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REVIEW

Antipsychotics in children and adolescents: Increasing use, evidence for efficacy and safety concerns

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Abstract

Second-generation antipsychotics (SGA) are increasingly used to treat children and adolescents. The European College of Neuro-psychopharmacology convened an expert panel to review relevant efficacy and safety data, and identify needs for further research. Controlled studies support the short-term efficacy of several SGA for treating psychosis, mania, and aggression within certain diagnostic categories. Except for clozapine, no clinically significant superiority in efficacy has been demonstrated for any specific antipsychotic, including both first- and second-generation agents, in children and adolescents. Major differences exist, however, with respect to type and severity of adverse effects; therefore the choice of treatment is primarily guided by tolerability and safety considerations. Children appear to be at higher risk than adults for a number of adverse effects, such as extrapyramidal symptoms and metabolic and endocrine abnormalities. While the safety profile during acute and intermediate treatment has been evaluated, the distal benefit/risk ratio during long-term treatment remains to be determined. Research is also needed to understand the mechanisms underlying antipsychotic-induced toxicities in order to develop effective preventive and treatment strategies.
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1. Introduction

Since their introduction into clinical practice, antipsychotic medications have been used in the treatment of children and adolescents with a variety of psychiatric conditions, including psychosis, physical aggression, mania, irritable mood,

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and Tourette's disorder (Findling et al., 2005). In recent years, the pediatric use of antipsychotics has substantially increased, due to an increment in prescription of second-generation antipsychotics (SGA), despite a limited evidence base in support of their efficacy and safety.

Pharmacoepidemiological studies using databases from both the U.S.A and several European countries have documented that the use, although showing wide variability in absolute terms across countries (Zito et al., 2008), has at least doubled during the last ten years (Cooper et al., 2004, Olfson et al., 2006; Aparasu and Bhatara, 2007; Kalverdijk et al., 2008; Rani et al., 2008). In the U.S., pediatric use (i.e., by patients under 19 years of age) accounted for 15% of total use in 2004–2005, as compared with 7% in 1996–1997 (Domino and Swartz, 2008). Moreover, the duration of treatment with these agents has been increasing (Kalverdijk et al., 2008; Rani et al., 2008).

This rapid increase and the recognition that many antipsychotics induce metabolic adverse effects, thus increasing the risk for obesity, diabetes type II, and associated cardiovascular morbidity (Newcomer et al., 2002; Guo et al., 2006; Bobes et al., 2007), have raised concerns about the proper utilization of these agents and stirred controversy among both experts and the general public (Elias, 2006, Harris, 2008). After having been hailed as a safer alternative to first-generation antipsychotics because of their lower tendency to induce neurological effects, the SGA are now recognized to have a high propensity for causing other, equally problematic, adverse effects, thus triggering a reconsideration of their benefit/risk ratio, especially in children (Tyrer and Kendall, 2008; Correll et al., 2006; Correll, 2008a,b; Sikich et al., 2008).

We report on the conclusions of an expert panel convened under the auspices of the European College of Neuropsychopharmacology in Barcelona, Spain, in August 2008, with the task of reviewing the clinical implications of the available data on antipsychotic use in children and adolescents, and identifying critical knowledge gaps in need of further research. The focus of the review was primarily on data from controlled clinical investigations conducted in children and adolescents.

2. Factors contributing to the increased pediatric use of antipsychotics

Multiple factors have likely contributed to the increased pediatric use of antipsychotics. In general, the rising of a medical model for explaining emotional and behavioral disturbances of childhood, as opposed to the psychosocial interpretations of mental illness that had prevailed until the 1980s, has led to greater utilization of medical interventions such as pharmacology. In parallel, it has become apparent that psychiatric disorders often have their onset in childhood, so that conditions such as depression, bipolar disorder, anxiety disorders, and obsessive–compulsive disorders, which were the almost exclusive domain of adult psychiatry, have been increasingly diagnosed and treated also in children and adolescents (Paus et al., 2008).

In particular, the recent tendency of including extreme levels of mood volatility and irritability in the diagnostic construct of bipolar disorder, together with the concomitant regulatory approval of several SGA for the treatment of bipolar disorder in both adults and adolescents, has likely contributed to increase the pediatric use of these medications in the U.S. (Tohen et al., 2007). Notwithstanding the nosological debate about the validity of child bipolar disorder (Moreno et al. 2007), it remains that children with severe mood dysregulation, volatile temper, and aggressive behavior can be profoundly impaired and in need of treatment.

Another major contributor to their popularity among clinicians was the belief that SGA were safer than first-generation antipsychotics, together with the fact that few "user friendly" alternatives may exist for many of these children. For instance, lithium has a narrow therapeutic window and requires repeated blood tests during treatment, and other antiepileptic mood stabilizers may also require blood monitoring. Indeed, SGA were introduced into the adult pharmacopoeia with the expectation that they would be safer, better tolerated, and therefore more clinically versatile than the first-generation antipsychotics. This expectation was based on the fact that the new agents have a much lower propensity to induce neurological adverse effects than the high potency first-generation antipsychotics with high affinity for the dopamine D2 receptor. Extrapyramidal effects were seen to be so intrinsic to the pharmacological activity of traditional antipsychotics that these drugs were called "neuroleptics" because of these effects. Based on their more benign neurological profile, the SGA were called "atypical." In addition, there was an expectation of greater efficacy, especially with respect to improving negative symptoms of schizophrenia. Due to the perceived ease of use, treatment with SGA became more accepted also for non-psychotic conditions, including mood disorders and aggression, both in adults and children (Olfson et al., 2006).

Finally, the rise of the use of antipsychotics in children occurred at a time when the availability of inpatient services for mental health treatment has been, at least in the U.S., greatly curtailed (Case et al., 2007), with consequent pressure on clinicians to stabilize patient behavior as quickly as possible. Antipsychotics can indeed be rapidly effective in decreasing symptoms of psychosis, mood dysregulation, or aggression, which would otherwise lead to hospitalization and prevent or delay discharge to less intensive levels of care.

3. Benefits and risks of antipsychotics in children and adolescents: clinical implications

A few short-term, placebo-controlled trials support the acute efficacy of risperidone, aripiprazole, olanzapine, and quetiapine in decreasing psychotic symptoms of schizophrenia in adolescents and manic symptoms of bipolar disorder in children and adolescents (Sikich, 2008; Chang, 2008; Findling et al., 2008; Kryzhanovskaya et al., 2009). Based on these studies, both risperidone and aripiprazole have recently been approved for the treatment of 13–17 year old adolescents with schizophrenia and of 10–17 year old youths with bipolar mania or mixed episodes in the U.S. In addition, risperidone was found to be effective in decreasing severe behavioral problems, such as aggression, self-injury, and tantrums, in the context of autism (Research Units on Pediatric Psychopharmacology Autism Network, 2002), and is approved for such a use in 5–17 year olds with autism in the U.S.

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In Europe, risperidone is approved for children with aggression in the context of conduct disorder, based on a number of positive, placebo-controlled studies, mostly in aggressive youths with subaverage IQ (Aman et al., 2002; Snyder et al., 2002; Buitelaar et al., 2001), but no SGA has thus far received approval for the treatment of youths with schizophrenia or bipolar mania outside of the U.S.

Antipsychotic treatment is often chronic, as conditions such as schizophrenia, mania, or aggression are persistent or recurrent, and treatment controls symptoms but is not curative. Only a few studies, however, have evaluated the long-term efficacy and safety of these medications in children. Most of the available data come from uncontrolled observational studies of risperidone when used for the management of severe disruptive behavior in children with autism, mental retardation, or normal intelligence over a period of 6–12 months (Aman et al., 2005; Haas et al., 2008; Fraguas et al., 2008; Gencer et al., 2008). At least one small-scale observational study examined outcomes during risperidone treatment in children with below average intelligence over 3 years (Reyes et al., 2006a). Most children with autism who, after showing improvement with risperidone, shifted to placebo under double-blind conditions had recurrence of the behavioral problems (Research Units on Pediatric Psychopharmacology Autism Network, 2005; Troost et al., 2005). Symptom recurrence upon risperidone discontinuation was also observed in non-autistic children with disruptive behavior disorder (Reyes et al., 2006b). Some data are also available on olanzapine use over 6 months (Dittmann et al., 2008). Many of these studies had a relatively modest sample size, which limits the ability to detect less frequent adverse effects (Vitiello et al., 2003).

In adults, one unexpected finding has been that, besides clozapine, the SGA have not consistently demonstrated better efficacy than first-generation antipsychotics, at least in the treatment of adult schizophrenia (Lieberman et al., 2005; Jones et al., 2006; Kahn et al., 2008), even though some agents might offer advantages (Kahn et al., 2008; Leucht et al., 2008; Leucht et al., 2003; Schooler et al., 2005). In children, few controlled studies have directly compared the effects of first- and second-generation antipsychotics. Clozapine has shown superiority over haloperidol or olanzapine in children and adolescents with schizophrenia (Kumra et al., 2008a,b; Shaw et al., 2006). On the other hand, no evidence of differences in efficacy among the remaining antipsychotics has emerged. A pilot, double-blind, randomized, 8-week trial of risperidone, olanzapine and haloperidol was conducted in a total of 50 patients age 8–19 years suffering from prominent psychotic symptoms (Sikich et al., 2004). The small sample size and the diagnostic heterogeneity of the sample prevented deriving inferences about efficacy, even though there were differences in adverse effects. A small, double-blind trial in children with autism reported greater efficacy in decreasing behavioral symptoms with risperidone, and also greater increase in plasma prolactin, than with haloperidol (Miral et al., 2008).

More recently, the Treatment of Early Onset Schizophrenia Spectrum Disorders study (TEOSS), a larger, publicly funded, four-site, randomized, double-blind, controlled clinical trial, compared olanzapine (2.5–20 mg/day), risperidone (0.5–6.0 mg/day), and molindone (10–140 mg/day) for the treatment of patients age 8–19 years (mean 13.8; less than one-third with age 16 or older) with a diagnosis of schizophrenia (66%) or schizoaffective disorder (34%) over a period of 8 weeks (Sikich et al., 2008). A total of 119 patients were randomized. At the end of the 8 weeks, the response rate (defined as at least a 20% reduction in the Positive and Negative Symptom Scale score plus the completion the 8-week acute treatment phase) was not different in the olanzapine (34%), risperidone (46%), and molindone (50%) groups.

Within the limitations imposed by the study sample size, TEOSS found no evidence to support the superiority of these SGA over a conventional antipsychotic. Although not different in efficacy, the three TEOSS medications showed a distinctive different safety profile: olanzapine induced more weight gain, hypercholesterolemia, and insulin elevation; risperidone increased serum prolactin; and molindone caused akathisia. The more recent introduction of ziprasidone and aripiprazole, with their specific tolerability profile, has further increased the heterogeneity of the SGA category with respect to safety/tolerability. Consequently, the safety/tolerability profile of these mediations and its implications for physical health, subjective well-being, and treatment adherence have emerged as the main considerations in the choice of an antipsychotic in youth (Arango et al., 2004).

The data in children and adolescents are overall consistent with those in adults, where a wide heterogeneity in tolerability profile within both first- and second-generation antipsychotics has been documented, with no evidence of specific efficacy of SGA on negative symptoms (Leucht et al., 2008). Moreover, also the SGA can, with a varying degrees, cause extrapyramidal adverse effects (Correll, 2008b), and metabolic adverse effects can emerge during treatment also with first-generation antipsychotics (Correll and Carlson, 2006; Correll, 2008a), thus blurring the separation between these two categories of antipsychotics.

There are indications that children are more sensitive than adults to the metabolic adverse effects of SGA, as well as to the extrapyramidal effects of the first-generation antipsychotics (Correll et al., 2006). Children tend to gain proportionately more weight and do so more rapidly during treatment than adults (Correll and Carlson, 2006). In a recent randomized trial comparing olanzapine versus quetiapine, in adolescent patients with a first psychotic episode, the increment in weight was 15.5 kg and 5.5 kg over 6 months respectively. These increments are rarely seen in adults (Arango et al., 2009). Consistently across studies and like in adults, olanzapine seems to be especially prone to inducing metabolic adverse effects and related adverse health outcomes (Sikich et al., 2008; Fraguas et al., 2008; Castro-Fornieles et al., 2008). Based on currently available data, it appears that olanzapine cannot be considered a first-line antipsychotic medication for the treatment of children and adolescents.

Because drug-induced metabolic changes can persist over time and may not be fully reversible upon drug discontinuation, the implications for distal health outcomes can be profound. Age-inappropriate weight gain and obesity increase the risk for a variety of negative outcomes, such as diabetes, hyperlipidemia, and hypertension, which are major risk factors for cardiovascular diseases and reduced

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quality of life and life expectancy (Correll and Carlson, 2006).

Also the effects on prolactin may be more marked in adolescents than in adults. One analysis combining the data from five clinical trials in 5–15 year old children treated with risperidone found a rapid rise of serum prolactin after starting treatment with a peak by 2 months, followed by a gradual return to normal levels by 5 months (Findling et al., 2003). However, in a different study, in 5–17 year old children with autism, the risperidone-induced increase in prolactin, though declining, was still significantly evident after 22 months of treatment (Anderson et al., 2007). In another study, hyperprolactinemia was present in 78.6% of youths treated with SGA for less than a month, and in 48.5% of those treated for longer than 1 year (Laita et al., 2007). Prolactin increase is an issue especially for children and adolescents treated with risperidone (Staller, 2006; Sikich et al., 2008), but can occur with other antipsychotics as well, including olanzapine (Dittmann et al., 2008), while aripiprazole seems to decrease prolactin plasma levels (Findling et al., 2008). Since youths may be less likely to express concern about sexual dysfunction, prolactin elevations may persist at subclinical levels. The long-term consequences of such elevations are currently unknown (Correll and Carlson, 2006).

In addition to the intrinsic pharmacological activity of the prescribed medications, treatment safety depends on the quality and intensity of the clinical management of the patients. The development of clinical guidelines for minimizing metabolic and endocrine adverse effects of antipsychotics children and adolescents represents a useful advancement (American Diabetes Association et al., 2004; Correll and Carlson, 2006; Correll, 2008a,b). Physical examination and both personal and family history taking before starting antipsychotic treatment can identify patients at high risk for metabolic syndrome, and periodic measurements of weight, body mass index, waist circumference, blood pressure, serum lipid and glucose during treatment can lead to early recognition of drug-induced adverse effects. Measuring serum prolactin is currently not routinely recommended by many experts, but reserved to cases with clinical symptoms of hyperprolactinemia (Correll, 2008b). However, reports that some children treated with antipsychotics present with very high increases in prolactin during the first few months of treatment that in some cases is sustained, and the role of hyperprolactinemia in osteoporosis and reproductive problems are reasons for concern.

4. Research implications

The large and steep increase in pediatric use stands in stark contrast with the relative paucity of data from controlled investigations in this age group, especially when considering that most of the use is for the management of non-psychotic conditions, such as aggression, disruptive behavior and mood dysregulation (Olfson et al., 2006). The limitations of the current evidence base for efficacy and safety are particularly evident with respect to data informing on outcomes during chronic treatment.

As mentioned above, these medications are often prescribed chronically as they are not curative and relapse is frequent upon discontinuation. The dearth of information leaves clinicians and families with making assumptions about long-term effectiveness and safety based on short-term investigations. The whole experience with SGA, however, shows that relying on relatively short-term information can lead to overoptimistic expectations. Therefore, a systematic investigation of the benefits and risks of chronic antipsychotic treatment is urgently needed.

Going beyond short-term (i.e., less than 6 months) and intermediate-term (i.e., less than 18 months) studies would have the potential to assess the distal risk/benefit ratio when both illness outcomes and drug-induced toxicities are taken into account. In fact, any treatment-associated risk should be weighed against the potential benefit of alleviating psychopathology and improving functioning.

As treatment is administered at a time of rapid brain development, there is a need to evaluate the possible impact, either favorable or detrimental, of antipsychotic medications on cognition and other aspects of brain maturation at various ages and duration of exposure. Only very limited data are currently available about cognitive functioning during antipsychotic treatment in children (Aman et al., 2008). In addition to helping identify the effects of medications on physical, mental, and sexual development, it will also be necessary to determine if such effects are either partially or fully reversible, and under which circumstances. In this context, more animal studies are also needed to assess the effects of antipsychotic exposure on neurotransmitter systems development (Moran-Gates et al., 2006).

As it is evident that both first- and second-generation antipsychotics are heterogeneous categories with respect to safety profile, conclusions cannot be easily extrapolated from one compound to another. While, on the one hand, this heterogeneity complicates the process of evaluating safety, because it requires separate investigations for each drug, on the other hand, it offers a variety of treatment options to clinicians and patients, with the potential for eventually tailoring treatment to the specific needs and characteristics of individual patients. Thus, the risk of metabolic adverse effects is much greater for certain drugs, such as clozapine and olanzapine, than for others, such as aripiprazole or ziprasidone.

However, antipsychotics with lower metabolic risk may cause other types of adverse effects, such as akathisia in the case of aripiprazole (Correll 2008a) and QTc prolongation in the case of ziprasidone (Haupt, 2006; Correll, 2008a,b), while no QTc prolongation has been detected in children with other antipsychotics (de Castro et al., 2008). Nevertheless, the clinical relevance of mostly modest QTc prolongations with ziprasidone is unclear in adults as well as youths, whereas age-inappropriate weight gain and metabolic dysfunction has clearly identified adverse health consequences.

Data in adults suggest that the risk of developing adverse outcomes such as diabetes during treatment with SGA can be predicted by the presence of pre-treatment risk factors (Cavazzoni et al., 2004). If predictors were identified in children, this information could help guide clinical practice by matching treatment to patient risk profile.

Information about the long-term and distal effects of medications can be only in part derived from controlled clinical trials. Retrospective analyses of large databases of

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naturalistically treated patients can provide useful clues to the presence of rare and infrequent adverse effects, such as agranulocytosis, diabetic ketoacidosis, or neuroleptics malignant syndrome. Prospective registries of naturalistically treated patients can inform on the risk of outcomes such as tardive dyskinesia or diabetes.

Research is also needed to identify effective strategies for preventing and managing antipsychotic-induced adverse effects (Klein et al., 2006; Correll, 2008a). A clear understanding of the precise mechanisms through which many antipsychotics induce weight gain seems to be an essential step toward developing specific remedies. While the obvious attention is on drug effects on the dopaminergic system, other neurotransmitters, such as histamine, glutamate, or acetylcholine, may be involved (Kim et al., 2007). As antipsychotic-induced adverse effects may be moderated by genetic polymorphisms (Correll and Malhotra, 2004), the identification of genetic risk for specific toxicities might lead to more targeted treatment approaches.

In conclusion, the current pediatric use of antipsychotics represents a situation of a clinical practice that has expanded much more rapidly than its evidence base. Both the clinical needs of children being treated and the potential seriousness of some of the drug-induced adverse events call for a vigorous research agenda to determine both the full therapeutic value and the distal risks of these medications during development. Given the substantial heterogeneity of the safety profile of both first- and second-generation antipsychotics, a personalized approach to treatment decisions, hopefully eventually guided by genetics and other neurobiological data, seems to be especially appropriate and potentially useful. In the meantime, until reliable risk indicators for antipsychotic-related adverse effects with significant impact on physical and psychiatric outcomes are known, treatment should rely on a carefully weighted choice of antipsychotics based on clinical consideration of patient characteristics and needs, and on routine and proactive monitoring of both therapeutic benefit and adverse effects.

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Contributors

Drs. Vitiello, Correll, van Zwieten-Boot, Zuddas, Parellada, and Arango participated in the data review and discussions and at the ECNP TEM.

Dr. Vitiello prepared the manuscript, which was critically reviewed by the other authors.

All authors approved the final version of the manuscript, which is being submitted for publication.

Conflict of interest

Drs. Vitiello and van Zwieten-Boot have no potential conflicts of interest.

Dr. Correll has been a consultant to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Supernus and Vanda, has served on the speaker's bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka and Pfizer, and has received grant/research support from the American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb, The Feinstein Medical Research Center, NARSAD, the National Institute of Mental Health.

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