Evidence for Clinicians

Evidence for clinicians: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Iliana Ortega MD

Clinical Fellow, Psychopharmacology Research Unit, University of Calgary, Mathison Centre for Mental Health Research & Education, Calgary, Canada

Correspondence: Iliana Ortega, Mathison Centre for Mental Health Research & Education, 1st Floor, TRW Building, Foothills Medical Center 3280 Hospital Drive NW Calgary, AB T2N 4Z6, Canada. Telephone (403) 955-8942, e-mail: iliana.garciaortega@gmail.com

For the current issue of the Journal, we asked Dr. Iliana Ortega to comment on and put into context the recent Cochrane Review on atypical antipsychotics for disruptive behaviour disorders (DBD).

BACKGROUND

This is an update of the original Cochrane Review, last published in 2012 (1). Children and youths with DBD may present to health services, where they may be treated with atypical antipsychotics. There is increasing usage of atypical antipsychotics in the treatment of DBD.

OBJECTIVES

The objective of this study was to evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating DBD in children and youths. The aim was to evaluate each drug separately rather than the class effect, on the grounds that each atypical antipsychotic has a different pharmacologic binding profile (2) and that this is clinically more useful.

SEARCH METHODS

In January 2017, we searched CENTRAL, MEDLINE, Embase, five other databases, and two trials registers.

SELECTION CRITERIA

Randomized controlled trials of atypical antipsychotics versus placebo in children and youths aged up to and including 18 years, with a diagnosis of DBD, including comorbid attention-deficit hyperactivity disorder (ADHD). The primary outcomes were aggression, conduct problems, and adverse events (i.e., weight gain/changes and metabolic parameters). The

secondary outcomes were general functioning, noncompliance, other adverse events, social functioning, family functioning, parent satisfaction, and school functioning.

DATA COLLECTION AND ANALYSIS

We used standard methodological procedures expected by Cochrane. Two review authors (JL and KS) independently collected, evaluated, and extracted data. We used the GRADE approach to assess the quality of the evidence. We performed meta-analyses for each of our primary outcomes, except for metabolic parameters, due to inadequate outcome data.

MAIN RESULTS

We included 10 trials (spanning 2000 to 2014), involving a total of 896 children and youths aged 5 to 18 years. Bar two trials, all came from an outpatient setting. Eight trials assessed risperidone, one assessed quetiapine, and one assessed ziprasidone. Nine trials assessed acute efficacy (over 4 to 10 weeks); one of which combined treatment with stimulant medication and parent training. One trial was a 6-month maintenance trial assessing symptom recurrence. The quality of the evidence ranged from low to moderate. Nine studies had some degree of pharmaceutical support/funding.

PRIMARY OUTCOMES

Using the mean difference (MD), we combined data from three studies (238 participants) in a meta-analysis of aggression, as assessed using the Aberrant Behaviour Checklist (ABC) Irritability subscale. We found that youths treated with risperidone show reduced aggression compared with youths treated with placebo (MD -6.49, 95% confidence interval [CI] -8.79

to -4.19 ; low-quality evidence). Using the standardized mean difference (SMD), we pooled data from two risperidone trials (190 participants), which used different scales: The Overt Aggression Scale Modified (OAS-M) Scale and the Antisocial Behaviour Scale (ABS); as the ABS had two subscales that could not be combined (reactive and proactive aggression), we performed two separate analyses. When we combined the ABS Reactive subscale and the OAS-M, the SMD was -1.30 in favour of risperidone (95% CI -2.21 to -0.40 , moderate-quality evidence). When we combined the ABS Proactive subscale and OAS-M, the SMD was -1.12 (95% CI -2.30 to 0.06 , moderate-quality evidence), suggesting uncertainty about the estimate of effect, as the CIs overlapped the null value. In summary, there was some evidence that aggression could be reduced by risperidone. Data were lacking on other atypical antipsychotics, like quetiapine and ziprasidone, with regard to their effects on aggression. We pooled data from two risperidone trials (225 participants) in a meta-analysis of conduct problems, as assessed using the Nisonger Child Behaviour Rating Form Conduct Problem subscale (NCBRF-CP). This yielded a final mean score that was 8.61 points lower in the risperidone group compared to the placebo group (95% CI -11.49 to -5.74 ; moderate-quality evidence). We investigated the effect on weight by performing two meta-analyses. We wanted to distinguish between the effects of antipsychotic medication only and the combined effect with stimulants, since the latter can have a counteracting effect on weight gain due to appetite suppression. Pooling two trials with risperidone only (138 participants), we found that participants on risperidone gained 2.37 kg more (95% CI 0.26 to 4.49; moderate-quality evidence) than those on placebo. When we added a trial where all participants received a combination of risperidone and stimulants, we found that those on the combined treatment gained 2.14 kg more (95% CI 1.04 to 3.23; three studies; 305 participants; low-quality evidence) than those on placebo.

SECONDARY OUTCOMES

Out of the 10 included trials, 3 examined general functioning, social functioning, and parent satisfaction. No trials examined family or school functioning. Data on noncompliance/attrition rate and other adverse events were available from all 10 trials.

AUTHORS' CONCLUSIONS

There is some evidence that in the short-term risperidone may reduce aggression and conduct problems in children and youths with DBD. There is also evidence that this intervention is associated with significant weight gain. For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. It is challenging to interpret the clinical significance of the differential findings on two different

ABS subscales as it may be difficult to distinguish between reactive and proactive aggression in clinical practice. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. Weight gain remains a concern. Caution is required in interpreting the results due to the limitations of current evidence and the small number of high-quality trials. There is a lack of evidence to support the use of quetiapine, ziprasidone, or any other atypical antipsychotic for DBD in children and youths and no evidence for children under 5 years of age. It is uncertain to what degree the efficacy found in clinical trials will translate into real-life clinical practice. Given the effectiveness of parent-training interventions in the management of these disorders, and the somewhat equivocal evidence on the efficacy of medication, it is important not to use medication alone. This is consistent with current clinical guidelines.

The full text of the Cochrane Review is available in The Cochrane Library: Low JH, Merry S, Hetrick SE, Stasiak K. Atypical antipsychotics for DBD in children and youths. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD008559. 10.1002/14651858.CD008559.pub3

EXPERT COMMENTARY

Since their introduction in the 1980s, second generation antipsychotics, and more recently third-generation antipsychotics (SGAs/TGAs) became the preferred option to treat a wide variety of mental disorders. Due to their pharmacological profile, this group of medications have a lower risk than older antipsychotics to induce neurological side effects including akathisia, dystonia, and tardive dyskinesia, among others (3–5). However, the use of these medications does not come without risks; they are associated with both neurologic and metabolic side effects including weight gain, hyperglycaemia, dyslipidaemia, hypertension, and metabolic syndrome, which increases the risk for cardiovascular disorders (6,7).

In Canada, there are 10 marketed SGAs/TGAs that include aripiprazole, asenapine, brexpiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. At present, their use in the paediatric population is mostly off-label as the only SGAs/TGAs to have received an official indication from Health Canada for use in children or adolescents are aripiprazole for use in adolescents 15 years of age and older with a diagnosis of schizophrenia (8,9) or 13 years of age and older for bipolar disorder and lurasidone for use in adolescents 15 years of age and older with a diagnosis of schizophrenia.

In the last decade, a dramatic increase in the prescription of SGAs/TGAs in children and adolescents has been well documented. This is particularly true in the treatment of DBDs including aggression in ADHD, oppositional defiant disorder, conduct disorders, and irritability related to autism spectrum disorders (10–12). This increased use does not come as a surprise given the lack of other effective interventions. This recent

Cochrane review highlights the little evidence available to support the use of these medications in young people, particularly with long-term use.

The increased use of SGA/TGAs is concerning, particularly in the paediatric population for several reasons including the nature of mental disorders. We know that the majority of these disorders have a chronic evolution (13) so if a medication appears to be effective, it may be continued for years or even decades. There is evidence to suggest youth are more susceptible to the adverse metabolic side effects of atypical antipsychotics compared to adults (14,15). A trend has been observed to use this group of medications for longer periods of time than in the past (16,17), and typically without following recommended systematic monitoring for side effects and modifiable cardiovascular risk factors (7,17).

In a recent publication from Chen et al. that studied the prescribing and safety monitoring practices for the use of SGAs/TGAs in children and youth in Alberta, Canada, the authors found that the most frequently dispensed antipsychotic was risperidone (N=3,908), followed by quetiapine (N=2,140), and aripiprazole (N=1,302). The majority of children prescribed risperidone had a diagnosis of ADHD or conduct disorder. Quetiapine was mainly prescribed for insomnia, neurotic disorders or depression, while aripiprazole was prescribed most frequently for conduct disorder or neurotic disorders. They also found that a very small proportion of the children who were prescribed an antipsychotic medication, received the recommended monitoring for metabolic side effects (17). Evidence-based monitoring protocols are available (<http://comesaguideline.org>) for prescribers of SGAs/TGAs to assist in minimizing the risk for poor outcomes, and their use is strongly encouraged. (18)

As physicians, we need to keep in mind our first commitment with our patients which should be 'primum non nocere-above all, do no harm' (19). Although the use of SGAs/TGAs definitely has a role in treating severe mental health disorders including behavioural problems in young people, there is a clear need for better evidence on the efficacy and safe use of antipsychotics.

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