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An Introduction to the Psychopharmacology of Children and Adolescents With Autism Spectrum Disorder

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TOPIC: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that requires a multidisciplinary approach to treatment. Psychopharmacology can play an important role within an array of services to help children and adolescents with ASD.

PURPOSE: This article reviews the current evidence supporting the use of various psychiatric medications to treat common symptoms that often compromise functioning: severe irritability, interfering repetitive behaviors, ADHD, anxiety, depression, and sleep dysregulation. Based on the accumulating research, the article also offers practice recommendations.

SOURCES: The article primarily draws on the science generated by investigators from the Research Units on Pediatric Psychopharmacology Autism Network. This body of work consists of randomized controlled trials, meta-analyses, open trials, and review articles.

CONCLUSIONS: There are currently no FDA-approved medications to treat the core symptoms of ASD. Consequently, all medications, besides risperidone and aripiprazole for severe irritability, are considered off-label. Additionally, due to reduced levels of effectiveness and higher rates of side effects, more typical medications such as antidepressants and stimulants should be used with caution. However, the evidence indicates that the thoughtful use of psychiatric medication in conjunction with other interventions may be beneficial in helping children and adolescents with ASD thrive at school and home.

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that is defined by deficits in social communication and interaction such as a limited ability for social and emotional reciprocity, altered use of nonverbal behavior for organizing social discourse, and challenges with establishing and maintaining relationships (American Psychiatric Association [APA], 2013). Children with ASD also struggle with restricted, repetitive behaviors, interests, and activities (RRBs). This may take the form of repetitive motor behavior, an overly intense preoccupation with a specific topic or activity, inflexible adherence to routine, or heightened/diminished sensory sensitivities.

As the estimated prevalence of this disorder has increased to 1 in 68 (Baio, 2014), ASD is a growing public health concern that requires the attention of psychiatric mental health nurse practitioners (PMHNPs). However, the challenge in providing care for individuals with ASD and their families is the need for a multidisciplinary approach to treatment involving combinations of early intensive behavioral intervention; special education; occupational therapy; speech and language therapy; physical therapy; vocational programming; and medical attention due to possible issues with seizures, gastrointestinal problems, feeding/nutrition concerns, pain, and infection (Perrin et al., 2016; Politte, Howe, Nowinski, Palumbo, & McDougle, 2015; Veenstra-VanderWeele, 2015; Volkmar, Rowberry, et al., 2014; Volkmar, Siegel, Woodbury-Smith, King, State, & American Academy of Child and Adolescent Psychiatry Committee on Quality Issues, 2014).

Even with the above treatments, however, individuals with ASD may still require psychopharmacological assistance due to impairing symptomology at home, school, and other settings (Volkmar, Siegel, et al., 2014). Unfortunately, the last review by a psychiatric nursing scholar about the psychopharmacology of ASD was in 2012 (Carbray, 2012). Since then a new practice parameter for the treatment of ASD has been published (Volkmar, Siegel, et al., 2014) and the literature focusing on the psychopharmacology of ASD has increased

substantially (Politte, Henry, & McDougle, 2014). This article draws primarily on randomized controlled trials, meta-analyses, open trials, and reviews by investigators from the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (Dominick, Wink, McDougle, & Erickson, 2015; Doyle, McDougle, & Stigler, 2014; Harfterkamp et al., 2014; Hirota, Veenstra-VanderWeele, Hollander, & Kishi, 2014; Ji & Findling, 2015; McCracken et al., 2014; Mohiuddin & Ghaziuddin, 2013; Pallanti, Benici, Cantisani, & Hollander 2015; Politte et al., 2014; Politte et al., 2015; Politte & McDougle, 2014; Scahill et al., 2015; Scahill, Tillberg, & Martin, 2014; Stigler, 2014; Stigler, Erickson, & McDougle, 2013; Vasa et al., 2014; Vasa & Mazurek, 2015; Veenstra-VanderWeele, 2015; Westphal, Kober, Voos, & Volkmar, 2014; Wink et al., 2014). Supported by the National Institute of Mental Health, RUPP is a consortium of pediatric researchers focused on conducting well-designed, multisite psychopharmacology trials to provide science-based evidence to inform clinical practice. The discussion below seeks to synthesize key findings from the RUPP Autism Network and other scientific work to provide evidence-based guidance for PMHNPs providing medication to children and adolescents with ASD. The reader is initially introduced to general considerations for the psychopharmacology of ASD. Next, different approaches are reviewed for treating key target symptoms that often impair the functioning of individuals with ASD: irritability, RRBs, anxiety, attention deficit hyperactivity disorder (ADHD) like symptoms, depression, and sleep.

General Considerations for the Psychopharmacology of ASD

The psychopharmacological treatment of children and adolescents with ASD can be challenging for a variety of reasons (Politte et al., 2014). There are no federal Food and Drug Administration (FDA)-approved medications to treat the core symptoms of the disorder: social communication deficits and RRBs (Mohiuddin & Ghaziuddin, 2013). Only risperidone and aripiprazole are approved by the FDA and then only for the management of severe irritability (Stigler, 2014). All other medications prescribed for ASD are considered off-label. Unfortunately, there is often a limited amount of research to guide the use of off-label treatments (Westphal et al., 2014). Additionally, children and adolescents with ASD often do not experience the same magnitude of benefit from common medications frequently used in child and adolescent psychiatric practice such as stimulants and selective serotonin reuptake inhibitors (SSRIs; Politte et al., 2014). They also experience side effects from stimulants and SSRIs more frequently than their typically developing peers (Scahill et al., 2014). As a result, specialists in the psychopharmacology of ASD often recommend initially using lower doses of medication than is often common and titrating the doses upward more slowly than is typical (Veenstra-VanderWeele, 2015).

There are additional issues. It can be hard to distinguish between symptoms resulting from ASD itself and genuine comorbidities (Mazefsky et al., 2012). For example, differentiating some RRBs from an obsessive–compulsive disorder can be difficult (Westphal et al., 2014). As a result, medications are often selected based on their phenotypic or apparent similarity to the symptoms of more common psychiatric disorders such as generalized anxiety disorder or ADHD (Anagnostou et al., 2014). Finally, even with evidence-based guidance, the path toward finding a medication that is helpful is often not straightforward, resulting in the child and family being subjected to several unsuccessful medication trials and/or polypharmacy (Logan et al., 2015). Consequently, clinicians have increasingly found that behavioral interventions are a safer and more efficacious initial approach to treating some of the common target symptoms (Doehring, Reichow, Palka, Phillips, & Hagopian, 2014). Behavioral interventions may also be used effectively in combination with medication to reduce dosing levels, multiple trials, and potential polypharmacy (Veenstra-VanderWeele, 2015).

Irritability

Irritability, manifested through severe temper tantrums, aggression, or self-injury, is a common target of treatment that can impair the functioning of children with ASD (Stigler et al., 2013) and often motivates parents to seek out treatment (O'Neill, Jenson, & Radley, 2014). The prevalence of these behaviors often ranges considerably. A recent study of over 700 8-year-olds with ASD indicated that nearly 60% exhibited temper tantrums (Logan et al., 2015). The prevalence of aggression can range from 25% to 68% (Carroll et al., 2014). The lifetime prevalence of self-injury is estimated at approximately 50% (Minshawi et al., 2014).

Though psychiatric medications are often used to manage irritability, initially it would be useful to address potential medical or environmental stressors (Pallanti et al., 2015). Individuals with ASD may be struggling with seizures, gastrointestinal problems, dietary issues, pain, or infection and have trouble communicating this to caregivers (Veenstra-VanderWeele, 2015; Volkmar, Rowberry, et al., 2014). Managing these medical issues could significantly reduce the discomfort that leads to irritability. Also, children with ASD are often quite sensitive to changes in their environment (APA, 2013) such as a new bus driver, a substitute teacher, or a family member in the hospital. These kinds of changes can trigger irritability and could potentially be decreased, if possible, in some manner other than psychiatric medication.

In addition, there is growing evidence to support using behavioral interventions to treat irritability (O'Neill et al., 2014). For example, Applied Behavioral Analysis (ABA) is a research-based intervention that explores how aspects of the environment influence an individual's behavior. ABA draws heavily on operant learning, which focuses on environmental antecedents that set the stage for particular behaviors as well as the consequences that may increase or decrease particular behaviors through reinforcement (Joseph, Soorya, & Thurm, 2015). A particular ABA technique referred to as Functional Behavior Analysis (FBA) is used to study the antecedents and/or consequences of problematic behavior such as temper tantrums, aggression, and self-injury. Based on the results of the FBA, appropriate interventions are then selected to modify the environmental antecedents and/or consequences to reduce the problematic behavior. Additionally, improving the child's overall social functioning through a behavioral intervention can reduce irritability. A recent study found that after implementing a comprehensive early intervention behavioral program, the Early Start Denver Model, the maladaptive behaviors of preschoolers with ASD declined substantially (Fulton, Eapen, Crncec, Walter, & Rogers, 2014).

Finally, sleep disturbance, anxiety, ADHD symptoms, or depression may also exacerbate irritability, so it may be beneficial to treat these issues before directly tackling irritability (Pallanti et al., 2015). The thinking is that problems with sleep, anxiety, and ADHD symptoms can increase the general level of arousal that may lead to problems with irritability. Additionally, the medications that would successfully treat sleep, anxiety, ADHD, or depression typically have a safer side effect profile compared with atypical antipsychotic medications.

As noted above, risperidone and aripiprazole are the only FDA-approved medications to treat severe irritability (Stigler, 2014). This was based on the results of several randomized, double-blind, placebo-controlled trials (RDBPC; Ji & Findling, 2015). In the trials investigating risperidone, subjects with ASD (ages 5–17) received doses from 0.5 to 4.5 mg/day. The results indicated that risperidone separated from the placebo in reducing irritability. There was also separation from placebo in the reduction of irritability in the trials focused on aripiprazole. The subjects (ages 6–17) in these studies were given doses ranging from 2.5 to 15 mg. However, the potential benefits from using these medications have to be balanced against the possible costs such as weight gain and metabolic problems (elevated lipids; elevated glucose; and the potential long-term risk of diabetes, type 2; Correll, 2011). In the past, risperidone was thought to cause more weight gain and metabolic issues than aripiprazole. However, a recent study found a similar level of metabolic problems for these two medications when treating individuals with ASD (Wink et al., 2014). Risperidone can also elevate prolactin, which may lead to galactorrhea and menstruation problems in females and gynecomastia in males (Politte et al., 2015). Aripiprazole is not associated with hyperprolactinemia.

Several other atypical antipsychotics were investigated as possible treatments for irritability in a recent review (Politte & McDougle, 2014). A small RDBPC ($n = 11$) found that giving 7.5 to 12.5 mg/day of olanzapine to 6- to 14-year-olds will significantly reduce irritability. However, caution must be exercised when using this medication, because it is associated with more weight gain and metabolic problems than risperidone or aripiprazole. Two open-label trials of quetiapine found limited effectiveness and tolerability. An open-label trial indicates that the researcher and the research subject know the treatment being used. Open-label clinical trials suggest a possible role for ziprasidone (mean dose of 98 mg/day) and paliperidone (mean dose of 7.1 mg/day). Ziprasidone seems to cause less problems with weight gain; however, there remain concerns that it may cause prolonged QTc interval (Dominick et al., 2015).

A recent meta-analysis evaluated the use of anticonvulsants (AC) to treat irritability in individuals with ASD (Hirota et al., 2014). The results indicated that Valproate (Depakote) demonstrated inconsistent evidence for reducing irritability. Lamotrigine (Lamictal) and levetiracetum (Keppra) were not found to be effective. A combination of topiramate and risperidone significantly reduced irritability compared with risperidone plus placebo. However, a trial of topiramate as monotherapy for irritability found no difference between this medication and placebo. Because of these results, more evidence is required before recommending this class of medications to treat irritability in ASD (Hirota et al., 2014). However, some researchers suggest a role for treating irritability with ACs when individuals with ASD do not respond to atypical antipsychotics or have trouble tolerating these medications (Politte et al., 2014). Additionally, there may be a role for ACs when a child or adolescent with ASD has comorbid epilepsy (Hirota et al., 2014).

There is some evidence that alpha 2 adrenergic agonists such as guanfacine and clonidine can reduce milder irritability in younger children (Stigler et al., 2013). This appears due to the calming effect of these medications, which results from inhibiting the synthesis of norepinephrine in the locus coeruleus (Newborn, Clerkin, Schulz, & Halperin, 2011). Norepinephrine plays a role in arousal and stress. High levels of arousal can lead to increased problems with irritability. Some providers start with immediate release guanfacine initially, because it is generally less sedating than clonidine and it has a longer half-life (13–14 vs. 8–12 hr; Politte et al., 2015). The recommended target dose ranges from 0.5 mg twice a day to 3 mg/day depending on tolerability. A recent study of extended-release guanfacine (Intuniv) indicated that blood pressure declined during the first month of treatment; however, it returned to baseline at the end of the second month of treatment (Scahill et al., 2015).

Recommendations

In summary, there are several strategies for treating severe irritability. Start by managing medical comorbidities or environmental stressors contributing to tantrums, aggression, or self-injury. Employ behavioral interventions to target problematic behavior or more comprehensive behavioral programming to enhance social and adaptive functioning. If medication is required, consider initially treating anxiety, ADHD, sleep, or depression that may be exacerbating behavioral dysregulation. If irritability needs to addressed more directly, alpha 2 adrenergic agonists such as guanfacine or clonidine, are safe options, particularly for milder forms of irritability in younger children. High levels of irritability may warrant FDA-approved medication such as risperidone or aripiprazole, particularly if there are concerns regarding the safety of the client or other individuals and if the client's educational placement is in jeopardy. If FDA-approved antipsychotics are not effective or tolerated, there is some evidence to support the use of paliperiodone, ziprasidone, or olanzapine.

Interfering Restricted, Repetitive Behavior

Interfering restricted, repetitive behavior (RRB) is one of the key diagnostic criteria for the ASD (APA, 2013). Young typically developing children (ages 2–5) also exhibit RRBs; however, children with ASD exhibit more frequent and a wider range of RRBs (Harrop, McConachie, Emsley, Leadbitter, & Green, 2014). Depending on the severity, RRBs in children and adolescents with ASD may significantly impair their functioning in settings such as home or school (Doyle et al., 2014).

Though psychiatric medication has often been used to manage RRBs in the past, there is growing evidence to support using ABA (Harrop, 2014), particularly for repetitive motor behavior (Joseph et al., 2015). As noted earlier, the first step may involve doing an FBA to determine the antecedents and/or consequences that might be triggering or reinforcing the RRB. Strategies that have been used in the past for RRBs are the reinforcement of an alternative behavior, response interruption, and extinction. However, full extinction of repetitive motor behavior is not typically advised without providing an alternative behavior to help manage the "frustration, anxiety, and other arousal states related to the original function" (Joseph et al., 2015, p. 61) of the repetitive behavior.

The SSRIs have been the medication class most often studied in the treatment of RRBs (Doyle et al., 2014). This work was informed by a common finding that children with ASD often have dysregulated serotonin functioning (Westphal et al., 2014). However, the results from trials of SSRIs to treat RRBs in children have not been positive (Carrasco, Volkmar, & Bloch, 2012). There has been limited evidence of efficacy and significant problems with side effects, particularly activation. Activation may be evidenced by hyperactivity, impulsivity, aggression, insomnia, stereotypies, or irritability. For example, an RDBPC of citalopram (mean dose of 16.5 mg/day) administered to 5- to 17-year-olds by the RUPP network (King et al., 2009) found no significant reduction in RRBs and significant problems with adverse events, particularly activation. Some researchers have also trialed SSRIs based on the thinking that RRBs are a form of OCD. However, FDA-approved medications to treat OCD such as fluvoxamine and clomipramine were found to be ineffective and often caused significant problems with side effects (Scahill et al., 2014).

Findings from SSRI trials with adolescent or adults with ASD have indicated less issues with efficacy and tolerability (Doyle et al., 2014). However, a recent meta-analysis of published and unpublished trials of SSRIs to treat RRBs in children and adolescents with ASD found significant evidence of publication bias. When a statistical procedure was employed to correct for this bias, the results indicated no significant benefit for using SSRIs to treat RRBs (Carrasco et al., 2012).

Atypical antipsychotics and atomoxetine have been studied in reducing RRBs. Although not FDA-approved for this purpose, risperidone (0.5–4.5 mg/day) and aripiprazole (2–15 mg/day) have been found in the RDBPCs discussed in the irritability section above to reduce stereotypies in individuals with ASD (Ji & Findling, 2015). Again, the benefit of using these medications would have to be balanced against side effects such as weight gain and metabolic problems. Other atypical antipsychotics such as olanzapine, quetiapine, and ziprasidone have not been found to be effective at reducing RRBs (Ji & Findling, 2015). Recently, an RDBPC of children and adolescents with ASD (6- to 17-year-olds) found some reduction in RRBs with atomoxetine dosed at 1.2 mg/kg per day (Harfterkamp et al., 2014).

The reason RRBs may often be refractory to behavioral and psychopharmacologic treatment is that they are driven by a "variety of pathological factors" (Yang et al., 2015, p. 1) such as the following: abnormal physiological arousal (McCormick et al., 2014); altered development of the striatum (Langen et al., 2014); biochemical dysregulation (Yang et al., 2015); the disrupted structural and functional interaction between overlapping neural circuits (Traynor & Hall, 2015); and the interplay among anxiety, intolerance of uncertainty, and sensory processing abnormalities (Wigham, Rodgers, South, McConachie, & Freeston, 2015).

Recommendations

Some types of RRBs such as repetitive motor behaviors can be improved through behavioral intervention. There is inadequate evidence to support the use of SSRIs to reduce RRBs. However, there are such limited psychopharmacological and behavioral tools to reduce RRBs (particularly insistence on

sameness and a fixated interest) that many providers will turn to an SSRI, especially in response to concerns expressed by parents and educators (Veenstra-VanderWeele, 2015). Consequently, if an SSRI is initiated, start at a lower dose than usual: "one fourth to one half of the lowest dose available" (Politte et al., 2015, p. 41). Titrate upward more slowly than is customary, and monitor carefully for activation and possible aggression. One researcher clinician specializing in the psychopharmacology recently suggested SSRIs with a shorter half-life (sertraline, citalopram, or escitalopram) would be preferable. One recent study suggests a possible use of atomoxetine for reducing RRBs. If an RRB is causing significant issues with safety at home, school, or elsewhere, there might be a role for risperidone or aripiprazole, if other treatment options fail.

Anxiety

Children and adolescents with ASD commonly struggle with anxiety (White et al., 2014). A recent review found that the prevalence of anxiety disorders ranged from 26% to 84% (Vasa & Mazurek, 2015). By comparison, the prevalence of anxiety for typically developing children ranged from 2.2% to 27%. Some commonly diagnosed anxiety disorders for children with ASD are specific phobias, OCD, social phobia, generalized anxiety disorder, and separation anxiety disorder (Lecavalier, Kaat, & Stratis, 2014).

High-functioning ASD youth with anxiety may benefit from modified cognitive behavioral therapy (CBT; Vasa et al., 2014; Vasa & Mazurek, 2015). The modifications may consist of using visual supports to help with learning, focusing on emotion regulation, and helping to reduce the perseveration on a special interest. The response rates for using modified CBT for this population range from 38% to 71%, which is comparable to the response rates for typically developing youth. Some research has also found that other types of behavioral treatment may be helpful in reducing the anxiety of lower-functioning children and adolescents with ASD (Vasa et al., 2014; Vasa & Mazurek, 2015).

Though the prevalence of anxiety disorders for individuals with ASD indicates this is an important comorbidity, there is very little research investigating the use of medication to treat these disorders (Vasa et al., 2014; Vasa & Mazurek, 2015). A recent systematic review only found four studies, none of which were randomized, placebo-controlled trials (Vasa et al., 2014). Two of the studies focused on the use of citalopram. In one of these, 59% of the subjects (ages 4–15 receiving a mean dose of 19.7 mg/day) showed improvement and in the other study 66% of the subjects (ages 6–16 receiving a mean dose of 16.9 mg/day) showed improvement. Another trial explored the use of fluvoxamine to treat anxiety in children with ASD. The results indicated no improvement from this medication and significant problems with side effects. Nine of the 18 subjects in this study struggled with activation. The fourth trial investigated the efficacy of buspirone for treating anxiety. Of the 22 subjects (ages 6–17 receiving a mean dose of 29.3 mg/day), 41% had a markedly positive response to buspirone and 32% had a moderately positive response. Several scholars also suggest that if children with ASD have trouble tolerating an SSRI then mirtazapine could be useful for treating anxiety (Politte et al., 2014; Scahill et al., 2014). An open-label study of mirtzapine found that 34.6% of the subjects were much improved or very much improved on a range of symptoms including anxiety (Scahill et al., 2014).

Recommendations

Children and adolescents with ASD and anxiety may benefit from CBT. Unfortunately, there is very limited research to inform the use of medication to treat this common comorbidity. If an SSRI is initiated, start at a lower dose than usual: "one fourth to one half of the lowest dose available" (Politte et al., 2015, p. 41). Additionally, titrate upward more slowly than is customary and monitor carefully for activation and possible aggression. One researcher/clinician specializing in the psychopharmacology of ASD recently suggested SSRIs with a shorter half-life would be preferable (Veenstra-VanderWeele, 2015). Some research supports the role of mirtazapine or buspirone, if an SSRI is ineffective or difficult to tolerate (Politte et al., 2014; Scahill et al., 2014). Others also indicate a possible role for duloxetine or venlafaxine when other medications prove unsuccessful (Politte et al., 2015).

ADHD Symptoms

In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2000), diagnosing a child with ASD with comorbid ADHD was not recommended. As accumulating evidence indicated that children with ASD frequently struggled with hyperactivity, impulsivity, and inattention, *DSM-5* (APA, 2013) permitted a comorbid diagnosis of ADHD. Current research suggests that the prevalence of ADHD in children with ASD ranges from 28.2% to 60.3% (Lecavalier et al., 2014; Salazar et al., 2015).

Several large studies of typically developing children with ADHD funded by the National Institute of Mental Health demonstrated a positive response rate to methylphenidate (MPH) of approximately 70% to 80% (Politte et al., 2014). However, past research in children with ASD and ADHD symptoms has shown a much lower response rates to MPH. In the largest randomized controlled trial of MPH to date, only 49% of subjects with ASD (ages 5–14 receiving 7.5 to 50 mg/day) responded positively (Ji & Findling, 2015; Mohiuddin & Ghaziuddin, 2013). Similarly, a more recent study of 64 subjects with ASD (ages 5–14 years of age receiving low [0.125 mg/kg], medium [0.25 mg/kg], and high

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[0.5 mg/kg] doses of MPH administered in the morning, noon, and a half dose at 4 pm) found that only half responded positively to MPH (McCracken et al., 2014). This study also found that the limited response rate to MPH was likely associated with variation in the genes involved with dopamine, norepinephrine, and serotonin regulation.

Along with issues related to the response rate for MPH, there are issues with tolerability (Pallanti et al., 2015). In several studies, children with ASD and ADHD exhibited higher rates of side effects from MPH than typically developing children and a larger percentage withdrew from the studies due to side effects (Scahill et al., 2014). In one study, 18% of the 72 subjects (ages 5–14) withdrew (Politte et al., 2014). Irritability was the most common adverse event that led to children dropping out. Other problematic side effects were social withdrawal, motor tics, stereotypies, decreased appetite, and insomnia. Because of the increased problems with side effects, some researchers have suggested starting with a small test-dose of immediate release MPH, particularly with younger children (Politte et al., 2015).

As yet, there are no studies of amphetamine-based stimulants to treat ADHD symptoms in children with ASD (Pallanti et al., 2015). There are, however, studies that investigate the use atomoxetine. The results of this research indicate mixed results regarding the efficacy of atomoxetine but limited problems with side effects (Veenstra-VanderWeele, 2016). In one study, 6- to 17-year-olds with ASD and ADHD received 1.2 mg/kg per day of atomoxetine. Twenty-one percent of them were rated as very much or much improved. Only one subject dropped out due to sedation. In another trial, 5- to 14-year-olds received 1.8 mg/kg per day of atomoxetine. Forty-eight percent were rated as much improved or very much improved. Decreased appetite was the only reported adverse event.

Alpha 2 adrenergic agonists such as guanfacine and clonidine have been also studied as treatments for ADHD symptoms in children with ASD (Mohiuddin & Ghaziuddin, 2013). There appears to be growing evidence of efficacy and better tolerability for these medications compared to other agents. Especially promising is a recent study investigating extended-release guanfacine (Intuniv) to treat ADHD symptoms in subjects with ASD ranging from 5 to 14 years of age (Scahill et al., 2015). The findings indicated that a 3 mg modal dose of extended-release guanfacine was effective for significantly reducing hyperactivity, impulsivity, and inattention. Additionally, when comparing the results to studies with other ADHD medications, extended-release guanfacine appeared to be as effective as MPH and more effective than atomoxetine. However, in an earlier study of extended-release guanfacine with typically developing children, many younger children (ages 6–12) dropped out of the trial due to problems with side effects (Sallee, Lyne, Wigal, & McGough, 2009). As a result, some scholars caution that younger children with ASD may have difficulty tolerating the 1 mg weekly increases of extended-release guanfacine (Scahill et al., 2014).

Recommendations

When targeting ADHD symptoms, it may be useful to target dysregulated sleep and anxiety first, because these issues can exacerbate ADHD symptoms. Alpha 2 adrenergic medications such as guanfacine may be better tolerated than stimulants such as MPH and be equally effective and, consequently, may be a safer initial option for treatment, especially with children. However, very young children may have difficulty tolerating the extended-release version of guanfacine and may respond better to the short acting formulation. Due to the increased likelihood of side effects from stimulants, consider using an initial test dose of short-acting MPH, particularly with younger children. If this is unsuccessful, consider a trial of atomoxetine. If these medications fail to demonstrate any benefit, there may be a role for an amphetamine-based stimulant. Severe impulsivity that may lead to risk of injury or elopement may respond to atypical antipsychotics such as risperidone or aripiprazole, if other forms of treatment fail.

Depression

In a recent study, the rates of depressive symptoms in children and adolescents with ASD were higher than found in neurotypical peers and non-ASD developmentally delayed peers (Gotham, Brunswasser, & Lord, 2015). Depressive symptoms rapidly rose for females with ASD during adolescence (Gotham et al., 2015). However, males with ASD had high levels of depressive symptoms throughout their school years and into young adulthood. The actual prevalence of depressive disorders varies considerably from one study to the next: a recent review found rates of 1% to 10.6% (Lecavalier et al., 2014) in children with ASD. An earlier study reported a 54% prevalence of depression for children with high functioning ASD (IQ $>$ 80), and 42% for lower functioning children with ASD (IQ $<$ 80; Mayes, Calhoun, Murray, Ahuja, & Smith, 2011). Several scholars suggest depression may present differently in children and adolescents with ASD compared with typically developing peers (Doyle et al., 2014; Lecavalier et al., 2014). However, there are currently no studies systematically examining this claim.

Recommendations

There is a very limited amount of research investigating the use of medication to treat depression in children and adolescents with ASD (Westphal et al., 2014). Fluoxetine and fluvoxamine have been studied with inconsistent evidence of efficacy and an increased likelihood of issues with side effects. Because past studies have identified serotonin dysfunction in individuals with ASD, some scholars continue to

recommend the possibility of using SSRIs to treat depression in children and adolescents with ASD (Westphal et al., 2014). One researcher specializing in the psychopharmacology of ASD suggests that SSRIs with a shorter half-life such as sertraline (26 hr), escitalopram (27–32 hr), and citalopram (35 hr) would have some utility (Veenstra-VanderWeele, 2015). If an SSRI is used, start at a lower than usual dose and titrate upward more slowly than is customary (Politte et al., 2015). Monitor carefully for activation and aggression. At a recent psychopharmacology update for the American Association of Child and Adolescent Psychiatry, a researcher specializing in the psychopharmacology of ASD also suggested the possibility of bupropion or mirtazapine, if an SSRI was not helpful (Veenstra-VanderWeele, 2015). Others researchers indicate that duloxetine and venlafaxine could have a role if SSRIs are not effective (Politte et al., 2015).

Sleep

Sleep is an important issue in ASD, because its dysregulation is linked to an exacerbation of the core symptoms of the disorder as well as concerning symptoms such as temper tantrums, aggression, and self-injury (Cohen, Conduit, Lockley, Rajartnam, & Cornish, 2014). Unfortunately, children and adolescents with ASD frequently have sleep-related issues. In a recent survey, parents reported that 40% to 80% of their children with ASD had sleep difficulties compared with a range of 25% to 40% for typically developing children (Cohen et al., 2014). A recent meta-analysis found that children with ASD also had shorter total sleep time, longer sleep onset latency, and less sleep efficiency (Elrod & Hood, 2015). Sleep efficiency is the percentage of time that someone is actually sleeping when lying down. Children with ASD and an intellectual disability seemed to have the most significant decreases in total sleep time.

To help with this, Malow and colleagues developed a practice pathway based on expert consensus to guide providers working with children who have ASD and insomnia (Malow et al., 2012). The pathway recommends initially identifying any possible medical or psychiatric comorbidities that may be causing sleep difficulties and treating these first. If there are not any comorbidities, the client and family are assessed for the appropriateness of starting sleep education. A recent randomized control trial of sleep education for parents of children with ASD found significant improvement in the sleep habits of their children and their behavior (Malow et al., 2014). If the family is unwilling or unable to benefit from sleep education, the next step would involve a referral to a sleep specialist. If the referral does not alleviate the sleep problems, then the provider could consider initiating a sleep medication or referring to a sleep specialist to manage the insomnia medication.

Unfortunately, like other areas of ASD psychopharmacology, there is a limited amount of research for treating sleep disturbances (Westphal et al., 2014). Two trials, one employing an RDBPC crossover design and the other an open design, looked at the use of melatonin in children with ASD and sleep problems. In the RDBPC crossover trial, 11 subjects (4 to 16 years of age) received 5 mg of melatonin. The results indicated decreased time for sleep onset, fewer awakenings throughout the night, and increased duration of sleep. The open trial focused on subjects with ASD from 6 to 16 years of age taking 3 mg of melatonin and also reported improved sleep functioning. Additionally, there was an improvement in behavior during the day, which was likely the result of better sleep regulation throughout the night.

Recommendations

The clinical pathway developed by Malow and colleagues can help children and adolescents with ASD struggling with insomnia. If the sleep problem does not resolve after initiating the clinical pathway, some research supports the use of melatonin. Researchers specializing in the psychopharmacology of ASD also suggest the possibility of using a melatonin receptor binding agent such as ramelteon (Veenstra-VanderWeele, 2015). Failing these two options, the following medications could be considered: clonidine (may only be helpful for sleep onset), hydroxyzine, trazodone, or mirtazapine (McDougle, 2012).

Conclusion

In conclusion, ASD is a complex neurodevelopmental disorder requiring a multidisciplinary approach to treatment. Psychopharmacology should be considered one element within an array of services needed to help a child or adolescent with ASD. There are no FDA-approved medications to treat the core symptoms of ASD. Consequently, all medications, besides risperidone and aripiprazole for severe irritability, are considered off-label. Children with ASD often struggle with particular symptoms such as severe irritability, interfering RRBs, ADHD, anxiety, depression, and sleep. However, due to lower rates of efficacy and higher rates of side effects, typical medications such as antidepressants and stimulants used to treat some of these target symptoms should be used cautiously. A growing body of research does indicate that behavioral approaches for treating the target symptoms can be effective as sole interventions or in combination with psychiatric medication. However, even with evidence-based guidance finding the appropriate intervention and/or medication for a child with ASD may still be challenging and require clinician patience and tenacity. The payoff, however, will be the reward of helping a child with ASD more

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effectively cope and thrive at school and home. This will undoubtedly result in making the effort worthwhile.

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