Safety Issues With Drug Therapies for Autism Spectrum Disorders

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Although currently no medication has been approved to treat autism spectrum disorders, survey data show that community practitioners are prescribing a broad range of medication treatments, including, but not limited to, antidepressants, stimulants, antipsychotics, alpha agonists, and anticonvulsants. Patients with autism spectrum disorders are also taking alternative treatments, including herbal remedies, immunologic treatments, and vitamin therapies, which may themselves produce side effects and/or create drug interactions with traditional medications. Although short-term data on the efficacy and safety of commonly prescribed treatments for autism spectrum disorders are increasing, few data are currently available on long-term treatment for autism spectrum disorders, but available studies and clinical experience can offer preliminary recommendations on the safety of and monitoring needs for the medications currently used for these disorders. Monitoring the safety and tolerability of drugs used in patients with these disorders should minimize the burden of side effects and optimize treatment outcome.
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Although no medication has yet been approved to treat autism spectrum disorders, clinicians appear to be frequently prescribing off-label psychotropic medications, and often in combination. In the late 1990s and early 2000s, several researchers conducted large surveys[1–3] of psychotropic use by patients with autism. Approximately 50% to 60% of individuals who responded to those surveys reported receiving psychotropic drugs, antiepileptic drugs, or vitamin treatments. Of those receiving psychotropics, more than half noted taking 2 or more medications for their disorder. The high rate of polypharmacy in these samples increases further when alternative treatments, including herbal remedies and vitamin therapies, are included. These alternative treatments represent a wide mixture of compounds, such as herbs, vitamins, nutritional supplements, and chemicals (such as chelating elements). Besides the possibility of direct associations with side effects, such compounds carry with them the possibility of creating drug interactions, which leads to the recommendation that clinicians should routinely ask patients and their families whether any alternative treatments are being used in conjunction with more standard medications.

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The surveys[1–3] of medication use in autism determined not just the number of medications given but the different classes as well (Table 1). The results of these surveys show that there is a relatively broad mix of psychotropics that are frequently used in the treatment of autism spectrum disorders. This article will examine the safety profile of each of these classes of medications, except for the anticonvulsants, and then give tactics that the clinician can use to manage their use. The anticonvulsants are thoroughly discussed in the neurology literature, and interested readers are referred to other reports.

Although studies[4] are underway that will yield more information on the side effects of medications used for autism spectrum disorders, few data are currently available on long-term treatment. As such, the following recommendations may change as more data on the safety and monitoring of medications used as treatment for autism spectrum disorders become available.

ANTIDEPRESSANTS

Safety

In 2000, a literature review[5] noted that there were 26 studies describing the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in treating patients with autism spectrum disorders. However, few studies of SSRIs for autism spectrum disorders have included a systematic review of associated adverse events. From clinical experience, it appears that the most common side effects seen with the SSRIs tend to be gastrointestinal side effects, nausea and vomiting, sedation, and drowsiness. Also, SSRIs are associated with activation, agitation, insomnia, and

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Table 1. Agents Most Commonly Employed in Autism Spectrum Disorders[a]

Antidepressants (primarily selective serotonin reuptake inhibitors): 20% to 25%
Neuroleptics (especially second-generation antipsychotics): 10% to 15%
Stimulants: 10% to 15%
Alpha agonists: 10%
Anticonvulsants: 5% to 10%

[a]Data from Langworthy-Lam et al.,[1] Aman et al.,[2] and Martin et al.[3]

increased activity, sometimes described as manic-like excitement or hypomania, as well as mood effects such as increased anxiety or mood lability. The frequency of these side effects has not yet been determined, but clinical experience suggests these responses are more common in atypically developing individuals, such as patients with autism spectrum disorders. At present, there are no validated predictors of the agitation and disinhibition sometimes seen associated with SSRI exposure. Such reactions should be a part of a description of possible side effect risk given to patients and their families.

Additionally, clinicians should keep in mind the U.S. Food and Drug Administration's (FDA's) black box warning for increased suicidal thinking and behavior in pediatric populations taking antidepressants. Although the FDA's review of antidepressants was drawn from clinical trial experience with pediatric patients with mood and anxiety disorders, the risk of increased suicidality must be mentioned when discussing the possible risks and benefits of antidepressant treatment with patients and their family members. Studies are underway that should help to clarify the degree of risk of disinhibition and self-injurious behavior in children with autism spectrum disorders.

While researchers and clinicians are attempting to learn more about predictors of side effects when treating autism spectrum disorders with antidepressants, higher doses of antidepressants seem to be associated with side effects more frequently than lower doses. Early studies of antidepressants in the treatment of patients with autistic spectrum disorders used higher dose ranges than what is currently common in clinical practice. For example, early fluoxetine treatment studies[6,7] with these patients employed doses ranging from 20 to 80 mg/day, even in school-aged populations. Perhaps it is not surprising that rather high rates of some of the more common SSRI side effects were observed. The side effect reports from those earlier studies may not reflect what will be seen in current clinical practice.

It is likely that the side effects of the SSRIs also vary according to their individual pharmacokinetic profiles, which differ in their degree of nonlinearity (Figure 1). In the drugs with the highest nonlinearity, even modest dose increases can cause large increases in bioavailable medication. With these medications, side effects may be less predictable and more commonly encountered as dosage is increased. The medications with lower nonlinearity may be more predictable with respect to adverse events associated with dose increases.

There are also differences in elimination half-lives among the SSRIs, which is important in minimizing side effects when switching medications, attempting to optimize dosage, and combining SSRIs with other treatments (see Figure 1). The medications with the highest nonlinear pharmacokinetic profiles tend also to possess longer terminal half-lives. Medicines with extended terminal half-lives need a longer period of time to clear before fully adding in a new drug than medications with shorter half-lives.

Although the SSRIs do carry some side effect risks, few laboratory abnormalities or medically significant side effects have been noted. However, some exceptions exist. Clomipramine, a tricyclic antidepressant with prominent serotonergic effects studied as a treatment to reduce repetitive behaviors in autism spectrum disorders, has additional cardiovascular risks and other side effects, including reduction in seizure threshold, that give it a very different side effect profile from the SSRIs. However, antidepressants in general have a good safety track record in the treatment of autism spectrum disorders within low-to-moderate dose ranges.

Management Tactics

Activation, which is one of the most problematic side effects of antidepressant treatment for autism spectrum disorder, may occur in up to 20% of patients treated with SSRI medications.[7] Activation is especially important to remember when treating younger patients, given some suggestion that young age carries a higher risk for activation than adult age. The best strategy to avoid activation is using the lowest effective dose and a slow titration schedule, much slower than what would be typical for a mood disorder in an adult. As a result, initiation of an SSRI and initial titration may require as long as 8 to 10 weeks to achieve moderate total daily doses. Open-label studies[8,9] of atypical antidepressants such as mirtazapine may suggest alternatives to SSRIs worth considering. Close monitoring of a patient's mood may aid in early detection of activation. In patients with autism spectrum disorders, mood lability, difficulty settling at night, irritability, and mild agitation may be harbingers of an activation syndrome. If it is suspected that activation is occurring, the clinician may be able to avoid it by reducing the dose or further slowing down the speed of titration of the antidepressant.

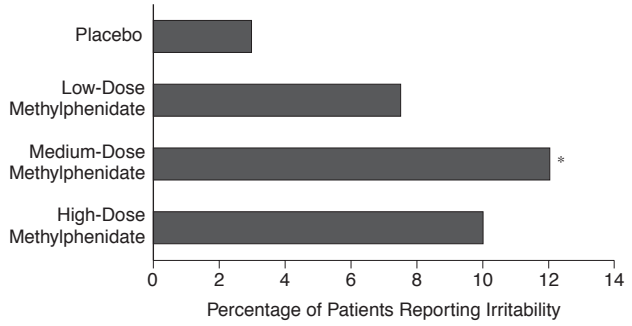
An important part of monitoring patients is awareness of concomitant drugs that may alter metabolism, including alternative treatments. Adverse events associated with alternative treatments may cloud the tolerability of a standard treatment given concomitantly, e.g., nausea associated with vitamin supplementation may inaccurately be

Figure 1. Nonlinearity and Half-Lives of the Selective Serotonin Reuptake Inhibitors[a]

Greatest Nonlinearity Side Effects Less Predictable More Side Effects as Dose Increases	Paroxetine Fluoxetine Citalopram Escitalopram Sertraline Fluvoxamine	Least Nonlinearity Side Effects More Predictable Fewer Side Effects as Dose Increases
Longest Terminal Half-Lives Longer Time to Fully Administer New Treatment	Paroxetine Fluoxetine Citalopram Escitalopram Sertraline Fluvoxamine	Shortest Terminal Half-Lives Shorter Time to Fully Administer New Treatment

[a]Based on references 25–30.

Figure 2. Irritability in Patients With Autism Spectrum Disorders Treated With Methylphenidate[a]



[a]Data from Research Units on Pediatric Psychopharmacology Autism Network.[11]
*$p < .01$ (medium dose).

assumed to be caused by an SSRI. Some herbal treatments may increase free drug concentrations of antidepressants or slow their metabolism, and in general should be avoided.

Clomipramine treatment requires electrocardiogram (ECG) monitoring at baseline and with dose increases. In order to avoid cardiac side effects and neurologic side effects, a maximum daily dose of 3 mg/kg/day should be observed and, in adolescents, no more than 250 mg/day should be taken. It should be appreciated that individuals with autism spectrum disorders may be at higher risk to experience neurologic side effects associated with clomipramine, given the substantial rate of seizures documented in individuals with autistic disorder.

STIMULANTS

Safety

Controlled studies[10,11] on the treatment of patients with autism spectrum disorders with stimulant medications suggest an elevated risk of adverse events compared with typically developing populations with other disorders, including attention-deficit/hyperactivity disorder (ADHD). Stimulant treatment of patients with autism spectrum disorders may be associated with reactions that in typically developing children would be considered unusual, such as confusion, possible psychosis, and perhaps higher rates of treatment-emergent tic disorder.

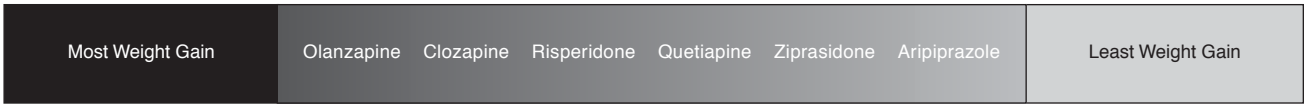
A recent 4-week, double-blind, crossover controlled study[11] by the National Institute of Mental Health Research Units on Pediatric Psychopharmacology (NIMH RUPP) Autism Network included 72 children aged 5 to 17 years with autistic disorder, pervasive developmental disorder not otherwise specified, or Asperger's disorder. These patients were randomly assigned weekly to the following treatment conditions: placebo or methylphenidate at approximately 0.125 mg/kg/dose, 0.25 mg/kg/dose, or 0.5 mg/kg/dose. Parent, teacher, and clinician ratings of response were obtained.

All doses of methylphenidate were associated with an increase in the frequency of side effects over placebo, and the increase reached significance at higher doses for several common stimulant-associated side effects, such as anorexia, insomnia, and irritability. The dropout rate due to inability to tolerate the medication was 18%, which is notably higher than the rate of discontinuation seen in typically developing school-aged populations treated with stimulant medications. Nearly half of the patients who dropped out of the study did so because of negative mood effects, specifically irritability (Figure 2).

Data from this study[11] showed that almost 25% of subjects taking the medium dose or the high dose reported reductions in appetite. There was also a relationship between dose and insomnia. Every dose of methylphenidate given in this study was significantly associated with an increase in insomnia compared with placebo.

Currently, increased attention surrounds growth effects of stimulants in the treatment of ADHD and other disorders. There are no data on longer-term treatment with stimulants in children with autism spectrum disorders, so information on growth effects in autism spectrum disorders can only be extrapolated from data in children with ADHD. Studies[12,13] of preschoolers and school-aged children with ADHD estimate a reduction in height of 1 to 2 cm per year of treatment with stimulants. Children with autism spectrum disorders are thought to be as vulnerable or more vulnerable to adverse effects as children with ADHD, so possible growth effects have to be included in a

Figure 3. Variation in Weight Gain With Second-Generation Antipsychotics[a]



[a]Based on reference 31.

discussion of the risks of stimulant treatment with the patient and family.

Management Tactics

To improve tolerance to stimulants, lower doses are recommended, given the increased sensitivity to side effects in patients with autism spectrum disorders. Longer titration periods than those that would be used in other populations may also improve tolerance, as may the use of extended-release preparations. Immediate-release or short-acting medications are very rapidly absorbed, reach peak plasma concentrations quickly, and then fall off equally quickly. These peaks and valleys may increase the risk of side effects.

Careful monitoring with a structured measure, such as a side effect rating scale, is helpful in identifying emerging adverse events. Growth in height should be measured every 4 to 6 months. If a patient's growth rate drops sharply over a 6-month period, the clinician should reconsider the use of stimulant medications to treat that patient.

It is not currently known if stimulants are more or less well tolerated than other ADHD treatments for autism spectrum disorders. At this point, there are no large-scale clinical observations to use as an estimate. Overall, the stimulants have a very good safety and tolerability record, so it can reasonably be said that the stimulants—although they may cause more side effects in individuals with autism spectrum disorders than in other populations—still represent a useful treatment option.

SECOND-GENERATION ANTIPSYCHOTICS

Safety

The second-generation antipsychotics are probably the most rapidly increasing category of psychotropics used for the treatment of autism spectrum disorders. As the use of these medications increases, so does the information on their safety. The most common adverse events seen with second-generation antipsychotics in autism spectrum disorders include sedation, increased appetite and weight gain, disrupted sleep, prolactin elevation, and extrapyramidal symptoms. Many of these common side effects seem to fade with time, even within the first 2 to 4 weeks of exposure.[14,15]

In a study[15–17] by the NIMH RUPP Autism Network, 63 children aged 5 to 17 years with autistic disorder and severe behavioral problems were treated with risperidone for up to 6 months. Sedation was reported by 24% of patients in the study,[15] with peak reporting occurring by week 4 and falling dramatically by week 8, suggesting that considerable adaptation to sedation can occur.

However, the relatively rapid adaptation that seems to occur with sedation is not so clearly seen with weight gain. Subjects taking risperidone had a 5.6-kg mean gain after 6 months of treatment.[17] An increase in weight at 1 month was highly correlated with weight gain after 6 months. Just as in adults,[18] variability regarding risk for weight gain with second-generation antipsychotics most likely exists in children (Figure 3). Full data from which to draw conclusions are not yet available for ziprasidone and aripiprazole, but they may prove to have the lowest potential for weight gain in pediatric usage. It is unclear if or how weight gain is related to diabetes, hepatotoxicity, triglyceridemia, or other side effects that have been observed with the second-generation antipsychotics. Regardless of concerns about its associated health problems in the short or long term, weight gain in and of itself is a frequent cause of discontinuation of second-generation antipsychotics. In an extension[19] of the RUPP study, only 50% of participants continued risperidone at 18 months, despite a symptom improvement rate of almost 70%.

In addition to sedation and weight gain, most second-generation antipsychotics, except clozapine and quetiapine, are associated with prominent initial increases in prolactin. A double-blind, placebo-controlled study[20] of risperidone in 118 children 5 to 12 years of age with severe disruptive behaviors and subaverage intelligence found increased serum prolactin during an initial treatment period of 6 weeks. At the endpoint of the 48-week extension study,[21] the prolactin levels appeared to be within the normal range, but they remained elevated over baseline. Although there is a suggestion that the adaptation that is evident with sedation also occurs with prolactin, the long-term consequences of increased prolactin in a young age group are unclear. An increase in prolactin may be related to reports of galactorrhea and gynecomastia, but these side effects occur very rarely. Despite these serious but uncommon side effects, the second-generation antipsychotics appear to be, on the whole, relatively well tolerated.

Management Tactics

As with stimulants, low doses of second-generation antipsychotics appear to be highly effective and carry a lower risk of side effects, including extrapyramidal symp-

Table 2. Monitoring Guidelines for Second-Generation Antipsychotics[a,b]

Clinical Parameter	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

[a]Reprinted with permission from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.[22]
[b]More frequent assessments may be warranted based on clinical status.
Abbreviation: BMI = body mass index.

toms, than higher doses. Baseline assessment and monitoring are key in managing side effects. Suggested baseline assessment includes a full physical examination, family history, and review of systems. Specifically, the patient should be examined for gynecomastia and galactorrhea, asked about a family history of syncope or sudden death, and assessed for other suggested preexisting health problems. For ziprasidone and clozapine, baseline and repeated ECG monitoring is recommended, given the observations of effects on cardiac conduction, especially effects on QTc. Monitoring for early weight gain is important, and indications should trigger aggressive efforts on the part of both the clinician and the family to constrain weight gain through diet, exercise, medication switching, and any other means available. A systematic, structured examination for extrapyramidal and movement disorders, using such scales as the Abnormal Involuntary Movement Scale, should be a part of standard practice. To monitor for metabolic effects, clinicians should perform a screening laboratory to measure liver function, blood count, glucose levels, and triglyceride levels. The American Diabetes Association has recently published monitoring guidelines[22] for individuals receiving second-generation antipsychotics (Table 2). These guidelines, while not fully empirically validated, provide prudent recommendations, and clinicians should become familiar with them.

ALPHA AGONISTS

Safety

The alpha agonists, including guanfacine and clonidine, are less frequently used in autism spectrum disorders than the other classes of medication that have been discussed. The small amount of information on their use in these disorders is contradictory and prohibits precise estimates of adverse events. One of the larger trials[23] studied guanfacine in divided doses of 1.5 to 3.0 mg/day in 34 children with ADHD and tic disorder. In this double-blind, placebo-controlled trial, the common side effects included mild blood pressure reductions, sedation, sleep changes, dry mouth, constipation, and loss of appetite.

A more recent study[24] by the RUPP Autism Network examined the effects of guanfacine in divided doses of up to 3.5 mg/day on 30 children and adolescents with pervasive developmental disorders or autistic disorder who also were exhibiting high levels of disruptive behavior. This open-label trial found no significant changes in any of the cardiovascular parameters monitored, including blood pressure. In this study, the most common causes for discontinuation were sedation, mood effects, and insomnia, not cardiovascular effects. Few dropouts were reported as due to adverse events. More studies are needed to determine the true risk of cardiovascular adverse events of these medications.

Management Tactics

In the absence of a consensus on the risk of adverse cardiovascular events with the alpha agonists, the clinician should monitor patients' blood pressure and pulse at baseline and with dose increases. ECG monitoring is only required if the patient has a family history of syncope or sudden death. Monitoring of sedation, mood effects, and insomnia should be performed at least every month, or more frequently if they emerge with treatment.

CONCLUSION

Medication use in the treatment of children and adolescents with autism spectrum disorders is becoming commonplace, and recent data have begun to establish a stronger evidence base for the efficacy of these treatments. But, as the use of medication for autism spectrum disorder increases, so does the evidence that each class of medication carries with it specific side effect risks. Becoming familiar with these risks is important for clinicians in order to provide accurate information on risks versus benefits, to be alert to minimize the burden of side effects where possible and, in so doing, optimize overall treatment. The greatest rationale for intensive monitoring and management of side effects is enhancing long-term compliance, which is critical to effective treatment.

Drug names: aripiprazole (Abilify), citalopram (Celexa and others), clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), escitalopram (Lexapro), fluoxetine (Prozac and others), guanfacine (Tenex and others), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, citalopram, clomipramine, clonidine, clozapine, escitalopram, fluoxetine, fluvoxamine, guanfacine, methylphenidate, olanzapine, paroxetine, quetiapine, risperidone, sertraline, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of pervasive developmental disorders.

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