Journal of Pharmacovigilance and Drug Research

April-June 2022
JPADR, 2022; 3(2): 4-10.
DOI: 10.53411/jpadr.2022.3.2.2



REVIEW ARTICLE

Journal home page: www.jpadr.com

Safety and tolerability of antipsychotic drugs in pediatric patients

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ARTICLE INFO

Received 14 February 2022;
Revised 28 April 2022;
Accepted 17 May 2022.

Keywords:
Antipsychotics, Pediatric, Safety, Tolerability, FGAs, SGAs

ABSTRACT

OPEN ACCESS

Introduction: Second-generation antipsychotics have seen a significant surge in use for a variety of pediatric psychiatric problems over the last decade, typically as off-label prescriptions. Although they were previously regarded to be safer than older, first-generation antipsychotics, owing to a lower incidence of neurological side effects, current research has raised serious concerns about their metabolic, endocrinological, and cardiovascular side effects.

Methods: The Cochrane Library, PubMed, Embase, and PsychINFO databases were searched for scientific articles between the periods 2009 and 2022. We included studies that reported pediatric patients taking second-generation antipsychotic drugs. The obtained information was evaluated, compiled, analyzed, interpreted, and conclusions were reached

Results: In total, 45 articles were reviewed. The most common and troublesome adverse effects were metabolic, with increasing evidence of a higher risk of type 2 diabetes mellitus. Furthermore, findings showed that different second-generation antipsychotics may have different safety profiles.

Conclusion: In this review, we discussed the safety and tolerability of second-generation antipsychotics in pediatric patients, as well as active monitoring measures that could help pediatricians and child psychiatrists prevent, detect, and manage side effects. The benefits of relieving often severe and debilitating manic, psychotic, and violent symptomatology must be weighed against the various risks of adverse effects associated with individual antipsychotic drugs in pediatric patients when making treatment decisions. Any antipsychotic treatment should begin and end with a consideration of side effects, as well as food and lifestyle advice. Patients and their families should be included in a risk-benefit analysis when considering an antipsychotic treatment. To improve patient outcomes, routine, proactive monitoring of side effects is required.

An official publication of Global Pharmacovigilance Society.

Introduction

Antipsychotic drugs (APs) are increasingly used to treat a variety of psychiatric disorders in pediatric patients. These drugs are not similar. Each has a distinct pharmacologic profile and may differ substantially in terms of adverse effects (Onishi *et al.*, 2021). However, when applied to pediatric patients, their safety and tolerability profiles differ from those seen in adult patients. It is important to note that the term pediatric patients refer to both children and adolescents. Children are defined as patients aged 6 to 12 years, while adolescents are those aged 13 to 17 years

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Available online 1 June 2022

(Dinnissen *et al*., 2020). The findings of this study emphasize the importance of continuous, thorough, and cautious monitoring of pediatric patients using second-generation antipsychotics

Antipsychotic Drugs: Types, Classes, and Mechanism of Action

Antipsychotic drugs, also known as antipsychotics or neuroleptics, are a class of psychotropic medication used to treat psychosis (such as delusions, hallucinations, paranoia, or disordered thinking), most commonly in schizophrenia but also in other psychotic disorders (Lally & MacCabe, 2015). They are also used, in the treatment of bipolar disorder, together with mood stabilizers (Grande, Berk, Birmaher, & Vieta, 2016).

Antipsychotics are categorized into two groups: typical or first-generation antipsychotics (FGAs) which include Chlorpromazine, Droperidol, Fluphenazine, Haloperidol, Loxapine, Perphenazine, Pimozide, Prochlorperazine, Thioridazine, Thiothixene, Trifluoperazine and atypical or second-generation antipsychotics (SGAs) which include Aripiprazole, Asenapine, Clozapine, Iloperidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, and Ziprasidone (Grinchii & Dremencov, 2020). First-generation antipsychotics were first introduced in the 1950s, and others were developed until the early 1970s. Clozapine was the first second-generation antipsychotic to be introduced in the early 1970s, followed by others (Aringhieri *et al*., 2018; Chokhawala & Stevens, 2022). The common activity of both of these groups appears to be postsynaptic blockade of brain dopamine D_2 receptors. Aripiprazole is an exception because it is a D2 partial agonist. Several major research studies support the role of these receptors in antipsychotics activity, noting a link between receptor binding and pharmacologic potency (Chokhawala & Stevens, 2022; Thompson, de Vries, & Sommer, 2020).

Second-generation antipsychotics differ from older antipsychotics in that their affinity for serotonin 5-HT receptors can exceed that of dopamine D2 receptors (Kalverdijk *et al*., 2017). In addition, also differ in how tightly they bind to D2 receptors. They also differ in other aspects of their pharmacology, making each medication distinct in terms of side-effect profile, dosing regimen, rate of absorption, rate and mode of elimination, and drug-drug interactions (Esther S. Lee, 2018; Grinchii & Dremencov, 2020). Several improvements have been made to the pharmacodynamics profile of these drugs during their development, including decreased dopamine receptor occupancy and serotonin receptor blockade in the cortical limbic pathways (Escudero, Gutierrez-Rojas, & Lahera, 2020). These modifications lowered the occurrence of serious adverse drug reactions resulting in a greater perceived level of safety compared to first-generation antipsychotics (Neumeier *et al*., 2021). This is one of the most important factors that has led to a significant increase in the use of antipsychotics, particularly the second-generation, to treat pediatric patients over the last two decades (Coronado, Dunn, Veronin, & Reinert, 2021).

Uses of Antipsychotic Drugs in Adult and Pediatric Patients

First-generation antipsychotics were initially shown to provide efficacious treatment for schizophrenia, acute and chronic psychosis, postpartum psychosis, acute mania and hypomania, and management of neuropsychiatric symptoms of dementia and bipolar disorders in adults (Saucedo Uribe *et al*., 2020). However, Extrapyramidal symptoms (EPS) such as stiffness, bradykinesia, tremor, and restlessness are caused by these medicines. They can also cause tardive dyskinesia and hyperkinetic, involuntary movements, which are especially noticeable in the face and extremities (Cakir, Yalin Sapmaz, & Kandemir, 2021; Shafiq & Pringsheim, 2018).

Second-generation antipsychotics were developed and initially used as treatments for psychotic illnesses in adults (Willner, Vasan, & Abdijadid, 2022). While there remains a public discussion about the use of antipsychotic medications in pediatric patients, the prescription of these drugs to young people continues to increase (Loy, Merry, Hetrick, & Stasiak, 2017; McClellan, Stock, American Academy of, & Adolescent Psychiatry Committee on Quality, 2013). Pediatric patients have been primarily using second-generation antipsychotics for non-psychotic conditions such as aggression, irritability, and dysfunctional behavior in the context of autism and pervasive developmental disorders, aggressive behavior in patients with disruptive behavioral disorders (DBDs), manic and mixed episodes in bipolar disorder, resistant attention deficit hyperactivity disorder (ADHD), Tourette's syndrome and other tic disorders, and obsessive-compulsive disorder (OCD) (Dinnissen *et al*., 2020; Esther S. Lee, 2018; Onishi *et al*., 2021)

In fact, it appears that aggression, rather than psychosis, is the most common symptom for which second-generation antipsychotics are prescribed to pediatric patients (Albers, Nair, & Shankar, 2021; Coustals, Menard, & Cohen, 2021; Walkup & Work Group on Quality, 2009).

Off-label Use of Second-Generation Antipsychotic Drugs

Second-generation antipsychotics were marketed as having fewer negative side effects, such as extrapyramidal symptoms, when compared to conventional antipsychotics (Pillay *et al.,* 2017). As a result, they were extensively used not only for the US Food and Drug Administration (FDA)-authorized indications but also for other disorders not approved. Given the uncertainties around the effectiveness and safety of second-generation antipsychotics, off-label usage is controversial (Sohn, Moga, Blumenschein, & Talbert, 2016). Several post-marketing clinical trials reported serious adverse side effects, including metabolic

syndrome, cardiovascular events, or mortality. Despite this, these medications are one of most prescribed classes of pharmaceuticals among pediatric patients in the United States (Hales, Kit, Gu, & Ogden, 2018; Sohn *et al*., 2016). Risperidone and aripiprazole are currently FDA-approved for treating pediatric patients with irritability associated with autism (5-16 years for risperidone and 6-17 years for aripiprazole). Risperidone, aripiprazole, olanzapine, and quetiapine have also been approved by the FDA for the treatment of adolescents with schizophrenia (ages 13-17) and youths aged 10 to 17 with bipolar I disorder who are experiencing mixed or manic episodes. Despite these limited FDA indications, second-generation antipsychotics are still widely prescribed in pediatric patients for a variety of additional conditions such as impulse regulation disorders (Walkup & Work Group on Quality, 2009).

Side Effects of Second-Generation Antipsychotic Drugs

Extrapyramidal side effects are less common in second-generation antipsychotics than in first-generation antipsychotics. Diabetes, weight gain, hyperlipidemia, hyperprolactinemia, and sudden death are among side effects of second-generation antipsychotics. These side effects can occur at any time during treatment, but others may only appear after long-term use (Klein *et al*., 2020). As per the FDA recommendations, all patients should have their personal and family history of diabetes mellitus, dyslipidemia, weight and height monitored, as well as their waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile (Saucedo Uribe *et al*., 2020). Each medicine has its own set of adverse effects. Dizziness, anxiety, sedation, and extrapyramidal adverse effects have all been linked to risperidone *(Kloosterboer et al*., 2021). Paliperidone can cause temperature sensitivity to hot or cold temperatures and QTc prolongation (Jarema, Bienkowski, Heitzman, Parnowski, & Rybakowski, 2017). Olanzapine has been associated most frequently with weight gain, increased appetite, and somnolence (Alisauskiene *et al*., 2021). Quetiapine is the least likely to cause extrapyramidal side effects. Its most common side effects are somnolence, orthostatic hypotension, and dizziness (Maan, Ershadi, Khan, & Saadabadi, 2022). Ziprasidone has almost no weight gain but can cause prolongation of QTc (Bouchette, Fariba, & Marwaha, 2022). Aripiprazole's most common side effects are agitation, headache, and akathisia-like restlessness (Preda & Shapiro, 2020). Asenapine can cause an increase in serum prolactin concentrations, weight gain, and prolongation of QTc (Marazziti, Mucci, Falaschi, & Dell'Osso, 2019). Clozapine can cause hyper salivation, tachycardia, hypotension, and anticholinergic side effects. Clozapine is unusual in that it suppresses dyskinesia. It can also cause clinically important agranulocytosis and leukopenia; and therefore, requires monitoring of white blood cells and absolute neutrophil count (Khokhar, Henricks, Sullivan, & Green, 2018). Clozapine can also cause the rare side effect of cardiomyopathy and myocarditis (de Leon, Ruan, Schoretsanitis, & De Las Cuevas, 2020; Sultan, Olfson, Correll, & Duncan, 2017).

Safety and Efficacy of Antipsychotic Drugs in Pediatric Patients

In terms of safety and efficacy in pediatric patients, it has not been proven for Asenapine, olanzapine, clozapine, iloperidone, lurasidone, and ziprasidone. Manufacturers of second-generation antipsychotics warn against their use in pediatric patients with a history of seizure disorders, since these medications may lower seizure threshold (DelBello, Tocco, Pikalov, Deng, & Goldman, 2021). Aripiprazole and quetiapine, are FDA-approved for the treatment of depressive episodes in bipolar I disorder or as adjunctive treatment for major depressive disorders in adults, but not in pediatric patients. Therefore, if prescribed for this age group, the risk of suicidality may still exist (Sohn *et al*., 2016).

Monitoring of Antipsychotic Drugs in Pediatric Patients

When evaluating side effects, a clinician should take into account the objective severity of the side effects, as well as the subjective distress in the individual patient, since both of these factors have a role in non-compliance and treatment failure (Urban & Cubala, 2017). Furthermore, prior to starting therapy, the healthcare team, patient, and parents should be informed about the risks of taking a second-generation antipsychotic. Because these medications are associated with significant weight gain and metabolic changes, a baseline for weight should be established and the patient weight and metabolic changes should be monitored on a regular basis (American Academy of Child Adolescent Psychiatry Committee on Quality Issues, 2020; Dinnissen *et al*., 2020). As a result, in clinical practice, proper monitoring of potential adverse medication reactions, as well as reducing adverse events once they have begun, is critical (Stroup & Gray, 2018). Available guidelines for antipsychotic use in pediatric patients emphasize the importance of conducting assessments before starting antipsychotics. Following up regularly and systematically, should include a review of treatment response, extrapyramidal and prolactin-related adverse effects, a review of various cardiometabolic parameters, such as length, weight, waist circumference, as well as blood pressure, pulse, and glucose and lipid levels (Du, Chen, Jin, Yuan, & Wang, 2020; Mead, Ayres, Blake, & Scott, 2021; National Institute for Clinical Excellence, 2019; Siegel *et al*., 2020; Walter *et al*., 2020). Moreover, several guidelines also recommend regular evaluation of the need of the antipsychotic treatment for nonpsychotic indications, as stated by the American Academy of Child and Adolescent Psychiatry (AACAP) (American Academy of Child Adolescent Psychiatry Committee on Quality Issues, 2020). In spite of all that, it's unclear how closely pediatric patients treated with antipsychotics are followed in clinical practice in accordance with these recommendations.

Recommendations for the Use of Antipsychotic Drugs in Pediatric Patients

According to the AACAP, recommendations for best assessment and treatment practices are stated in accordance with the strength of the underlying empirical and/or clinical support, as follows (American Academy of Child Adolescent Psychiatry Committee on Quality Issues, 2020):

Recommendation 1. A thorough diagnostic assessment, attention to comorbid medical conditions, a review of other drugs the patient is being prescribed, the creation of a multi-disciplinary plan, including education and psychotherapeutic interventions for treatment and monitoring of improvement, and a thorough discussion of the risks and benefits of psychotropic treatment with both the youth and their guardians are all included in these guidelines and principles.

Recommendation 2. Once a clinician determines that a patient may benefit from therapy with a second-generation antipsychotic, the choice of a particular medication, the dosing schedule, and the safety monitoring should all be guided by the latest scientific evidence and most recent data.

Recommendation 3. Because there is limited short- and long-term safety data for second-generation antipsychotics in pediatric patients, it is important to pay close attention to family history (when available) and personal history of underlying medical conditions.

Recommendation 4. To reduce the danger of adverse effects, the goal of treatment should be to utilize the smallest effective dose possible. The upper limit of dosage for a second-generation antipsychotic should not exceed the maximum recommended dose for adults, based on currently available research.

Recommendation 5. Scientific evidence suggests that different doses are required for different conditions and target symptoms. Furthermore, differences in dosing among individuals may occur as a result of allelic variations. The proper target dose should be determined using both current scientific evidence and the patient's clinical response, while also monitoring the patient for side effects and tolerance.

Recommendation 6. If a second-generation antipsychotic is clinically beneficial but side effects are a concern, gradually reducing the dose and observing the response is recommended. If the negative effects have subsided, increasing the dose gradually can be considered again.

Recommendation 7. In clinical practice, a significant number of hospitalized pediatric patients take multiple psychotropic medications. Unfortunately, there is limited information regarding the long-term use of combinations of medications in pediatric patients. As a result, using second-generation antipsychotics as part of a polypharmacy regimen requires careful consideration, and they should be avoided if at all possible.

Recommendation 8. Consideration of medication combinations should only begin after patients are refractory to medication trials of each second-generation antipsychotic and, perhaps older antipsychotic agents or other evidence-supported agents (such as mood stabilizers) at the appropriate target dose(s) and adequate length of treatment.

Recommendation 9. If a patient fails to have an adequate response after reaching the target dose for an adequate trial length (generally four to six weeks), the need to switch to an alternative second-generation antipsychotic is not always indicated. Re-evaluation of the initial diagnosis, assessment for comorbid conditions, and the redefining of targeted symptoms may lead to try a trial of a different class of medication in these patients.

Recommendation 10. There is limited short-term safety and even less long-term safety data in pediatric patients treated with second-generation antipsychotics. Increased monitoring of the potential side effects is therefore needed. Ideally, monitoring of BMI, blood pressure, fasting blood glucose and fasting lipid profiles should follow the recommendations found in the consensus statement by the American Diabetes Association and the American Psychiatric Association.

Recommendation 11. Parents and patients should be warned about the possibility of weight gain before starting therapy with second-generation antipsychotics, and recommendations for healthy nutrition and exercise should be given. At baseline and regular intervals, BMI should be plotted on age specific diagrams. Consideration of weight management interventions and increased regularity of blood glucose and lipid levels should be implemented if second-generation antipsychotic induced weight gain exceeds 90th percentile BMI for age, or a change of five BMI units takes place in those pediatric patients who were obese at the beginning of treatment.

Recommendation 13. Elevated lipid levels, even early in life, have been linked to the development of cardiovascular disease later in life, according to research. As a result, while using second-generation antipsychotics, these risks should be carefully considered, especially in pediatric patients who have gained significant weight and have a positive family history. When a patient's family history is unavailable, it's very important to think carefully about medication selection and monitoring. Further examination or management should be undertaken in pediatric patients who have significant weight changes.

Recommendation 15. Because there is minimal data on the cardiovascular effects of second-generation antipsychotics in pediatric patients, doctors should consider following the American Heart Association's guidelines. These guidelines include obtaining a detailed family history of sudden or

inexplicable deaths, obtaining a detailed patient history of syncope episodes or palpitations, and considering alternative therapies. A baseline EKG and subsequent monitoring should be carefully considered.

Recommendation 18. The necessity for a second-generation antipsychotic should be assessed on a regular basis. Multiple aspects, including the severity of symptoms, psychosocial situations, and the natural course of the condition being treated, should be considered when determining therapy length.

Recommendation 19. Withdrawal dyskinesia is one of the risks associated with abruptly stopping these medications. As a result of symptom exacerbations, the abrupt removal of a medicine that has been alleviating symptoms may potentially clinically destabilize a patient. The withdrawal of a second-generation antipsychotic should be carefully planned, and the clinician should keep a close eye on the patient. These medications should not be abruptly stopped unless a significant and/or dangerous side effect has emerged.

AACAP practice parameter limitations

The AACAP practice criteria were developed to help doctors in psychiatric decision-making. These guidelines aren't meant to be the exclusive standard of care. The physician must make the final decision about a patient's care based on all of the circumstances provided by the patient and his or her family, diagnostic and treatment choices available, and accessible resources (Walkup & Work Group on Quality, 2009).

Conclusion

The findings of this study emphasize the importance of continuous, thorough, and cautious monitoring of pediatric patients using second-generation antipsychotics. The benefits of relieving often severe and debilitating manic, psychotic, and violent symptomatology must be weighed against the various risks of adverse effects associated with individual antipsychotic drugs in pediatric patients when making treatment decisions. Any antipsychotic treatment should begin and end with a consideration of side effects, as well as food and lifestyle advice. Patients and their families should be included in a risk-benefit analysis when considering an antipsychotic treatment. To improve patient outcomes, routine, proactive monitoring of side effects is required. Long-term studies are needed to better monitoring by all specialists working in the field of pediatrics (physical and mental) health. The long-term effectiveness of second-generation antipsychotics in pediatric patients has to be improved, however empirical data on pediatric populations is currently lacking. While there is an increasing body of evidence evaluating the use of second-generation antipsychotics in pediatric patients, methodologically robust trials evaluating the efficacy and acute and long-term safety of these medications are still needed.

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