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Atypical antipsychotic medications in the management of disruptive behaviors in children: Safety guidelines and recommendations

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ABSTRACT

Use of atypical antipsychotic medications (AAMs) in the treatment of Disruptive Behavior (DB) in children and adolescents has increased dramatically worldwide. However, with exception of using risperidone (i.e., for the management of irritability associated with Autism, manic and mixed episodes associated with Bipolar I Disorder, and Schizophrenia) and aripiprazole (i.e., for manic and mixed episodes associated with Bipolar I Disorder and Schizophrenia), the Food and Drug Administration (FDA) has not approved the use of AAMs in children and adolescents. Although research on use of these medications in children and adolescents has increased, mechanisms of action and long-term outcomes remain poorly understood or unknown. Particularly concerning is that use of these medications in children and adolescents may impact cognitive, social, and physical development, as side effects may interfere with activities in their educational setting, peer networks, and recreational settings. Overall, AAMs frequently are prescribed off label, control DB through sedation rather than targeting actual causes of DB, and lead to many negative side effects with unknown long-term effects. Reconsidering the use of AAMs in managing DB is encouraged strongly.

Contents

1. Introduction

Despite concerns about tolerability and long-term effects, traditional antipsychotic medications are used for the treatment of a variety of psychotic and non-psychotic conditions in children and adolescents (Sivaprasad, Hassan, & Handy, 2006). In more recent times, atypical antipsychotic medications (AAMs) are being used more frequently due to the lower occurrence of negative side effects with these medications relative to traditional antipsychotic medications (Croarkin, Emslie, & Mayes, 2008; Erdogan et al., 2008; Sivaprasad et al., 2006; Zito, Safer et al., 2008). In one study (Sivaprasad et al., 2006), a postal survey in a region of the United Kingdom was sent to 57 community and inpatient psychiatrists in 2003 so that an estimate of their use of AAMs could be obtained for the previous year. Of the 39 respondents, 95% of them reported prescribing AAMs to children and adolescents, and 65% reported prescribing these medications for non-psychotic conditions (Sivaprasad et al., 2006). Similarly, Zito, Safer et al. (2008) noted increases in the use of AAMs in the Netherlands and Germany. These results suggest that, in fact, AAMs are widely used with children and adolescents.

Similar results are noted in the United States as well. Another study (Staller, Wade, & Baker, 2005) examined the current prescribing patterns of outpatient child psychiatrists in central New York. The files

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of children and adolescents who ranged in age from 1- to 18-years from eight outpatient locations in central New York and who were seen for appointments on one day in 2002 were reviewed ($N = 1292$). Findings indicated that 74% of these children and adolescents received psychotropic medication and that 50% received two or more of these medications. The most commonly prescribed medications included stimulants, antidepressants, antipsychotics, alpha-agonists, and mood stabilizers. Further, these children and adolescents were diagnosed most commonly with Attention-Deficit/Hyperactivity Disorder, other Disruptive Behavior Disorders (DBD), Anxiety Disorders, and Depressive Disorders. Of the children and adolescents who were prescribed antipsychotic medications, 77% did not have a diagnosis of a Psychotic Disorder (Staller et al., 2005).

Olfson, Blanco, Liu, Moreno, and Laje (2006) also examined trends in the use of antipsychotic medications in conjunction with outpatient visits across the United States. This study found that office visits by youth that included antipsychotic medications increased from approximately 201,000 in 1993 to 1,224,000 in 2002. From 2000 to 2002, male visits (1913 per 100,000) involving treatment with antipsychotic medications were significantly higher in number than female visits (739 per 100,000). In addition, visits for White, non-Hispanic youth (1515 per 100,000) were significantly higher than those for youth from other ethnic groups (426 per 100,000). Overall, this study found that 9.2% of all mental health visits and 18.3% of visits to psychiatrists included treatment with antipsychotic medications. From 2000 to 2002, 92.3% of visits involving treatment with antipsychotic medications utilized AAMs. Diagnoses that were treated in these sessions were varied and included DBDs (37.8%), Mood Disorders (31.8%), Pervasive Developmental Disorders (PDD) or Intellectual Disability (17.3%), and Psychotic Disorders (14.2%; Olfson et al., 2006). This study concluded that a sharp national increase in the use of AAMs for the treatment of children and adolescents in office-based medical practice has occurred, especially for DBDs and other non-Psychotic Disorders. These increases may be particularly concerning as the basis of support for the use of AAMs is limited to short-term safety and efficacy (Olfson et al., 2006).

Thus, partly due to improved tolerability and efficacy profiles of AAMs, these medications are being used increasingly to treat a growing number of children and adolescents presenting with a variety of disorders, including Disruptive Behavior (DB), Mood, Developmental, Psychotic, and Eating Disorders (Croarkin et al., 2008; Erdogan et al., 2008; Findling, 2003; Findling, Aman, Eerdekens, Derivan, & Lyons, 2004; Mehler-Wex, Romanos, Kirchheiner, & Schulze, 2008; Stigler & McDougle, 2008; Ritchie & Norris, 2009; Troost et al., 2005; Zito, Safer et al., 2008). Although AAMs are indicated in the treatment of adults only, they often are used in off-label treatments in the United States to address the DB exhibited by children and adolescents (Findling, 2003). It is not uncommon for different medications to be used off-label in the treatment of children and adolescents who are exhibiting emotional and behavioral symptoms. In fact, 50 to 75% of pediatric medications are prescribed off label (Zito, Derivan, Kratochvil, Safer, Fegert, & Greenhill, 2008).

There are two exceptions to the off-label medication use of AAMs. These exceptions include the FDA approved usage of risperidone in the treatment of irritability associated with Autism for children who range in age from 5- to 16-years, in the treatment of manic and mixed episodes associated with Bipolar I Disorder in children who range in age from 10- to 17-years, and in the treatment of Schizophrenia in children who range in age from 13- to 17-years. The second exception includes the FDA approved usage of aripiprazole in the acute treatment of manic and mixed episodes of Bipolar I Disorder in children who range in age from 10- to 17-years and in the treatment of Schizophrenia in children who range in age from 13- to 17-years (Croarkin et al., 2008; Greenaway & Elbe, 2009; Scott & Dhillon, 2008; Stigler & McDougle, 2008). AAMs also are used often to treat children and adolescents with other PDDs, DBDs, Eating Disorders, Movement Disorders, other Mood Disorders, Anxiety Disorders, and other Psychotic Disorders, however (Findling, 2003; Greenaway & Elbe, 2009; Mehler-Wex et al., 2008; Ritchie & Norris, 2009; Stigler & McDougle, 2008). Overall, the most common reason that AAMs are prescribed to children and adolescents appears to be for managing "pernicious, pervasive, persistent aggression in the context of DBDs" (Findling, 2003, p. 10).

Although both traditional antipsychotics and AAMs may have some utility in treating some DB, as well as other disorders, exhibited by children and adolescents, this usage is problematic. Children and adolescents are not smaller adults and may not respond to medications in a similar manner as adults. For example, use of tricyclic antidepressants has been shown to be safe and efficacious in treating adults with Depression, but use of these medications in children and adolescents has led to more adverse events (AE) and side effects than were noted in adult populations (Findling, 2003). A similar scenario may be playing out with AAMs as well. For example, children and adolescents appear to be at higher risk for sedation, weight gain, and Movement Disorders that are associated with extrapyramidal symptoms (EPS) as well as other adverse effects that are prompted by AAMs (Findling, 2003; Zito, Derivan, et al., 2008). Thus, before the real utility of AAMs can be determined, previous research examining the efficacy of AAMs in children and adolescents needs to be examined.

2. Previous research

Despite growing use of AAMs in children and adolescents, the research informing such use is lacking (Findling, 2003). Although research in this area is fairly new, the use of antipsychotic medications in treating DB is not. These medications have been used over the past 20 (Croonenberghs et al., 2005) to 50 (Zito, Derivan, et al., 2008) years to treat DB. A majority of the research literature focuses on the use of risperidone in treating DB in children and adolescents; however, other medications including olanzapine, aripiprazole, quetiapine, ziprasidone, and others are starting to be examined as well. This research will be examined here.

2.1. Risperidone

Risperidone is a potent postsynaptic dopamine and serotonin receptor blocker and is the most well studied AAM (Findling et al., 2004; Troost et al., 2005). The short-term efficacy of risperidone in managing behavioral problems associated with Autism Spectrum Disorders (i.e., PDDs) is well established (Troost et al., 2005). Risperidone is approved for use in a number of European countries (De Deyn & Buitelaar, 2006; Reyes, Olah, Csaba, Augustyns, & Eerdekens, 2006), and it has received FDA approval for treating irritability occurring in conjunction with Autism, for treating mania and mixed episodes that occur with Bipolar I Disorder, and for treating Schizophrenia. Much research has explored the effects of risperidone when used to treat DBDs in the short term as well. The effects of the long-term use of this medication are less well known, however (Troost et al., 2005).

Risperdone is one of the better studied AAMs, with a number of the studies that have been completed for children and adolescents summarized here. For example, Troost et al. (2005) examined the use of risperidone for the treatment of Autism Spectrum Disorders over a 6-month period. A total of 36 children who ranged in age from 5- to 17-years, who were diagnosed with an Autism Spectrum Disorder, and who exhibited severe tantrums, aggression, or self-injurious behavior started an eight-week open-label treatment trial with risperidone (i.e., with doses starting at 0.5 mg/day and increasing to 2.5 mg/day by day 29). Participants were seen every 4 weeks for assessment of efficacy, safety, and dose adjustments and were seen weekly during the discontinuation phase. Ratings included the Clinical Global Impression (CGI) scale of symptom change (completed by a clinician) and the irritability subscale of the Aberrant Behavior