restrict the scientific study of aggression, including the difficulties of consistently defining and reliably assessing aggression and of maintaining subjects for studies with long baseline periods (Volavka and Citrome, 1999). For reasons such as these, there is a dearth of controlled studies of aggression in youth.

The Center for the Advancement of Children's Mental Health at Columbia University has joined with the New York State Office of Mental Health and leading experts across the United States to address the current need for knowledge in this area. Working together, this team has created "evidence-based" and "consensus-based" Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY) (see Pappadopulos et al., 2003). The American Academy of Child and Adolescent Psychiatry's practice parameters for the prevention and management of aggressive behavior may also be of interest to researchers and clinicians who work with aggressive youth (American Academy of Child and Adolescent Psychiatry, 2002).

Here, we review the available research evidence that comprises the scientific evidence base which, in combination with expert consensus, informs the clinical recommendations offered in the treatment recommendations. Although past reviews have focused on the pharmacological treatment of aggression (e.g., Pine and Cohen, 1999; Stewart et al., 1990), the current review concentrates on the use of atypical antipsychotics, which are commonly used in inpatient and day treatment settings to treat aggression and which have received greater attention among researchers in recent years. The atypical antipsychotics are commonly used in concert with psychosocial interventions, as well as with other psychotropic agents. Thus we also provide a brief, nonexhaustive overview of the evidence concerning the use of psychosocial interventions and of alternative pharmacological treatments. Some, but not all of this information may generalize to the treatment of aggression in lower-intensity outpatient settings.

Aggression is a frequent cause of hospitalization for youth and is commonly associated with conduct disorder (CD) and oppositional defiant disorder (ODD) (e.g., the "disruptive behavior disorders") and attention-deficit hyperactivity disorder (ADHD) (e.g., Findling et al., 2000b; Connor et al., 2002). While the scope of the current article does not allow for a complete review of the etiology of aggression, a complete review of the neurobiological, genetic, and biosocial perspectives on aggression can be found in Stoff and Cairns (1997).

Multiple definitions of severe aggression have been proposed. Common across these definitions is that aggression is physical behavior with the potential (and often the intent) to damage an inanimate object or harm a living being (Volavka and Citrome, 1999). The behavior targeted in our review is what Vitiello and colleagues (1990) have termed "impulsive aggression," or "impulsive, unplanned, unprofitable, and poorly controlled aggression," as opposed to "predatory aggression," or "planned, profitable, and self-controlled aggressive behavior" (Vitiello et al., 1990). This may also include verbal aggression in which a child makes clear threats of violence toward himself/herself or others (Silver and Yudofsky, 1991). To date, relatively few studies address the issue of subtyping comorbid aggression into clinically meaningful categories (e.g., see Vitiello et al., 1990). This review, therefore, does not address the clinical effects of treatments on different subtypes of aggression, though this is an area that future research should address.

METHOD

The studies described below were obtained from a *Medline* and *PsycINFO* search for literature primarily from 1990 to the present using combinations of the following keywords: "aggression," "children and adolescents," "psychotropic medications," "atypical antipsychotics," "typical antipsychotics," and "psychosocial treatments." The original search found approximately 150 articles. Recent (1996–present) double-blind, placebo-controlled studies in which aggression was measured were all included. For information on the typical antipsychotics, earlier literature (i.e., from 1984) was used because the focus of recent literature has generally shifted to the atypical antipsychotics. Case reports as well as adult literature regarding the safety of the atypical antipsychotics were used where controlled data for youth were lacking. Information was also used from presentations at scientific meetings, which have not as of yet been published in the peer-reviewed literature.

RESULTS

PSYCHOSOCIAL INTERVENTIONS

Psychosocial and environmental interventions are often used to treat aggression in inpatient and day treatment settings and among patients with less severe aggression (Irwin et al., 1991). Data from clinical trials reveal that approximately 50% of youth show a significant reduction in symptoms shortly after being hospitalized, even without active medication treatment (Malone and Simpson, 1998). This kind of nonspecific therapeutic intervention has been effective for children with CD who were hospitalized for chronic and severe aggression (Malone et al., 1997), especially aggression characterized by affective and/or explosive characteristics (Malone et al., 1998). In a double-blind, placebo-controlled study, Sanchez et al. (1994) found that

this effect may be magnified among children from stressed home environments. These data illuminate the importance of including placebo controls in the study of aggression treatment and response, and the necessity of viewing uncontrolled studies (including those in this review) as preliminary.

In some cases, psychosocial interventions alone may be effective treatments (Pelham et al., 2000). When psychotropic medications *are* prescribed, they may be most effective when administered as part of a comprehensive psychotherapeutic and educational program or within a "therapeutic milieu" (Irwin et al., 1991). Unfortunately, there have been few studies comparing the differential efficacy of specific psychosocial treatments for aggression.

A number of specific psychosocial interventions have been shown to be effective in reducing aggression (Foxx, 1998). For example, contingency management programs (e.g., token economies where youth receive tokens for appropriate behavior) have had positive effects on behavior in a variety of settings (e.g., Pelham et al., 2000; see Foxx, 1998, for a review). In addition, systematic training for social skills, problem solving, and anger management and behavioral therapy enhance patients' abilities to interact appropriately with peers and adults (Kazdin, 1998). Interventions that teach parenting skills may help alter the behavior of children with aggression (Kazdin, 1998). Adaptations of individualized clinical behavior therapy (e.g., behavioral "report cards") can also be used to address specific problems such as bullying or provocative behaviors among youth (Pelham et al., 2000). Although limited, preliminary studies on psychoeducation for youth (Webster-Stratton and Hammond, 1997) and parents (Goldberg-Arnold et al., 1999) offer promising findings. For an extensive review of psychosocial treatments for youth with CD, see Brestan and Eyberg (1998).

In summary, a substantial body of evidence indicates that the nonpharmacological therapeutic milieu may play a vital role in the treatment of aggression in youth. However, because most studies have not focused specifically on aggression per se, there is a need for more controlled research focusing specifically on behavioral and psychosocial interventions for carefully defined aggression among well-characterized samples of youth in specific settings.

PHARMACOLOGICAL INTERVENTIONS

Typical antipsychotics

Before the recent and increasing use of atypical antipsychotics to treat aggression, typical antipsychotics (especially haloperidol) were the core treatment for aggression in children and adults (Whitaker and Rao, 1992). The empirical evidence base for the use of these medications in youth is relatively small (for reviews, see Gillberg, 2000; Whitaker and Rao, 1992). In Campbell and colleagues' (1984) double-blind, placebo-controlled study comparing lithium and haloperidol in children with CD, aggressive type, subjects on haloperidol (mean optimal dose=2.95 mg/day) were less hyperactive, aggressive, and hostile than on placebo. Similarly, molindone has been associated with reduced aggression among 31 children with CD (Greenhill et al., 1986).

Safety concerns about the use of typical antipsychotics in children stem from associations between these medications and tardive and withdrawal dyskinesias in long-term treatment (Campbell et al., 1997; Richardson et al., 1991). Although usually reversible with dose reductions or drug withdrawal, serious tardive dyskinesias occur in approximately one in three children treated with typical antipsychotics (Gillberg, 2000). An evaluation of 104 children admitted to a hospital over a 6-month period reported statistically significant associations between parkinsonism and long-term neuroleptic treatment (Richardson et al., 1991). In a literature review, Gillberg (2000) reported on 40 children who suffered from neuroleptic malignant syndromes, 15% of which resulted in the child's death. It is possible that various typical antipsychotics are associated with differential side effects. For example, Sallee et al. (1997) conducted a double-blind, placebo-controlled study of haloperidol (mean dose=3.5 mg/day) and pimozide (mean dose=3.4 mg/day) and found that serious side effects were three times more likely with haloperidol than with pimozide.

Overall, although typical antipsychotics appear to be effective for treating aggressive target symptoms in various disorders, the risk of serious and potentially fatal side effects, including dyskinesias and neuroleptic malignant syndromes, raises concern about their use in children and adolescents and has likely led to the increase in the use of atypical antipsychotics among youth.

Atypical antipsychotics

The atypical antipsychotics, which include risperidone, clozapine, olanzapine, quetiapine, and ziprasidone, are distinguished from typical antipsychotics by their reduced propensity for extrapyramidal symptoms (EPS). There is indeterminate evidence regarding the pharmacological mechanisms of action through which the atypical antipsychotics may inhibit aggression. Some inves-

tigators have proposed that their antiaggressive action comes from the atypical antipsychotics' effects on the serotonin and/or dopamine neurotransmitter systems (see Citrome and Volavka, 1997; Coccaro and Siever, 1995), but a fully satisfactory explanation has not been established. Additional research is needed to elucidate further the mechanisms of action for atypical antipsychotics' effects on aggression.

Despite the increasingly common use of atypical antipsychotics to treat symptoms of aggression in youth (Pappadopulos et al., 2002), relatively little controlled evidence has accumulated regarding the efficacy and safety of these practices. Thus this review also has drawn from case reports and as of yet unpublished studies made available from active research programs of participating coauthors. The order and relative lengths of the following sections are based on the amount of research available and are not necessarily indications of the relative safety and efficacy of the respective antipsychotics. Constraints of length have precluded the inclusion of every published report; an extensive list of additional case reports and open-label trials is available from the corresponding author upon request.

Risperidone

Risperidone for Aggression. In a meta-analysis of controlled trials of risperidone among adults with schizophrenia, risperidone has been found to be associated with significant reductions of aggression associated with schizophrenia (Aleman and Kahn, 2001). Among children, open-label trials (e.g., Buitelaar, 2000) and chart reviews (e.g., Frazier et al., 1999) have demonstrated risperidone's association with reduced aggression in complex, comorbid disorders, including those involving psychosis. Holford et al. (2000) found significant behavioral improvements among 34 children with mental retardation and conduct problems who were treated with low-dose open-label risperidone for 1 year. On a mean dose of 1.47 mg/day, subjects showed improvements on the Clinical Global Impressions scale (CGI), Aberrant Behavior Checklist, and the Nisonger Child Behavior Rating Form (N-CBRF), among others, and the benefits of risperidone were maintained throughout the 1-year trial. Case reports indicate that risperidone is also associated with reduced aggression among youth with normal intelligence (e.g., Schreier, 1998); in addition, one open-label (Malone et al., 1999) and one large, multisite controlled trial indicate that risperidone may reduce aggression in children with autistic spectrum disorders (McDougle et al., 2001).

There are several double-blind, placebo-controlled studies (randomized controlled trials; RCTs) examining risperidone's efficacy in treating aggression in youth with subaverage and average IQ. Findling and colleagues (2000b), in a 10-week, double-blind, placebo-controlled study of 20 child and adolescent outpatients with aggression and average intellectual functioning, reported significant reductions in aggression as measured by the Rating of Aggression Against People and/or Property (RAAPP) among subjects treated with a relatively low dose of risperidone (mean=0.028 mg/kg per day). Similarly, Van Bellinghen and De Troch (2001) found statistically significant improvements on several behavioral measures in a 4-week controlled trial of risperidone (mean total dose=1.2 mg/day) in 13 children with low IQ and severe behavioral problems. Another controlled study of risperidone (mean final dose=2.9 mg/day) in 38 adolescents with aggression and subaverage cognitive abilities also found that risperidone was associated with statistically significant reductions in aggression (Buitelaar et al., 2001).

In one of the largest RCTs to date, 118 children with CD, ODD, or disruptive behavior disorder not otherwise specified with mild to moderate mental retardation or borderline IQ were randomly assigned to risperidone (mean dose=1.23 mg/day) or placebo. In this 11-site study, risperidone-treated subjects showed significant improvements on multiple behavior measures including the Conduct Problem subscale of the N-CBRF (Aman et al., 2000), compared with controls. Fifty of these same subjects completed a 48-week open-label follow-up trial and continued to show significant reductions in aggression (Findling et al., 2000a).

In a similarly designed multisite Canadian RCT, Turgay and colleagues (2000) treated 110 children with IQs ranging from 35 to 84 who displayed significant aggression with risperidone (mean dose=0.033 mg/kg per day) or placebo. Like Findling and colleagues (2000a), these investigators found significant reductions in N-CBRF conduct problem ratings favoring risperidone over placebo as early as week 1 that continued throughout the treatment period. In addition, risperidone was associated with significant decreases in the total scores of the Aberrant Behavior Checklist, the Behavior Problems Inventory, and the Aggressive/Destructive subscale of the Behavior Problems Inventory. The only patient to discontinue treatment because of serious side effects was a member of the placebo control group.

Safety of Risperidone. Several of the studies and case reports documenting risperidone's association with reduced aggression (see above) found that weight

gain was a significant side effect (Buitelaar et al., 2001; Findling et al., 2000a,b; Frazier et al., 1999; Ratzoni et al., 2002; Schreier, 1998; Turgay et al., 2000). Sikich (2001) found that 16 psychotic youth treated blindly with risperidone (mean dose=4.0 mg/day) gained a mean of 1.5 lb/week. Weight gain was also common in Lombroso and colleagues' (1995) 11-week, open-label study of low doses of risperidone (maximum dose=2.5 mg/day) in 7 children, in Armenteros and colleagues' (1997) 6-week, open pilot trial of risperidone in 10 adolescents (mean dose=6.6 mg/day), and in recent chart reviews (e.g., Martin et al., 2000). Open yearlong studies indicate that the rate of weight gain may slow after 6 months of risperidone treatment (e.g., Holford et al., 2000). In a study directly comparing weight gain associated with risperidone and olanzapine treatment of youth, Sikich (2001) found no significant difference in the rate of weight gain associated with the two agents. In a prospective study evaluating weight gain over a 12-week period, olanzapine produced more weight gain than risperidone or haloperidol (Ratzoni et al., 2002). Similarly, in adults, risperidone is associated with less weight gain than olanzapine or clozapine (Wirshing et al., 1999).

EPS appear to be associated with relatively high doses of risperidone in youth. In a double-blind study in which 16 psychotic youth were treated with an average of 4.0 mg of risperidone per day, Sikich (2001) found that 62% had mild EPS and 25% had moderate to severe EPS. Similarly, open-label studies (e.g., Armenteros et al., 1997; Lombroso et al., 1995) indicate that relatively moderate to high doses of risperidone (e.g., maximum dose of 2.5 mg in the Lombroso et al. study; mean dose=6.6 mg/day in the Armenteros et al. study, as opposed to mean dose=1.23 mg/day in the Aman et al. [2000] study described above) may be associated with EPS. However, the rates of EPS observed are substantially lower than reported with typical antipsychotics (Keepers and Casey, 1991). In addition, in the majority of studies addressing aggression with lower doses of risperidone, acute EPS were mild and transient. In a study of children with Tourette's disorder, two of nine subjects on risperidone experienced stiffness, but there was no evidence of drug-induced parkinsonism on the Simpson-Angus Scale (Gaffney et al., 2002). In their studies of risperidone in children, Buitelaar (2000), Finding et al. (2000b), and Jefferson et al. (1998), found no cases of EPS.

Risperidone's possible association with tardive or withdrawal dyskinesias has also been documented (Buitelaar, 2000; Lore, 2000; Malone et al., 1999). Risperidone treatment of youth has also been associated with mild and often transient sedation (Buitelaar et al., 2001; Findling et al., 2000b; Frazier et al., 1999; Holford et al., 2000; Schreier, 1998) and with significant elevations in prolactin levels in studies of low-dose risperidone in developmentally delayed youth (Aman et al., 2000; Findling et al., 2000a; Holford et al., 2000). Subjects treated with higher doses of risperidone have also experienced increases in prolactin level (Frazier et al., 1999; Sikich, 2001). Sikich (2001) found the increases in prolactin associated with risperidone to be greater than those associated with either haloperidol or olanzapine. The physiological consequences of these prolactin elevations are not clear but might include galactorrhea (see Gupta, 2001).

Isolated reports indicate that risperidone may be associated with acute leukocytopenia (Edleman, 1996) and hepatic side effects. Kumra and colleagues (1997) describe two cases in which long-term risperidone treatment in children was associated with hepatic side effects believed to be secondary to excessive weight gain and fatty deposits in the liver. However, Szigethy et al. (1999) did not find an increased risk for hepatotoxicity in children on risperidone treatment. Thus the evidence in this area is unclear and deserves further attention.

In summary, risperidone seems to be effective in reducing aggression among youth with a variety of complex, comorbid disorders, including those that involve subnormal intelligence. Weight gain, EPS, and hyperprolactinemia are commonly observed, especially with higher doses of risperidone. The long-term course and impact of these side effects is unclear and should be explored.

Clozapine

Clozapine for Aggression. Several studies indicate that clozapine may be associated with reductions in aggression among adults. A chart review of 75 adult inpatients with schizophrenia (Rabinowitz et al., 1996) found that after 6 months of clozapine treatment (mean final dose=350 mg/day), significant reductions in physical and verbal aggression occurred as measured on the total and hostility scores of the Brief Psychiatric Rating Scale and from staff notes.

Clozapine was associated with reduced aggression in a retrospective study of 331 adult schizophrenic patients, and this association was independent of clozapine's antipsychotic and sedative effects (Volavka, 1999). Clozapine was most effective in reducing aggressive behavior as opposed to other symptoms present, even among patients who exhibited the most severe pretreatment aggression. There is little evidence regarding the effect of clozapine on aggression among youth; however, in

one case series, reduced aggression was found among 10 youth with bipolar disorder, schizophrenia, or psychotic disorder not otherwise specified (Kowatch et al., 1995).

Safety of Clozapine. Reports in adults indicate that clozapine may be associated with cardiovascular side effects (e.g., Ihde-Scholl et al., 2001), electroencephalogram (EEG) changes, agranulocytosis, hyperglycemia seizures (Remschmidt et al., 2000), and several individual cases of new-onset diabetes (e.g., Henderson et al., 2000). Studies comparing the atypical antipsychotics' respective weight gain liabilities in adults have found that clozapine results in the most weight gain (Allison et al., 1999) and is responsible for the most prolonged weight gain of all atypical antipsychotics (Wirshing et al., 1999).

It has been theorized that the rate of agranulocytosis may be higher among younger patients. Alvir et al. (1993) found that, of 11,555 patients (principally adults) given clozapine between February 1990 and April 1991, 73 patients experienced agranulocytosis; 2 of these patients died as a result. The risk for agranulocytosis was significantly higher among patients younger than 21 years old than among patients aged 21–30 years or 31–40 years. In contrast, dose appeared to have no effect on the risk for agranulocytosis. In a study of 73 youth treated with clozapine, 7 subjects experienced granulocytopenia (neutropenia) (Rosen et al., 1996). This is of note and highlights the importance of careful blood monitoring because neutropenia may predict later agranulocytosis (Pollmacher et al., 1997).

Hyperglycemia may be associated with clozapine (100–1,000 mg/day) in adolescents, as evidenced by 11 reports received by the U.S. Food and Drug Administration (FDA) between January 1993 and March 2001. Clozapine was discontinued or dose was decreased among six of these patients, three of whom experienced improved glycemic functioning (Koller et al., 2001). Additional severe side effects observed in adults on clozapine have been reported to occur in youth as well. In a double-blind study comparing the effects of clozapine and haloperidol in the treatment of childhood-onset schizophrenia, Kumra et al. (1996) found that 4 of 21 patients discontinued clozapine because of serious side effects, including seizures (n=3) and sinus tachycardia (n=1). In another open trial of clozapine in 36 adolescents, 17% of patients discontinued clozapine because of serious side effects that were primarily cardiovascular (Remschmidt et al., 1994). Turetz et al. (1997) observed nonspecific excitatory electrocardiogram (ECG) changes in 82% of 11 adolescents with schizophrenia treated with clozapine (mean dose=227.3 mg/day), although there were no clinical signs of convulsive disorder.

The majority of reports in the pediatric population show a clozapine side effect profile similar to that in adults, with the most common side effects being sedation, hypersalivation, and weight gain (e.g., Frazier et al., 1994; Kowatch et al., 1995). Prolactin elevations have been reported among youth but have not been reported to exceed normal limits (Wudarsky et al., 1999). In summary, the literature indicates that clozapine may reduce aggression in youth, although its rare but serious association with agranulocytosis and with seizures, significant weight gain, and tachycardia indicates that careful monitoring is required when clozapine is administered.

Olanzapine

Olanzapine for Aggression. Given its relatively recent availability, there have been few large, controlled studies of olanzapine in children (Findling et al., 2000c). An open-label trial of olanzapine in children, adolescents, and adults found that olanzapine (mean final dose=7.8 mg/day) was associated with reductions in self-injurious behavior and aggression against both people and property (Potenza et al., 1999). In a case report, Horrigan et al. (1997) reported that 10 mg of olanzapine per day was associated with reduced aggression toward others, aggression toward property, and explosive rage outbursts. Preliminary data suggest that intramuscular (IM) olanzapine may be effective and safe for acutely agitated bipolar adults (Meehan et al., 2001). However, the current lack of controlled data regarding olanzapine's efficacy in reducing aggression among youth prevents firm conclusions from being drawn at this time.

Safety of Olanzapine. The risk of EPS with olanzapine appears to be relatively low (Semerci, 2000), the majority of EPS observed are mild to moderate (Sikich, 2001), and most studies report either few or no EPS. Kumra et al. (1998) examined eight youth with treatment-resistant, early-onset schizophrenia who were treated sequentially with clozapine and olanzapine. Incidences of EPS were minimal. While on olanzapine, no patients experienced neutropenia, abnormal EEG changes, or seizures, whereas four of these patients had required anticonvulsant medication during previous trials of clozapine. Similarly, in open-label trials, no statistically significant changes in EPS from baseline were found (Frazier et al., 2000; Malone et al., 2001).

In addition to reports of mild sedation (Kumra et al., 1998; Malone et al., 2001; Potenza et al., 1999) and of modestly elevated prolactin (Sikich, 2001;

Wudarsky et al., 1999), weight gain and increased appetite have been reported in studies of olanzapine treatment of youth with a variety of diagnoses (Kumra et al., 1998; Malone et al., 2001; Nguyen and Murphy, 2001; Potenza et al., 1999; Semerci, 2000; Sikich, 2001). Diet, exercise, and behavioral treatments are the most commonly recommended strategies for preventing and treating atypical antipsychotic–associated weight gain (Allison and Casey, 2001; Kinon et al., 2001). These strategies should be examined in controlled studies with olanzapine and with other atypical antipsychotics.

Olanzapine may be associated with hyperglycemia, hyperlipidemia, and diabetes among youth. A query of the FDA MedWatch drug surveillance system found that, between January 1996 and May 2001, there were nine spontaneous-adverse-event reports of hyperglycemia in adolescents taking olanzapine (10–20 mg/day), seven of whom developed hyperglycemia and two of whom experienced an exacerbation of preexisting diabetes (Koller et al., 2001). Domon and Webber (2001) describe a 15-year-old male who developed both hyperglycemia and hypertriglyceridemia associated with olanzapine; these symptoms resolved when olanzapine was discontinued, despite the patient's not changing his diet or being administered insulin or oral hypoglycemics. There are also reports of the development of diabetes associated with olanzapine in youth (e.g., Selva and Scott, 2001).

Quetiapine

Quetiapine for Aggression. Quetiapine is the third atypical antipsychotic to be released in the United States. To the best of our knowledge, there are no published studies investigating the efficacy of quetiapine for the treatment of aggression.

Safety of Quetiapine. There have been consistent reports of weight gain (Allison et al., 1999) and new-onset diabetes (e.g., Procyshyn et al., 2000) associated with quetiapine in adults. Preliminary data from Shaw et al. (2001) from a 6-week open trial of 15 psychotic youth found that quetiapine was generally well tolerated with the exception of weight gain (mean=4 kg over 6 weeks). Other preliminary epidemiological data in adults suggest that clozapine, olanzapine, and quetiapine increase the risk of type II diabetes compared with typical antipsychotics (Sernyak et al., 2002). In an inpatient unit where 14 patients (adolescents and adults) developed severe hypertriglyceridemia associated with olanzapine (mean dose=15.6 mg/day) and quetiapine (mean dose=225 mg/day), 4 of these patients developed new-onset diabetes (Meyer, 2001).

There are only scattered reports of quetiapine's association with side effects other than weight gain and diabetes. Preliminary research found quetiapine to be associated with the development of cataracts in beagles (Stip and Boisjoly, 1999). However, this has not been confirmed by research or clinical experience in humans and no research has been conducted in children. Although one open-label study found quetiapine to be associated with tachycardia in 9 of 10 young patients (McConville et al., 2000), another open-label study found that the only serious side effect was sedation, although one patient experienced seizure-like activity (Martin et al., 1999). Several case reports (e.g., Healy et al., 1999) describe youth who experienced no apparent side effects on quetiapine. While quetiapine may be a promising agent, the lack of data investigating its safety and efficacy in the treatment of child and adolescent aggression indicates that more research is needed.

Ziprasidone

Ziprasidone for Aggression. We have been unable to locate any published studies investigating the effects of ziprasidone on aggression. Patel et al. (2002b) reported a retrospective chart review of the effects of ziprasidone use in 13 hospitalized children with a variety of psychiatric diagnoses. Nine of the 13 patients were improved or much improved on the CGI-Severity scale, at a mean maximum dose of 52.3 mg/day (Patel et al., 2002b). In a double-blind, placebo-controlled study, ziprasidone was associated with improvements in tic frequency and severity among 28 patients aged 7–17 years with Tourette's syndrome or chronic tic disorder (Sallee et al., 2000). IM ziprasidone may reduce acute agitation associated with psychosis in adults (Daniel et al., 2001). Future research should examine the efficacy and safety of ziprasidone, including IM ziprasidone, in acutely aggressive children.

Safety of Ziprasidone. A study of ziprasidone in 302 schizophrenic and schizoaffective adults found that the most common side effects were mild dyspepsia, nausea, dizziness, and transient somnolence (Daniel et al., 1999). Ziprasidone may cause QTc prolongation; QTc prolongation caused by other medications has been associated with potentially fatal ventricular arrhythmias (Gury et al., 2000). An FDA-commissioned study by Pfizer compared the effect on the QTc interval of patients given ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, or haloperidol at the highest recommended dose (for all drugs except thioridazine). The QTc effect of ziprasidone 160 mg was found to be approximately 10 msec greater than the effects of haloperidol, que-

tiapine, risperidone, and olanzapine, but there was no further QTc prolongation in the presence of metabolic inhibition (FDA Psychopharmacological Drugs Advisory Committee, 2000). No cases of Torsade's have been reported with ziprasidone, and the clinical significance of its ECG changes, if any, is still unclear. In Patel's case series in children, the most common reported side effects were akathisia and agitation (Patel et al., 2002b).

There are few findings from clinical experience and only one controlled study thus far of ziprasidone in youth. As noted above, this double-blind, placebo-controlled study investigated tics rather than aggression (Sallee et al., 2000). The most common side effect was transient, mild sedation, and there was no statistically significant difference in weight gain on ziprasidone. The side effects of ziprasidone in youth must be further investigated, but these preliminary findings suggest that ziprasidone's side effect profile may be relatively mild.

Stimulants

Aggression is a common symptom among children with ADHD. Furthermore, ODD/CD and ADHD commonly co-occur among children and adolescents (MTA Cooperative Group, 1999). A double-blind, placebo-controlled trial of methylphenidate in 18 urban children with ADHD found that subjects on this medication showed improvements in ADHD symptoms, had fewer incidents of physical aggression, time-out for deviant behavior, and negative peer interactions, with no reports of serious side effects (Bukstein and Kolko, 1998). When 74 children with CD with or without ADHD were given either methylphenidate or placebo, results showed that behaviors specific to CD were significantly reduced for those given methylphenidate (Klein et al., 1997). Connor et al. (2002) conducted a meta-analysis of 28 studies from 1970–2001 (combined *N*=683) in which youth were given stimulants to treat overt and covert aggression associated with ADHD. They found that stimulants had significant beneficial effects in the treatment of ADHD-related aggression and that these effects were independent from, but similar in magnitude to, their effects on the core symptoms of ADHD.

Mood stabilizers

Several studies have demonstrated that mood stabilizers are associated with reductions in aggression in youth. In a double-blind, placebo-controlled study, Campbell et al. (1995) studied 50 children hospitalized for treatment-refractory severe aggressiveness and explosiveness with CD. They found that subjects on lithium showed statistically significant reductions in aggression on several measures, including the Children's Psychiatric Rating Scale. Similar results were found in a double-blind study of 40 aggressive children with CD in which aggression was measured on the Global Clinical Judgments Consensus Scale, the CGI scale, and the Overt Aggression Scale (OAS) (Malone et al., 2000). Common side effects that may be associated with lithium include enuresis, fatigue, ataxia, increased thirst, nausea, vomiting, urinary frequency, and weight gain (Silva et al., 1992). However, in a double-blind study of 61 children with CD, Campbell et al. (1984) demonstrated that both lithium and haloperidol were associated with significant behavioral improvements but that lithium had fewer side effects than haloperidol.

Mood stabilizers other than lithium have also been used to treat aggression in youth. A double-blind, placebo-controlled, crossover-design study of children with explosive temper and mood lability reported reduced aggression (as measured by the Modified Overt Aggression Scale [MOAS]) associated with divalproex (Donovan et al., 2000). However, when administered in doses of 400–800 mg/day, carbamazepine did not reduce aggression significantly in children with CD (Cueva et al., 1996). Evidence appears inconclusive for the safety and efficacy of mood stabilizers other than lithium.

Selective serotonin reuptake inhibitors

A placebo-controlled study of fluoxetine found statistically significant reductions in impulsive aggressive behavior among 40 nondepressed adults with personality disorder (Coccaro and Kavoussi, 1997). Case reports indicate that selective serotonin reuptake inhibitors (SSRIs) were effective in reducing aggression in male youth with various aggressive disorders (Ghaziuddin and Alessi, 1992; Poyurovsky et al., 1995). No serious side effects were reported in any of these cases.

a2-Agonist

In a meta-analysis of 11 double-blind, controlled, and randomized studies from 1980 and 1999, the α2-agonist clonidine demonstrated a moderate effect size of 0.58±0.16 on symptoms of ADHD alone and with comorbid CD, developmental delay, and tic disorders (Connor et al., 1999). Results from an open pilot study of clonidine (maximum optimal dose=0.4 mg/day) in aggressive children indicate that this medication may be associated with reductions in aggression as measured by the RAAPP and only mild side effects (Kemph et al., 1993). Cantwell et al.

(1997) reported harmful side effects in four children who were treated with clonidine for ADHD. One child died of exercise-related syncope, which may have been related to clonidine treatment. These findings raise questions about the use of α-agonists in youth that must be addressed by future studies.

β-*Blockers*

A literature review conducted in 1993 on the use of β-blockers to treat aggression in youth found that 145 (83%) of 175 patients in 31 reports of studies of adults and children showed improvements, although no double-blind studies of children and adolescents were found (Connor, 1993). β-Blockers may also be an effective adjunctive treatment in reducing aggression among a variety of populations. Maoz et al. (2000) conducted an open trial of combined haloperidol and propanolol in 34 adults with schizophrenia who received 7 days of haloperidol, with some receiving subsequent haloperidol-propanolol treatment for 8 weeks. After 4 weeks of combination treatment and on a variety of doses, subjects showed significant declines on several dimensions of aggression. In a 5-month, open-label study of nadolol as an adjunctive treatment for aggression and/or inattention/overactivity in developmentally delayed children, adolescents, and young adults, nadolol led to significant improvement on the OAS and subjects experienced few side effects (Connor et al., 1997). The capacity of β-blockers to reduce aggression in youth is also suggested by case reports (e.g., Lang and Remington, 1994).

There have been reports of the following side effects associated with β-blockers among children: sedation, mild hypotension, lowered heart rate, bronchoconstriction, hypoglycemia (in patients with diabetes), dizziness, sleep disruption, and, possibly, growth hormone abnormalities (Coffey, 1990). It is possible that β-blockers are associated with bradycardia, hypotension, and bronchoconstriction in patients with asthma and that they may affect growth hormone regulation, but future research is needed (Riddle et al., 1999). While β-blockers may offer promise in reducing aggression, Connor (1993) noted that β-blockers should only be used as part of a multidisciplinary treatment of aggression in youth.

DISCUSSION

SUMMARY

Empirical support exists for the clinical efficacy of several nonpharmacological and pharmacological treatments for aggression in youth. Controlled research regarding the use of the typical antipsychotics to reduce aggression in youth is scarce, and the side effects associated with these medications are of concern. Currently, the majority of controlled research on atypical antipsychotics for the treatment of aggression in children comes from studies of risperidone. Although risperidone may be associated with EPS, if dosed appropriately the severity and frequency of EPS are considerably less with risperidone than with typical antipsychotic treatment (Keepers and Casey, 1991; Sikich, 2001). Risperidone is associated with weight gain, though in adults this weight gain is notably less than that associated with olanzapine or clozapine (Wirshing et al., 1999). At this point, however, it is unclear whether these differences are as marked in the pediatric population (Sikich, 2001). Preliminary data on olanzapine and clozapine suggest that these medications may be associated with reduced aggression, although side effects such as the increased risk of agranulocytosis among youth on clozapine (Alvir et al., 1993) are of concern. The increasing evidence regarding weight gain and glucose intolerance with both of these agents should be taken into consideration. It also appears that β-blockers, the α-agonist clonidine, and stimulants (for ADHD-related aggression) may be efficacious in reducing aggression in youth.

LIMITATIONS

There are several limitations to the findings described in this overview. Unfortunately, a good portion of the evidence presented is based on open-label studies and case reports and should be considered preliminary rather than definitive. Some of the data presented also come from preliminary analyses of controlled studies that have not been fully peer-reviewed. Furthermore, much of the data on the side effects of these medications is taken from studies involving disorders other than those with aggression. We cannot be certain that these medications will be associated with the same side effects in patients with disorders primarily involving aggression, e.g., CD *without* psychosis or ODD *without* bipolar disorder.

IMPLICATIONS FOR FUTURE RESEARCH

Our overview of treatments for aggression in youth illuminates many questions on which future research must focus. First, there is inadequate information about the efficacy of the newer atypical antipsychotics, more selective β-blockers, newer mood stabilizers, and SSRIs in reducing aggression in youth. This is particularly important because preliminary data suggest that ziprasidone may be

less likely to be associated with significant weight gain than other atypical antipsychotics. On the other hand, ziprasidone may be associated with other, currently undiscovered side effects. Research in children needs to explore further the potential long-term side effects of all atypical antipsychotics in children.

In addition, studies are needed that compare the efficacy of the atypical antipsychotics in the treatment of aggression in youth to that of other classes of medications. Given Malone and colleagues' (2000) finding that lithium is most efficacious in treating specific subtypes of aggression, further research should probe the atypical antipsychotics' efficacy in treating different subtypes of aggression. In addition, future trials might divide subjects by age group (e.g., ages 8–12 versus ages 13–18) to investigate the possibility that they respond differently to the same dose of a particular atypical antipsychotic or to different antipsychotics. Controlled trials comparing atypical antipsychotics with mood stabilizers in the treatment of aggression are needed. In addition, the β-blockers may be effective in reducing aggression among youth, but further controlled trials should examine their short- and long-term safety and efficacy. More generally, controlled trials are needed to fill in our knowledge gap regarding dosage strategies. In addition, the length of an adequate trial for particular antipsychotics is an important factor in treatment and deserves further attention in controlled studies. Future controlled trials might examine the effects of combining various atypical antipsychotics with one another or with medications from other classes (such as Campbell and colleagues' [1984] study) to treat aggression in youth.

Finally, we note that there is a need for controlled studies that directly compare the side effects associated with each atypical antipsychotic. In the absence of such direct comparisons, meta-analyses such as Wirshing and colleagues' (1999) review of antipsychotic-associated weight gain or retrospective analyses of patients receiving different treatments over the same period in the same setting (e.g., Martin et al., 2000) will provide valuable information. Future studies might use such strategies to investigate different side effects such as EPS, glucose abnormalities, hepatic abnormalities, and sedation. Finally, given the importance of psychosocial interventions, it would be interesting and informative to investigate combinations of various types of psychosocial interventions and different types of psychotropic medications for the treatment of aggression in youth.

When one considers the frequency with which aggressive youth are treated with psychotropic medications (Pappadopulos et al., 2002; Patel et al., 2002a), as well as the gaps in our knowledge of the long-term safety and efficacy of these practices, it is clear that controlled trials are urgently needed in this area. Nonetheless, the preliminary findings we have presented offer promise that, as the current evidence base continues to grow, more definitive scientific findings will be available to inform the safe and effective treatment of aggression in youth.

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