Psychopharmacology of Autism Spectrum Disorders

Gabriel Kaplan, MD[a,b,*], James T. McCracken, MD[c]

KEYWORDS

- Autism spectrum disorders • Autism • Stimulants • Irritability
- Repetitive behaviors • Hyperactivity • Antipsychotics
- Psychopharmacology

Readers of this issue of *Pediatric Clinics* will become aware that autism spectrum disorders (ASDs) comprise a very heterogeneous group of illnesses that present with a wide range of impairments, from moderate to catastrophic. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised) (DSM-IV-TR),[1] ASDs are diagnosed in the presence of 3 core deficits: (1) impairment of social interactions, (2) impaired communication, and (3) repetitive and stereotyped patterns of behavior, interests, and activities. Though not required to make a diagnosis, frequent associated/comorbid symptoms are observed such as aggression, self-injury, impulsivity, decreased attention, anxiety, depression, and sleep disruption,[2] which can become a major source of additional distress and interference in functioning. While advances in the field of psychopharmacology have led to significant improvement in the symptoms and outcomes of many psychiatric diseases, unfortunately this has been less true for treating core symptoms of ASD. Regarding medications, Sir Michael Rutter recently wrote "…studies have been striking (and surprising) in their evidence on no clinically meaningful benefits with respect to the core symptoms of autism."[3] Therefore, an array of behavioral and educational approaches, reviewed elsewhere in this issue, is the cornerstone of a comprehensive treatment plan for ASD core symptoms and delays. Because such therapies are intensive and require the cooperation of the patient, the development of the aforementioned severe and challenging behaviors can threaten overall treatment success. Fortunately, progress has been made in the use of psychotropic medications to manage these common and often impairing associated features. Medications can be beneficial in reducing the

[a] Department of Psychiatry, Hoboken University Medical Center, 308 Willow Avenue, Hoboken, NJ 07030, USA
[b] Department of Psychiatry, University of Medicine and Dentistry of New Jersey, 65 Bergen Street, Newark, NJ 07107, USA
[c] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Los Angeles, CA 90024, USA
* Corresponding author. 535 Morris Avenue, Springfield, NJ 07081.
E-mail address: drgkaplan@gmail.com

severity of disruptive behaviors and other problems that interfere with psychosocial and educational interventions, impair social functioning and learning, and result in safety risks to self or others.

Pediatricians are often the first professionals to start the ASD diagnostic process, although patients are usually later referred to specialist care for more comprehensive evaluations. However, families continue consulting with their primary doctor to obtain advice on the benefits of the multiple available ASD-specific treatment options, as well as medical monitoring and follow-up care. This course of action is in line with The American Academy of Pediatrics' recommendation that encourages physicians to take on guiding and supportive roles, as ASD are chronic syndromes that will persist, often with significant deficits, into adulthood.[4] Therefore, understanding the role of psychopharmacologic treatments in ASD, usual dosing, side effects, and monitoring guidelines has become important to primary care pediatrics.

It should be noted that most psychotropic use in ASD is off-label, as there are currently just two medications approved by the Food and Drug Administration (FDA), and only for the treatment of associated behaviors. Because ASDs are chronic, markedly impairing in many cases, and of poorly understood etiology, there is justifiably a high desire for effective treatments. This desire sometimes leads to premature enthusiasm for agents and interventions that appear promising in early reports but later do not withstand the rigor of evidence-based research methods.[5] Consequently, this article principally discusses information supplied by randomized controlled trials (RCTs), universally accepted as the primary source of evidence-based data. Other types of studies are mentioned only if they provide noteworthy, clinically relevant information.

Regarding this article's organization, rather than reviewing medications class by class, it addresses the most commonly associated behaviors separately; namely, aggression, repetitive behaviors, hyperactivity, depression and anxiety, and sleep disorders. Study results, benefits, and potential adverse effects of agents recommended for specific maladaptive conditions are described under distinct headings. Because the lack of biological markers to assess treatment progress has led researchers to develop sophisticated, psychometrically valid rating scales to evaluate outcomes, a section is dedicated to review tools frequently used to determine outcomes. In addition, paragraphs throughout the article on clinical implications provide a bridge between research and clinic. By offering information that is current, relevant, and organized in a user-friendly manner, the aim is to form a concise but informative reference guide for primary pediatric clinicians, who are often asked by caretakers to provide input in the selection of appropriate and efficacious agents for an ASD patient.

TOOLS USED TO MEASURE OUTCOMES
Clinical Global Impression Scale

The Clinical Global Impressions (CGI) Scale[6] is a standardized assessment tool used by clinicians to rate the severity of illness, change over time, and efficacy of medication. It is not ASD specific but is one of the most well-known and widely used scales in psychopharmacology studies, and is brief and convenient to use. It consists of 3 subscales. The first one, Severity of Illness, which is often used both before and after treatment, is a 7-point scale that rates the severity of the patient's mental illness at the time of assessment as: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. The second subscale, Clinical Global Impression-Improvement (CGI-I), is also a 7-point scale that assesses

how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention, and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. The third subscale, Clinical Global Impression-Efficacy Index, which attempts to integrate benefits against side effects, does not appear in the studies reviewed here.

Aberrant Behavior Checklist

The Aberrant Behavior Checklist (ABC) is a 58-item caregiver report checklist developed specifically to assess maladaptive behaviors in individuals with developmental disabilities, using a simple 4-point rating scale (0–3) with higher scores reflecting more problems. ABC items are grouped into 5 subscales: (1) Irritability (ABC-I), agitation, crying (15 items); (2) Lethargy, social withdrawal (16 items); (3) Stereotypic behavior (7 items); (4) Hyperactivity, noncompliance (ABC-H) (16 items); and (5) Inappropriate speech (4 items). The ABC is frequently used in pharmacologic trials in autism as one of the main end points for treatment evaluation.[7] Most studies reviewed in this article have used ABC-I and ABC-H as outcome measures.

Children's Psychiatric Rating Scale

The Children's Psychiatric Rating Scale (CPRS)[8] is a 63-item scale developed by the Psychopharmacology Branch of the National Institute of Mental Health (NIMH) to rate childhood psychopathology. Each item is rated from 1 (not present) to 7 (extremely severe). Four factors have been derived from these items: Autism Factor (social withdrawal, rhythmic motions/stereotype, abnormal object relations, unspontaneous relation to examiner, underproductive speech), Anger/Uncooperativeness Factor (angry affect, labile affect, negative and uncooperative), Hyperactivity Factor (fidgetiness, hyperactivity, hypoactivity), and Speech Deviance Factor (speech deviance, low voice).

Children's Yale-Brown Obsessive Compulsive Scale Modified for Pervasive Developmental Disorder

The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) is a semistructured clinician rating that measures the current severity of obsessions and compulsions in youth with obsessive-compulsive disorder. Obsessions and compulsions are then each rated on a 0 to 4 scale across 5 severity items: Time Spent, Interference, Distress, Resistance, and Degree of Control. The modified CY-BOCS[9] for use in children with pervasive developmental disorder (PDD) eliminates the obsessions checklist and severity scales while retaining the compulsions checklist, which was expanded to include repetitive behaviors commonly seen in children with PDD. Furthermore, the modified version relies more on parental input rather than the child's input.

TREATMENT OF ASD-ASSOCIATED/COMORBID SYMPTOMS
Aggression, Irritability, and Self-Injury

Aggression and related symptoms are the associated problems that often elicit the most concern in ASD. Although behavioral and environmental approaches are recommended as the initial treatment, more severe or even dangerous behaviors usually result in requests for urgent pharmacologic intervention. Such behaviors can lead to injury, removal from less-restrictive classrooms or placements, and hospitalization. Patients can present with a variety of aggressive acts directed to self, others, and property. The prevalence of such acts is high. For instance, in a study of 1380 subjects with ASD, 68% demonstrated aggression to a caregiver and 49% to noncaregivers.[10] The following classes of medications are used to treat aggressive behaviors.

Antipsychotics

The efficacy of these agents was first documented in the 1970s by Magda Campbell at NY Bellevue Hospital. In her now classic studies,[11] Campbell pioneered the use of RCTs in child psychopharmacology, a field that had been largely dominated up to that point by case reports and naturalistic studies. Antipsychotics have now become commonly used agents in ASD,[12] perhaps influenced by observations of possible benefits on a variety of commonly associated behaviors and the fact that the only two FDA-approved agents for the condition are aripiprazole and risperidone.

Haloperidol Campbell and colleagues[11] studied ASD children with severe aggression aged 2.6 to 7.2 years and randomized them to haloperidol or placebo in combination with language training. Haloperidol at an average dose of 1.7 mg/d resulted in significant improvement in withdrawal and stereotypy in children 4.5 years and older, as assessed by the CPRS. In addition, there were beneficial effects on learning when the antipsychotic was combined with behavioral treatment. Later studies[13] confirmed the initial beneficial findings, including an improvement in aggression, as haloperidol was shown to be more effective than placebo for negativism, angry affect, and lability of affect. However, sedation was common, and about one-third of children developed motor symptoms such as dystonias and withdrawal dyskinesias. As a result, concern over the possible high risk of tardive dyskinesia emerged,[14] and the potential for these side effects made haloperidol a less favored option once atypical antipsychotics became available.[15]

Risperidone Dissatisfaction with conventional antipsychotics, due to extrapyramidal side effects and lack of efficacy in negative symptoms of schizophrenia, led to intense efforts to find alternatives. Risperidone, the first in a new class of agents termed atypical antipsychotics, was approved for schizophrenia in adults by the FDA in 1993. Given the expectation of improved efficacy and lower rates of adverse effects, atypicals became first-line agents for many conditions requiring neuroleptics, including ASD. Following the Campbell tradition, risperidone was rigorously studied by the NIMH Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. RUPP conducted a multiphase trial comparing the effects of risperidone in comparison with placebo for the treatment of aggressive behaviors in patients aged 5 to 17 years with ASD. There was an initial double-blind, 8-week RCT study[16] with 101 participants, followed by a 4-month open-label trial ending in an 8-week randomized, double-blind, placebo-substitution study of risperidone withdrawal.[17] The studies found that risperidone, in mean doses of 2.08 mg/d, was effective for reducing moderate to severe tantrums, aggression, and self-injurious behavior in children with autism. Outcomes were assessed by the ABC-I and CGI-I. These gains were stable over time and did not necessitate dose increases, but relapse was seen in the majority if the medication was withdrawn at 6 months. The investigators found no evidence of dyskinesia or dystonia. However, the observed weight gain of 5.6 kg for the risperidone group was more than twice the expected weight gain over a 6-month period. The FDA approved risperidone in 2006 for the treatment of irritability associated with autistic disorder, including symptoms of aggression, deliberate self-injury, temper tantrums, and quickly changing moods, in children and adolescents aged 5 to 16 years, with a maximum recommended dose of 3 mg/d. A meta-analysis that reviewed all risperidone RCT studies for subjects with ASD published after 2000 found that the agent yielded a large mean effect size of 1.21.[18]

Aripiprazole Two large controlled studies documented the short-term efficacy of aripiprazole for severe aggression and irritability in subjects 6 to 17 years old with

autistic disorder. A fixed-dose 8-week study[19] found that the agent at 5, 10, or 15 mg/d was superior to placebo. The second RCT[20] was also 8 weeks long but used flexible doses reaching a mean of 8.6 mg/d by the end of the study. Symptoms in both studies were rated with the ABC-I and the CGI-I. The most commonly reported adverse events associated with aripiprazole treatment were sedation and weight gain in both studies, and extrapyramidal symptoms mostly in the fixed-dose study, but these events rarely led to treatment discontinuation. Aripiprazole was approved by the FDA for the treatment of irritability associated with autistic disorder in patients aged 6 to 17 years in 2009. Aripiprazole dosing and response can vary considerably; the usual recommended clinical dose for maintenance is between 5 and 15 mg/d.

Other antipsychotics Other agents in this class lack large-scale controlled studies. Small open-label reports suggest variable benefits of olanzapine[21] and ziprasidone,[22] which have possible support, versus quetiapine,[23] which has not appeared to be beneficial.

Adverse effects All antipsychotics in children carry the risk of potentially serious side effects such as neuroleptic malignant syndrome, galactorrhea, dyskinesias, cardiovascular changes, and allergic reactions. Fortunately, these serious adverse events are estimated to be rare or uncommon; a large review estimated the annualized risk for tardive dyskinesia to be less than 0.5%, and remission of the disorder after drug discontinuation is a common observation.[24] Nevertheless, it is of obvious importance to systematically monitor for the appearance of such untoward effects and develop strategies to minimize them. Although a comprehensive discussion of this topic is beyond the scope of this article, an excellent review is available elsewhere.[25] **Box 1** lists common adverse effects and suggestions for monitoring adverse effects including observation, laboratory tests, and specific rating scales such as the Abnormal Involuntary Movement Scale (AIMS).[26]

Methylphenidate

The role of methylphenidate (MPH) in treating attentional problems in typically developing children is well documented.[27] Two RCTs examined MPH's potential benefit for the treatment of aggression in ASD[28,29] in subjects 5 to 11 years old. Although the results showed superiority over placebo on the ABC-I, the trials were small and of short duration, and one study[28] had a high percentage of children with intolerable side effects, often including agitation, mood changes, and abnormal movements. Overall, MPH is less commonly used for the treatment of aggression.

Box 1 Antipsychotic side effects and monitoring strategies		
Side Effect	**Monitor Frequency**	**Monitor Strategy**
Sedation, lethargy	Each visit	Observation, caretaker report
Parkinsonism	Each visit	Observation, caretaker report
Tardive dyskinesia	Every 6 months	(AIMS)
Weight increase	Each visit	Monthly weight measures
Hyperglycemia	Every 6 months	Laboratory
Hyperlipidemia	Every 6 months	Laboratory
Hyperprolactinemia	Every few visits	If symptoms reported, obtain level

Divalproex

A 12-week randomized double-blind, placebo-controlled study[30] evaluated the use of divalproex sodium for aggression in 55 children aged 5 to 17 years, in which the agent demonstrated modest superiority to placebo. The primary outcome measures were the ABC-I and CGI. There was a trend for responders to have higher valproate blood levels compared with nonresponders. Adverse effects reported in the study were minimal.

Other agents

Naltrexone, an opioid receptor antagonist, and clonidine, an α2-adrenergic agonist, were studied in RCTs and showed superiority to placebo.[31] However, small samples and other study limitations made the findings difficult to generalize, so these agents are not considered a first choice for treating aggression.

Clinical implications

Aggressive behaviors toward self and others displayed by some ASD children result in grave concern, possibly more restrictive placements, and are significant predictors of inpatient treatment.[32] Consequently, many of the pharmacologic investigations in this population are geared toward addressing this potentially dangerous set of behaviors. The atypical antipsychotics risperidone and aripiprazole are the most studied agents in ASD, are approved by the FDA for treating irritability (not ASD per se), and have shown solid evidence of effectiveness. Older haloperidol studies also provide favorable evidence for its off-label use. However, the level of evidence is also high for the risk of developing clinically limiting side effects for all antipsychotics, such as the extrapyramidal effects of conventional agents or the metabolic changes of atypical neuroleptics.[11,16,20] Close monitoring of patients using these agents is essential. Divalproex and MPH are off-label options with modest evidence of effectiveness. The decision to initiate pharmacologic treatment should be based on severity of symptomatology, degree of impairment, risk to self or others, and prevention of hospitalization. While no widely endorsed clinical algorithms for treatment of aggression exist, clinicians generally attempt initial treatment with lower-risk alternatives to antipsychotics. However, in the context of poor response or tolerability, or severe and dangerous symptoms, such agents are often replaced by one of the two FDA-approved antipsychotics for rapid management and stabilization. Length of recommended treatment is difficult to derive from published evidence, but treatment benefits appear to be durable for up to 6 to 12 months. Efforts to reduce and possibly discontinue such treatment at the end of this period should be strongly considered.

Repetitive Behaviors

Restricted repetitive and stereotyped patterns of behavior, interests, and activities (RRBs) have been described since the work of Kanner[33] as core features of ASD, and their presence is also currently necessary to meet DSM-IV-TR[1] diagnostic criteria. RRBs can be classified into lower-level repetitive motor behaviors such as rocking and limb movements, and higher-level routines and rituals such as the classically described insistence on sameness. RRBs and stereotypies are not unique to ASD and can be found in many other developmental disorders, although researchers agree that these tend to be more frequent in ASD.[34] Behavioral therapies are the first line for RRBs but the behaviors can be quite difficult to manage; because of the major challenges that uncontrolled RRBs can pose to educational and social performance, and risks of danger and actual harm to self or others, pharmacologic treatment is often considered. The following agents have been evaluated and are often prescribed for the target of RRBs.

Selective serotonin reuptake inhibitors

Researchers reasoned that selective serotonin reuptake inhibitors (SSRIs) could be effective for RRBs, because of the consistent reports of serotoninergic dysfunction in ASD and because such symptoms share aspects of the phenomenology of obsessions and compulsions known to respond to SSRIs. Antidepressants are the most common class of psychotropics prescribed for individuals with ASD,[12] and although their benefits have been described in many case reports and uncontrolled studies,[35] such benefits have not been confirmed in large RCTs. Rigorous studies were conducted in youth with ASD only for fluoxetine and citalopram. Fluoxetine at a mean dose of 9.9 mg/d was better than placebo for RRBs according to the CY-BOCS in a study of 39 children aged 5 to 16 years.[36] On the other hand, a later study of 158 subjects with autism 5 to 17 years old[37] compared fluoxetine with placebo; using the CY-BOCS-PDD measure of repetitive behaviors during a 14-week treatment period, no fluoxetine benefit was observed. In addition, a 12-week RCT of citalopram studied 149 children aged 5 to 17 years with ASD and high levels of RRBs, who were begun on 2.5 mg of citalopram daily with weekly increases up to a maximum dose of 20 mg/d (mean dose 16 mg/d). The outcome was evaluated by CY-BOCS and again, no significant differences were found between the placebo and citalopram groups.[38] One-third of children in these studies were reported to experience serotoninergic activation type side effects, specifically increased activity, mood changes, and insomnia. On the other hand, open label studies of escitalopram have been more positive on benefits for irritability.[39] Therefore, taken together, the literature on the benefits and safety of SSRIs in ASD is quite mixed, despite the high frequency of their community use.

Atypical antipsychotics

RRBs were examined as secondary outcomes in the same studies mentioned in the aggression section. For instance, in the RUPP studies, risperidone achieved significantly greater reduction of repetitive behavior than did placebo (35% vs 15% reductions from baseline respectively), as reflected in scores on the compulsion subscale of the CY-BOCS modified for ASD.[40] Similarly, both aforementioned aripiprazole studies[19,20] showed that the agent significantly improved RRBs over placebo as measured by CY-BOCS when secondary analyses were conducted.

Divalproex

In a small study of 13 individuals with ASD who participated in an 8-week double-blind, placebo-controlled trial of divalproex sodium versus placebo, a significant group difference for divalproex on improvement in repetitive behaviors as measured by the CY-BOCS was noted.[41]

Clinical implications

RRBs constitute a frequent problematic behavior in children with ASD but treatment choices are difficult given the relative absence of support for efficacy of a particular medication class. Adverse effects of medications used for this target are commonplace and can be difficult to tolerate. Clinicians are advised to recognize current treatment limitations and to restrict drug therapy to those patients who display clear anxiety or distress associated with RRBs, or where RRBs are severe.

Hyperactivity

Clinicians have long noted the high prevalence of inattentive and hyperactive symptoms in children with ASD, and research has found that 28% to 78% of children with ASD meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD).[42,43] Furthermore, children who meet both diagnostic criteria have more

severe clinical difficulties than children with ASD alone.[44] Although current DSM-IV criteria do not allow the comorbid coding of both diagnoses,[1] it seems that DSM-V, scheduled to appear in 2013, will resolve this dilemma.[45] Multiple agents have been investigated to treat hyperactivity.

Stimulants

Amphetamines and MPH are the options of choice to treat attentional hyperactive problems in typically developing children.[27] Stimulants are the third most common class of drug prescribed in ASD.[12] MPH has been used preferentially in this population. A retrospective chart review of 195 subjects aged 2 to 19 years found that stimulants appeared to be ineffective and poorly tolerated for the majority of patients with ASD. There is only one published large MPH RCT study, which was conducted by the NIMH RUPP Autism Network.[46] The study of 72 children aged 5 to 13 years was designed to evaluate the efficacy and safety of multiple daily doses of immediate release MPH. Three strengths were used of about 0.15 mg/kg, 0.25 mg/kg, and 0.5 mg/kg. These doses, lower than those recommended for typically developing children, were used to minimize the possibility of side effects. All doses were superior to placebo in reducing hyperactivity and impulsiveness as measured by the ABC hyperactivity subscale, the primary outcome measure. However, even the highest effect size of 0.54 in this study was much lower than that usually achieved in typically developing children.[47] Irritability was a common complaint and overall, 18% of subjects discontinued the trial because of adverse effects, at least double the intolerance seen in typically developing children with ADHD.

Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor, approved by the FDA for treatment of ADHD symptoms in typically developing children and adults. Atomoxetine was examined in a small placebo-controlled, crossover pilot trial[48] for the treatment of hyperactivity of children with ASD. In this study, there were 16 children aged 5 to 15 years treated for 6 weeks at doses of 1.2 to 1.4 mg/kg per day, not exceeding a total dose of 100 mg/d. For the ABC-H, the primary outcome measure, improvement significantly favored atomoxetine. Adverse events were described as tolerable, with no tendency to increase stereotypy. Atomoxetine had an effect size similar to that shown in the MPH trial by the RUPP,[46] with effects mainly seen on hyperactive-impulsive behaviors. However, this study was small and allowed concomitant administration of other psychotropics, placing further limitations on generalizability.

Atypical antipsychotics

Secondary analyses of the ABC-H scale from large RCTs demonstrated that risperidone[16] and aripiprazole[20] are associated with large reductions of hyperactivity in children with ASD.

Other agents

Clonidine, an α2-agonist, was associated with a superior reduction in disruptive behaviors over placebo in a small, controlled trial.[49] Guanfacine, an α2A-adrenergic agonist, has been reported to demonstrate modest improvement in a retrospective study, in particular in irritability and explosive behavior. An additional open-label study of 25 children with ASD and high levels of ADHD symptoms suggested moderate benefit over 8 weeks.[50] However, no RCTs have been conducted for this class of agent.

Clinical implications

Hyperactivity is a frequent symptom that, when severe, interferes with educational and social interventions. As such, it is often the subject of requests for pharmacologic treatment. Unfortunately, none of the highly effective treatments for typically developing children have the same robust response in ASD, and the rate of side effects even at low doses is remarkably high. MPH is the best studied agent and although its use is off-label, it has the strongest evidence for modest effectiveness. MPH requires starting at doses roughly half that of usual doses in typically developing patients with ADHD and close monitoring of side effects, particularly irritability. α-Agonists deserve more research exploration, and often form a solid second-line treatment choice. While antipsychotics have also shown effectiveness for marked hyperactivity, their off-label use for this indication and potential significant toxicity make them a less favored choice.

Depression and Anxiety

The literature on effects of psychotropics for the treatment of depression and anxiety is sorely limited, despite the frequent description of dysphoria and apparent anxious behaviors in individuals with ASD. Although there is strong empirical support for the SSRIs as treatment for children with anxiety disorders, it is uncertain if benefits seen in typical children translate to children with ASD. It is interesting that some positive support exists for use of these medicines in adults with ASD,[51,52] but the high rate of significant adverse reactions to SSRIs in children, such as disinhibition, hyperactivity, and somatic complaints, greatly temper any enthusiasm for their common usage in youth with ASD.

Sleep Disorders

ASD patients experience sleep disorders at a much higher rate than typically developing children.[53] Various types of sleep problems have been described in this population, and may occur as a result of complex interactions between biological, psychological, social/environmental, and family factors, including child-rearing practices that are not conducive to good sleep.[54] Insomnia is the predominant sleep concern, and while its nature is also most likely multifactorial, abnormalities in the melatonin system have received the greatest level of consideration.[55] As per the ASD treatment principles discussed earlier and childhood insomnia treatment guidelines, pharmacology is recommended only when psychosocial treatments fail. A comprehensive review of such first-line approaches is described elsewhere.[56] Sleep disorders tend to be considered more benign than other associated problems such as aggression and repetitive behaviors; however, ongoing abnormal sleep patterns are very disruptive to the overall quality of family life and interfere with patient daytime functioning. Physicians receiving requests for medication are confronted with the lack of FDA-approved treatments for this problem. Although melatonin has been used off-label for many years, studies were sparse until several recent RCTs were conducted that, though of small sample size, have yielded encouraging results.[55] These studies found that melatonin in doses of up to 6 mg/d was effective and caused no significant side effects. However, long-term treatment has not been thoroughly examined.

SUMMARY

As reviewed in this article, clear progress has been made in defining approaches to evaluate the use of psychopharmacologic agents in ASD. While core features of ASD have shown limited improvement from treatment with well-known psychotropics,

several high-quality studies have shown success using various drug classes for the management of commonly associated behaviors. Although effective, these medicines also carry a high risk of untoward effects that limit their widespread use. Therefore, psychopharmacologic approaches should always be viewed as one component of a broader, comprehensive treatment that addresses educational, behavioral, and social functioning with multimodal interventions. Within this framework, pediatricians can play an important role in the oversight of ASD treatment benefit and safety.

At present, evidence-based support exists for the role of psychotropics, particularly atypical antipsychotics, in the treatment of the following targeted symptom domains: (1) aggression and severe irritability; (2) hyperactivity; and (3) repetitive behaviors. The broad benefits in behavior observed in antipsychotic studies make these agents a common treatment choice, especially in the face of severe symptoms and failure of other agents with lesser side-effect burdens. Substantial unmet need exists for interventions targeting mood and anxiety symptoms and severe, persistent insomnia. Therefore, polypharmacy, as well as the use of complementary medicine agents, are commonplace in community treatment of individuals with ASD, even though these practices have not been thoroughly tested. Reducing medication exposure by lowering dosing and evaluating appropriateness for discontinuation should be considered when treatment goals are achieved. Given the increased psychotropic use in ASD, primary care pediatricians can benefit from greater familiarity with recommended dosing, types of side effects, and suggested monitoring in order to render the safest care possible. It is hoped that in the near future, emerging knowledge of underlying molecular pathophysiology in ASD will point to new and more effective medical interventions.

ACKNOWLEDGMENTS

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. text revision. 4th edition. Washington, DC: APA; 2000.
2. Levy SE, Mandell DS, Schultz RT. Autism. Lancet 2009;374:1627–38.
3. Rutter M. A selective scientific history of Autism. In: Hollander E, Kolevzon A, Coyle J, editors. Textbook of ASD. Washington, DC: APPI; 2011. p. 5–21.
4. Myers SM, Johnson CP. Management of children with ASD. Pediatrics 2007; 120(5):1162–82.
5. Krishnaswami S, McPheeters ML, Veenstra-Vanderweele J. A systematic review of secretin for children with autism spectrum disorders. Pediatrics 2011;127(5): e1322–5.
6. Guy W. ECDEU assessment manual for psychopharmacology—revised (DHEW Publ No ADM 76-338). Rockville (MD): U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. p. 218–22.
7. Aman MG, Singh NN, Stewart AW, et al. The Aberrant Behavior Checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic 1985;89:485–91.
8. Rating scales and assessment instruments for use in pediatric psychopharmacology research. Psychopharmacol Bull 1985;21(4):714–1124.

9. Scahill L, McDougle CJ, Williams SK, et al. Children's Yale-Brown Obsessive Compulsive Scale modified for pervasive developmental disorders. J Am Acad Child Adolesc Psychiatry 2006;45(9):1114–23.
10. Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. J Autism Dev Disord 2011;41(7):926–37.
11. Campbell M, Anderson LT, Meier M, et al. A comparison of haloperidol and behavior therapy and their interaction in autistic children. J Am Acad Child Psychiatry 1978;17:640–55.
12. Mandell D, Morales K, Marcus SC, et al. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorders. Pediatrics 2008; 121:e441–8.
13. Anderson LT, Campbell M, Grega DM, et al. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984; 141(10):1195–202.
14. Campbell M, Armenteros J, Malone RP, et al. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. J Am Acad Child Adolesc Psychiatry 1997;36(6):835–43.
15. Posey DJ, Stigler KA, Erickson CA, et al. Antipsychotics in the treatment of autism. J Clin Invest 2008;118:6–14.
16. RUPP. Risperidone in children with autism and serious behavioral problems. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. N Engl J Med 2002;347:314–21.
17. RUPP. Risperidone treatment of autistic disorder: longer term benefits and blinded discontinuation after six months. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Am J Psychiatry 2005;162:1361–9.
18. Sharma A, Shaw S. Efficacy of risperidone in managing maladaptive behaviors for children with autistic spectrum disorder: a meta-analysis. J Ped Health Care 2011. [Epub ahead of print]. DOI:10.1016/j.pedhc.2011.02.008.
19. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry 2009;48(11):1110–9.
20. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics 2009;124:1533–40.
21. Potenza MN, Holmes JP, Kanes SJ, et al. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol 1999;19(1):37–44.
22. Malone RP, Delaney MA, Hyman SB, et al. Ziprasidone in adolescents with autism: an open-label pilot study. J Child Adolesc Psychopharmacol 2007; 17(6):779–90.
23. Martin A, Koenig K, Scahill L, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9(2):99–107.
24. Correll CU, Kane JM. One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review. J Child Adolesc Psychopharmacol 2007;17(5):647–56.
25. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry 2008;27: 9–20.
26. Guy W, editor. ECDEU assessment manual for psychopharmacology: Publication ABM 76-338. Washington, DC: US Department of Health, Education, and Welfare; 1976. p. 534–7.

27. Kaplan G, Newcorn JH. Pharmacotherapy for child and adolescent attention-deficit hyperactivity disorder. Pediatr Clin North Am 2011;58(1):99–120.

28. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. J Autism Dev Disord 2000;30:245–55.

29. Quintana H, Birmaher B, Stedge D, et al. Use of methylphenidate in the treatment of children with autistic disorder. J Autism Dev Disord 1995;25:283–94.

30. Hollander E, Chaplin W, Soorya L, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. Neuropsychopharmacology 2010;35:990–8.

31. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. J Child Adolesc Psychopharmacol 2008;18(2):157–78.

32. Mandell DS. Psychiatric hospitalization among children with autism spectrum disorders. J Autism Dev Disord 2008;38(6):1059–65.

33. Kanner L. Autistic disturbances of affective contact. Nerv Child 1943;2:217–50.

34. Leekam SR, Prior MR, Uljarevic M. Restricted and repetitive behaviors in autism spectrum disorders: a review of research in the last decade. Psychol Bull 2011;137(4):562–93.

35. McCarthy M, Kolevzon A. Serotonin reuptake inhibitors and other serotonergic medications. In: Hollander A, Kolevzon A, Coyle JT, editors. Textbook of autism spectrum disorders. Washington, DC: American Pyschiatric Publishing; 2011. p. 439–55.

36. Hollander E, Phillips A, Chaplin W, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology 2005;30:582–9.

37. SOFIA. Available at: http://www.autismspeaks.org/about-us/press-releases/autism-speaks-announces-results-reported-study-fluoxetine-autism-sofia. Accessed July 28, 2011.

38. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. Arch Gen Psychiatry 2009;66(6):583–90.

39. Owley T, Walton L, Salt J, et al. An open-label trial of escitalopram in pervasive developmental disorders. J Am Acad Child Adolesc Psychiatry 2005;44(4):343–8.

40. McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the RUPP Autism Network study. Am J Psychiatry 2005;162:1142–8.

41. Hollander E, Soorya L, Wasserman S, et al. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. Int J Neuropsychopharmacol 2006;9(2):209–13.

42. McCracken JT. Disruptive behaviors. In: Hollander E, Kolevzon A, Coyle JT, editors. Autism spectrum disorders. Washington, DC: American Psychiatric Publishing; 2010. p. 159–67.

43. Murray MJ. Attention-deficit/hyperactivity disorder in the context of autism spectrum disorders. Curr Psychiatry Rep 2010;12(5):382–8.

44. Gadow KD, DeVincent CJ, Pomeroy J. ADHD symptom subtypes in children with pervasive developmental disorder. J Autism Dev Disord 2006;36(2):271–83.

45. APA DSM-5 Development. Available at: http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=383. Accessed July 28, 2011.

46. RUPP. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Arch Gen Psychiatry 2005;62(11): 1266–74.

47. Paykina N, Greenhill L. Attention deficit hyperactivity disorder. In: Findling RL, editor. Clinical manual of child and adolescent psychopharmacology. Washington, DC: American Pyschiatric Publishing; 2008. p. 33–87.

48. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. J Am Acad Child Adolesc Psychiatry 2006;45(10):1196–205.

49. Jaselskis CA, Cook EH Jr, Fletcher KE, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992; 12(5):322–7.

50. Scahill L, Aman MG, McDougle CJ, et al. A prospective open trial of guanfacine in children with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2006;16(5):589–98.

51. Fatemi SH, Realmuto GM, Khan L, et al. Fluoxetine in treatment of adolescent patients with autism: a longitudinal open trial. J Autism Dev Disord 1998;28(4): 303–7.

52. McDougle CJ, Naylor ST, Cohen DJ, et al. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996; 53(11):1001–8.

53. Richdale A. Sleep problems in autism: prevalence, cause, and intervention. Dev Med Child Neurol 1999;41:60–6.

54. Cortesi F, Giannotti F, Ivanenko A, et al. Sleep in children with autistic spectrum disorder. Sleep Med 2010;11(7):659–64.

55. Sánchez-Barceló EJ, Mediavilla MD, Reiter RJ. Clinical uses of melatonin in pediatrics. Int J Pediatr 2011;2011:892624.

56. Vriend JL, Corkum PV, Moon EC, et al. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. J Pediatr Psychol 2011;36(9):1017–29.