Antipsychotic Medications

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Autism spectrum disorder (ASD) is a complex developmental disorder with specific language, social, and developmental symptoms. Most notable are deficits in verbal and nonverbal communication skills; social impairments; and difficulties engaging in social interactions. Inflexibility of behavior, attention, and focus; difficulty coping with change; and other restricted and repetitive behaviors are also major characteristics. Behaviors are manifest as stereotyped or repetitive behaviors, insistence on sameness, restricted and fixated interests often of extreme focus, and hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment. Despite not being among the core behaviors listed in formal diagnostic criteria, irritability and aggression are among the most problematic behaviors for children with ASD (Brosnan & Healy, 2011).

In response to disruption to preferences for sameness, social and communication frustrations, reaction to sensory stimuli, and several other causes, children with ASD commonly experience severe irritability and even aggression toward others and themselves (Sullivan et al., 2019). There is a tendency for irritability and aggression to be more common and more severe for children with ASD who require substantial support and for those with concurrent intellectual developmental disabilities (Hirota et al., 2020). Irritability and aggression are manifest in multiple behaviors, all of which lead to important functional impairments and represent dangers to the person with ASD, age peers, caregivers, and educators (Axmon et al., 2017).

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Irritability and aggression are part of severe functional impairments that result in disruptions of educational, therapeutic, or daily living activities for approximately 20% of children diagnosed with ASD (McGuire et al., 2016).

Irritability refers to motor or vocal outbursts of anger, frustration, pain, or other distress. These behaviors are often called temper tantrums, meltdowns, rages, or severe emotional reactions. Behaviors may include screaming, shouting, crying, running away (also known as eloping or bolting), avoiding others, and pronounced withdrawal. There is usually resistance to attempts to pacify the person experiencing irritability. Efforts to self-calm and self-sooth such as self-stimulation and self-injurious behaviors increase during irritable phases (Hirota et al., 2020).

Aggression include acts with potential to harm other people, property, or themselves. Aggressive behaviors include destroying items within reach, and hitting, kicking, pinching, or biting others. Sometimes there is a lashing out at anything or anyone within reach and other times aggression is directed toward the source of the frustration. Aggression can also be self-directed with head banging, self-biting, or head smacking. Irritability and aggression are top priority targets of interventions because they dramatically interfere with safety, daily life, and effective therapeutic and educational interventions.

The causes of irritability and aggression are often difficult to identify. In some cases, gastrointestinal dysfunction, dental orofacial pain, sleep problems, epilepsy and epileptiform abnormalities, and medication side effects cause, or at least influence, the onset and direction of irritable and aggressive behaviors (McGuire et al., 2016). There are a variety of social causes that increase stress such as peer bullying, parental and family stress, and environment-person mismatch (Leaf et al., 2020). Treatment of irritability and aggression are best started by assessing and addressing the above medical and social stress contributors before developing a treatment plan.

Applied behavior analysis is the most strongly recommended first-line treatment of irritability and aggression for children with ASD (Fisher et al., 2019). This form of treatment is most effective when a functional behavior assessment (FBA) is used to determine the antecedent, discriminant stimuli, and behavioral consequences that elicit and maintain the behavior. Antecedent stimuli and situations frequently trigger irritability and aggression and are targets of behavioral interventions. Discriminant stimuli refer to signals that a reinforcing or punishing consequence is likely to occur. Consequences are the delivery of reinforcers that maintain or increase behaviors. Punishment can be an effective consequence that reduces a set of behaviors, but have the negative outcome of increasing emotional responses and often increasing other forms of irritability and aggression (Sullivan et al., 2019). Changing antecedents, reinforcement-based strategies, educational interventions, and behavior reductions strategies can be extremely effective in reducing or eliminating irritable and aggressive behaviors.

The evidence supports use of behavioral approaches to address irritable and aggressive behaviors, but there are challenges (Yu et al., 2020). Expertise and time are required to conduct an FBA sufficient to identify aspects of the environment that would result in positive change when altered. Educators, caregivers, and other professionals with influence over the environment need to be coordinated, understand

the treatment strategy, and be fully motivated and capable to carry out the plan. Implementing an effective treatment plan is challenging. When the very best plan is poorly implemented the potential effectiveness is reduced dramatically, often to zero positive effect. A related concern is sustainability. Complex plans often begin with quality implementation but enthusiasm for the plan, time and expense of data collection and monitoring, and support for services wane over time. Quite often sustainable plans are difficult to develop. Even though plans based on applied behavior analysis principles are effective in a research environment there are multiple implementation factors that make these interventions a challenging treatment strategy for children with ASD who are demonstrating irritability and aggression.

There are many reasons to consider pharmacological interventions for children with ASD who have irritable and aggressive behaviors (Fallah et al., 2019). Many parents and teachers find that implementing, maintaining, and evaluating the effectiveness of the behavior plan is extraordinarily difficult. Implementing a medication regimen, in contrast, is relatively easy (D'Alo et al., 2020). The children or adolescents simply swallow a pill and are monitored for notable changes in behavior. This is analogous to weight loss efforts where eating less and exercise are excellent forms of treatment; yet, it would be far easier for most people to swallow a weight-loss pill. Also, professionals who conduct an FBA are not common in many communities (Yu et al., 2020). Most communities have extensive waiting lists for such professionals. Medication is frequently administered by family physicians (Wink et al., 2018). Behavioral systems require many hours of observation, consultation, coaching, and monitoring. This can be an extremely resource intensive practice. Antipsychotic medications tend to be relatively inexpensive (Ruiz et al., 2016). Adjusting and monitoring medication affects require comparatively less professional time, therefore expenses and resources (Ruiz et al., 2016). Finally, irritability and aggression are disruptive behaviors. Behavior analysis plans tend to require an extended period before they become effective in dramatically reducing irritable and aggressive acts (Vinson & Vinson, 2018). In cases where these behaviors are violent or destructive, waiting for the behavioral system to take effect may not be a viable option. Antipsychotic medications work relatively quickly and can result in significant reductions in irritability and aggression (Tromans & Adams, 2018).

Antipsychotic medications are the second most widely prescribed psychotropic medication for children and adolescents after stimulant medications (Posey et al., 2008). Most prescriptions for this class of medication are off-label use for aggressive behaviors that are secondary to attention deficit hyperactivity disorder, major depressive disorder, bipolar disorder, oppositional defiant disorder, and conduct disorder (Accordino et al., 2016; de Kuijper & Hoekstra, 2018; Stepanova et al., 2017). These conditions are significantly removed from the intended purpose of the class of drugs called atypical antipsychotic or second-generation antipsychotics. The primary original purpose was to address many of the symptoms involved schizophrenia and related diagnoses. However, children, adolescents, and adults with ASD frequently demonstrate stereotyped behaviors, irritability, self-harm, and aggression. Noting that in some cases this typology of behavior also occurs in persons with schizophrenia, applications of antipsychotic medications to people with ASD were

tried on a case study basis, then open label and RCTs (Coury et al., 2012). There have been attempts to use antiepileptic drugs and mood stabilizing medications to manage aggression in ASD, yet those studies have been inconclusive (Stepanova et al., 2017). Stimulant medications have also been used to decrease symptoms similar to persons with ADHD and are effective in addressing hyperactivity but have minimal effects on irritability, self-harm, and aggression.

Despite behavioral interventions proved to be effective in managing irritability and aggression for children and adolescents with ASD, the high cost of psychosocial intervention, pragmatic problems with implementation, time and effort requirements, and difficulty accessing these treatments all contribute to increased clinical reliance on antipsychotics as a quick, available, and fast-acting alternative to behavioral interventions (Crespi, 2019). The US Food and Drug Administration (FDA) approved risperidone and aripiprazole for the treatment of severe irritability and aggression in children with autism aged from 5 years in the case of risperidone or 6 years in the cases of aripiprazole through adulthood (Maneeton et al., 2018a; Rizzo & Pavone, 2016). However, there is a compelling body of evidence supporting extensive weight gain and metabolic adverse effects of atypical antipsychotics for children and adolescents, especially with long-term use (Croteau et al., 2019). Moreover, long-term consequences of atypical antipsychotics on the developing brain and body of youth, especially those with ASD, remain largely unknown (Allison & Casey, 2001; Stigler et al., 2009). With a variety of advantages and disadvantages to the use of atypical antipsychotic medication for children and adolescents with ASD, a detailed understanding of the medications is required prior to consideration (Masi et al., 2001).

Antipsychotic Medications

Antipsychotic medications, formerly known as major tranquilizers and neuroleptics, are the primary class of drugs used to treat psychotic disorders such as schizophrenia. The use of first generation or typical antipsychotic medications became widespread in the 1950s to treat the positive symptoms of schizophrenia such as delusions and hallucinations (Kim et al., 2006). This class of medications are less effective with negative symptoms such as apathy, executive function deficits, paucity of language, and lack of interest in social interactions. Included in this class are chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, and trifluoperazine. The use of typical antipsychotics diminished in the 1970s as concerns over extrapyramidal side effects such as tremors, body rigidity, impaired gait, and other Parkinsons-like movements grew with quality research and careful clinical observations (Alfageh et al., 2019). With long-term use, these antipsychotic medications are associated with tardive dyskinesia (TD), which consists of involuntary and repetitive body movements such as facial grimaces, loss of tongue control, and smacking of lips.

Involuntary jerking or writhing movements can also occur. In addition, neuroleptic malignant syndrome, a severe reaction that includes high fever, confusion, rigid muscles, swings in blood pressure, sweating, and fast heart rate also occurs. Neuroleptic malignant syndrome usually occurs within the first few weeks of taking this class of medication and requires immediate medical attention and monitoring (Vanwong et al., 2017). As such, second generation or atypical antipsychotics, which were believed by many to have a less severe profile of side effects, have largely replaced the first generation or typical antipsychotic medications (Accordino et al., 2016).

Both typical and atypical antipsychotics block dopamine D2 receptors in dopaminergic pathways (Bourin, 2018). Given that excess dopamine along the mesolimbic pathway has been associated with psychotic experiences, decreased release of dopamine is likely the primary mechanism of effectiveness. However, typical antipsychotics are not especially selective in their effects and also affect dopamine D2 receptors in the nigrostriatal pathways among other loci, which results in some of the unintended motor and cognitive effects (Correll & Schenk, 2008). The focus of typical antipsychotics on the D2 receptors is effective in reducing the overactive dopaminergic activity in the mesolimbic pathway responsible for symptoms such as delusions and hallucinations. However, this focus also leads to common, problematic, and sometimes permanent side effects.

Atypical antipsychotics also affect D2 receptors, but also serotonin (5-HT) and norepinephrine receptors. Because atypical antipsychotics also block dopamine D2 receptors and are not especially selective to the mesolimbic pathway there is still the possibility of extrapyramidal side effects. However, atypical antipsychotics affect 5-HT2A receptors, which reverses some of the effects on the multiple dopamine system pathways; therefore, reducing the frequency and severity of some of the negative side effects when compared to typical antipsychotics (Ho et al., 2011).

The 5-HT receptors affected by atypical antipsychotics are especially important in addressing issues in ASD. Hallucinations and delusions are not the target behaviors for children with ASD. By activating 5-HT receptors there is a blockage of dopamine and inhibition of norepinephrine release. This combination leads to a decrease in aggression behaviors, an increase in sociability, and decreases in anxious and depressive symptoms for persons with schizophrenia (Crespi, 2019). There is clear evidence of decrease in aggressive behaviors for children with ASD, but the evidence of increased sociability and decreased anxiety and depression are mixed for persons with ASD (Accordino et al., 2016).

There are a host of atypical antipsychotics available. They all differ slightly in their binding on the various dopamine receptors (i.e., D1, D2, D3, and D4), serotonin receptors (i.e., 5-HT1A, 5HT-1B, 5-HT2A, 5-HT2c, 5-HT6, 5-HT7), and norepinephrine receptors (i.e., α1, α2, M1, M3, H1) (Stepanova et al., 2017). The medications in this class include: amisulpride, aripiprazole, asenapine, blonaserin, cariprazine, clozapine, iloperidone, lurasidone, melperone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, and zotepine.

Use and Prescribing Issues for Children with ASD

There are only two medications, risperidone and aripiprazole, that are approved by the US FDA for the management of symptoms associated with ASD (McClellan et al., 2016). However, close to half of children with ASD are receiving psychopharmacological interventions with stimulants, α-agonists, antipsychotics, and antidepressants (D'Alo et al., 2020). In addition, many families use natural remedies, supplements, and chelating agents, all of which may cause adverse effects and interact with prescribed medications (Linke et al., 2017).

Although there are challenges to prescribing and monitoring atypical antipsychotics alone, polypharmacy complicates the issue (Rezaei et al., 2010). Atypical antipsychotics are frequently prescribed with other psychotropic medications to address the common multi-symptom profiles of children and adolescents with ASD. The most common co-prescribed class of medications involve stimulant medications to address attention issues. Many people with ASD are also diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) (Ozdemir et al., 2020). However, stimulant medications are frequently prescribed to address inattentive symptoms even if a dual diagnosis of ADHD and ASD are not made (Spencer et al., 2013). Although anxiolytics, antidepressants (selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors), and anti-seizure medications are generally contraindicated for use with atypical antipsychotics such use is not uncommon. In a minority of cases, patients receive multiple prescriptions from a single psychiatrist. The following situations are far more common: a psychiatrist prescribes the atypical antipsychotic and a family physician or other specialist prescribes additional medications, family physician prescribes all medications, or family physician prescribes atypical antipsychotic and other specialists prescribe additional medications (Brophy et al., 2018). The commonality is that multiple prescribing physicians are often not aware of the medication that the others are prescribing. Although all cases represent justifiable practices it is quite likely that a psychiatrist has the most experience with atypical antipsychotics, monitoring side effects, and interactions. Lack of experience with the diversity of responses to atypical antipsychotics can be problematic. Often pharmacists are the professionals that carefully examine multiple prescriptions to identify interactions and other potentially problematic issues. Although it is not uncommon for persons to have prescriptions filled at multiple pharmacies making identification of possible medication interactions more challenging (Hazell, 2018). Because of the potential severity and permanence of side effects, coordination and communication among parents, patients, and medical professionals is required any time atypical antipsychotics are being considered.

Efficacy. Most efficacy studies of atypical antipsychotics are open label trials where the participants, the parents, and the researchers are aware of medications being prescribed (Downs et al., 2016). Methodologies range from case studies, open label with no placebo, open label with clinical convenience samples, open label with randomization, and double-blind randomized control trials (RCTs). There are

consistent findings throughout all research designs that risperidone and aripiprazole result in moderate to high levels of improvement in irritable and aggressive behaviors (Bartram et al., 2019). The two FDA-approved atypical antipsychotics, risperidone and aripiprazole, have the highest level of evidence for the treatment of irritability and aggression for people with ASD. However, there have been several studies of both typical and atypical antipsychotics (Ichikawa et al., 2017).

The first antipsychotic medication evaluated for children with ASD was the first-generation or typical antipsychotic, haloperidol. In 1978, there was a 12-week RCT for 40 children from 2 to 7 years of age (Campbell et al., 1978). The purpose was to investigate if the medication created positive change in behaviors common to children with ASD such as social withdrawal, stereotyped behaviors and movements, and other psychiatric symptoms as measured by the *Children's Psychiatric Rating Scale*. Results showed statistically and clinically significant improvement in several areas including social withdrawal, learning, attention, and maladaptive behaviors such as anger, irritability, cooperativeness, and labile mood. The study has been replicated several times (e.g., Anderson et al., 1989; Campbell et al., 1997; Kim et al., 2006). However, a high frequency of TD and withdrawal-caused extrapyramidal effects were noted. Although haloperidol was demonstrated to be an improvement over placebo for a host of behaviors for children with ASD, an extraordinarily high incidence of severe side effects was considered problematic (Perry et al., 1989). Clinical use of haloperidol is now relatively rare and is not typically considered a safe medication for children and adolescents with ASD.

Most research on antipsychotic medications for children and adolescents with ASD involves second-generation antipsychotics. Clozapine was the first atypical antipsychotic to be used for people with ASD (Rothärmel et al., 2018). There are studies of children and adults with ASD that show significant improvements in irritability and severe aggression when treated with clozapine. However, an increased risk of agranulocytosis, extremely low white blood cell counts, was identified (Rothärmel et al., 2018). This severe side effect is one reason that clozapine is not widely used for children with ASD.

Risperidone has been approved by the US FDA as a safe and effective treatment for severe aggression, self-injurious behavior, and irritability. This is also the most extensively studied antipsychotic mediation for children, adolescents, and adults with ASD. Several open label studies demonstrate the effectiveness of risperidone on target symptoms of irritability and aggression in self injury. Several years later there were a series of RCTs of children and adolescents with ASD. For example, an eight-week study of 101 children indicated that 69% of the risperidone treated subjects were considered to show clinically important improvement in irritability (Sharma & Shaw, 2012). Reports are that 58–86% of children and adolescents respond positively to risperidone. Meta-analyses report the consistent finding of positive effects on irritability and aggression in over 40 different studies (Barnard et al., 2002; Park et al., 2016; Sharma & Shaw, 2012).

Aripiprazole has also been approved by the US FDA and is a safe and effective treatment for stereotyped behavior, irritability, hyperactivity, and aggression. There are multiple studies based on RCTs, open label trials, retrospective chart reviews,

and case-control strategies. There is also mixed evidence that aripiprazole has positive effects on adaptive behavior in low functioning children with ASD. Effectiveness rates have ranged from 54 to 78% on multiple variables (Findling et al., 2014). The medication has been shown to be well-tolerated for a long period of time and the response has been maintained over multiple years in longitudinal studies (Chandrasekhar et al., 2020; Hazell, 2018; McClellan et al., 2016; Maneeton et al., 2018b; Ozdemir et al., 2020; Rizzo & Pavone, 2016; Tromans & Adams, 2018). A study comparing risperidone and aripiprazole resulted in similar responses over the same general variables of interest. Risperidone and aripiprazole have functionally similar side effect profiles. As with risperidone, multiple meta-analyses report positive effects of aripiprazole for children and adolescents with ASD (Ghanizadeh et al., 2014).

Olanzapine is not been well studied with extensive RCTs, yet there are open label trials and case reports. There is evidence that 50–75% of participants are effective responders in terms of significant decrease in irritability and aggression (Hollander et al., 2006). However, the likelihood of sedation and weight gain is high when compared to risperidone (Kemner et al., 2002). Yet, few studies were reported to have participants who experienced the EPS that have been widely reported with other atypical antipsychotics (Tural Hesapcioglu et al., 2020).

There are some open label trials of quetiapine, but no RCTs as yet. There is some evidence that this medication improves inattention, hyperactivity, and conduct problems (Golubchik et al., 2011). Response rates range from 40 to 60% (Corson et al., 2004). However, in several of the studies there was significant discontinuation and attrition because the medication was poorly tolerated (Golubchik et al., 2011). The safety profile for quetiapine is not entirely clear.

Ziprasidone has also not been widely studied. A six-week open label study showed a 50% clinical response rate in the areas of irritability and mood lability. Ziprasidone is notable for not causing significant weight gain (Malone et al., 2007). However, there have been concerns that the mechanism of ziprasidone may trigger a prolongation of corrected QT, which may lead to ventricular arrhythmia. Part of the standard prescribing practice is to include a baseline ECG (McDougle et al., 2002).

Paliperidone has not been extensively studied with RCTs, yet there are open label studies and several case reports of successful treatment of aggression in children, adolescents, and adults (Stigler et al., 2012). RCTs are needed to determine the side effect profile and overall effectiveness of paliperidone.

Lurasidone was extensively studied in a six-week RCT of 150 children from 6 to 17 years of age with ASD (Loebel et al., 2016). The participants were randomly assigned to a low dose, high-dose, or placebo group. Lurasidone was shown to be no better than placebo for reducing irritability, overactivity, or aggressive behaviors. Side effects of vomiting and sedation were noted. Lurasidone is the only atypical antipsychotic that demonstrated no significant benefit over placebo (McClellan et al., 2017).

Side Effects

Issues related to side effects, especially when prescribed to young children are critical factors in prescription practices. Research on side effects focuses on four major areas: Movement disorders, impairments in brain development, sedation, and weight gain. These side effects have been studied mostly in adults diagnosed with schizophrenia, but are studied far less often for children and other people with autism.

Movement disorders. Antipsychotic medications can cause movement disorders, such as TD, which is a problematic and often permanent extrapyramidal reaction. TD is a complex syndrome of hyperkinetic involuntary movements, including orofacial dyskinesia, athetosis, dystonia, and is the most severe side effect of long-term treatment with typical antipsychotic medication (Margolese et al., 2005). There is a relatively lower TD risk in patients treated with atypical antipsychotics when compared to typical antipsychotics.

The antipsychotic-induced extrapyramidal symptoms (EPS) include different iatrogenic movement disorders, which can be divided into acute and tardive syndromes (Gualtieri et al., 1980). Acute syndromes (e.g., acute dystonia, akathisia, parkinsonism) will develop within hours or days after antipsychotic treatment. Atypical antipsychotics can decrease the risk of acute EPS; thus, atypical antipsychotics are first-line medications instead of typical antipsychotics (Correll & Schenk, 2008). However, even though the risk of acute EPS with atypical antipsychotics is less than with typical antipsychotics, the risk is not zero. Moreover, with the increase of the doses of atypical antipsychotics used in clinical practice and more frequent high-dose therapy, an increasing number of acute EPS may be found in patients treated with atypical antipsychotics (Shankar et al., 2019).

Impairments in brain development. Kim et al. (2006) observed that antipsychotic drugs block the dopamine neurotransmission, enhance the release of glutamate, and eventually kill striatal neurons. Many studies of drug-induced neuronal growth have found that antipsychotic drugs made cells look grossly abnormal under a microscope. Patients' long-term exposure to psychiatric drugs frequently damage parts of the patient's brain (e.g., basal ganglia where dopaminergic neurons are clustered), and produce chronic brain impairment (CBI), which is similar outcome to that of close-head injury or post-concussive syndrome (Linke et al., 2017).

CBI syndrome includes four primary symptoms: (1) Cognitive dysfunctions such as short-term memory dysfunction, impaired new learning, inattention, and distraction. (2) Apathy or loss of energy and vitality, indifference, and fatigue with some patients losing their motivation to join creative activities or activities that require higher order mental processes, such as school. Some patients also gradually lose empathy and affection, and they are no longer sensitive to people around them. This outcome conflicts with the goals of many social skills therapies for people with ASD. (3) Worsening emotional regulation, loss of empathy, increased impatience, irritability, anger, and frequent mood changes with depression and anxiety. This cluster of symptoms often has a gradual onset of months or years. Differentiating between these symptoms being due to CBI, stress, cognitive deterioration,

dementia, or development of mental health issues is extremely difficult. (4) Anosognosia, the lack of awareness of these symptoms of brain dysfunction, is a common aspect of CBI. Patients cannot identify the mental symptoms of brain dysfunction. Most of the time, someone other than the patient identifies these changes. These are difficult symptoms to assessment for a patient with ASD because many of the symptoms of CBI present as similar to many characteristics common for people with ASD. Besides CBI, antipsychotic drugs also lead to the atrophy of the dopaminergic pathways caused by antipsychotic drugs in long-term treatment of schizophrenic patients (Breggin, 2011). The recent evidence shows that more antipsychotic treatment could cause smaller gray matter volumes (Alonazi et al., 2019)

Sedation. There are several side effects related to sedation. Common symptoms include nausea, restlessness, vomiting, headache, drowsiness, memory loss, and slow motor reflexes. Sedation reflects the impairment of cognitive functions such as attention, memory, and psychomotor performance, which will interfere with patients' daily activities, such as school and work performance, play, and social activities (Coté et al., 2000). The adverse sedation events are associated with inadequate pre-sedation medical evaluation, medication errors, inadequate withdrawal procedures, drug overdoses and drug interactions, especially the mixed-use of three or more drugs (Hindmarch & Shamsi, 1999). The adverse events occurred more frequently in a non-hospital-based facility than in a hospital-based setting (Crespi, 2019). Therefore, uniform monitoring and training standards should be instituted to reduce the occurrence of adverse sedation events. Many patients will become tolerant to the sedative effects over time. The term tolerance is operationally defined as a loss of efficacy to a given effect at a given dose or the need for higher doses for the same effect (Hindmarch & Shamsi, 1999).

Weight gain. Different antipsychotic medications will have different influences on patients' weight gain (Yoon et al., 2016). In most cases, clozapine causes weight increase (Dayabandara et al., 2017). Furthermore, clozapine is associated with a high incidence of weight gain of more than 10% of original body weight (Handen et al., 2017). In comparison studies, researchers also found that clozapine could cause more weight gaining than that of either haloperidol or risperidone, but almost cause the same weight as zotepine and olanzapine (Ruiz et al., 2016). Researchers made comparisons among risperidone, olanzapine, aripiprazole, olanzapine, and placebo. They found that the children and adolescents treated with the atypical antipsychotic drugs risperidone, olanzapine, and aripiprazole gained more weight compared to placebo, and that the effect appears to be greatest with olanzapine (Wink et al., 2015; Wink et al., 2017). As shown in the above research, clozapine and olanzapine are identified to cause the highest weight gain (Wink et al., 2018). The high likelihood of weight gain with these medications is attributed to their actions at serotonin 5-HT2A and 5-HT2C, dopamine D2 and D3, histamine H1 and muscarinic M3 receptors. The different influences on weight gain can be explained by the different affinity of medications at these receptors (Scahill et al., 2016).

For most antipsychotic medications, long-term therapy is associated with more weight gain than is short-term therapy (Almandil et al., 2013). To generalize research to cases, a patient treated with olanzapine for more than six weeks could

gain one kilogram, while others who receive treatment for six weeks or less maintain the original weight (Vanwong et al., 2017). However, the rate of weight gain will not remain unstable all the time. There is rapid weight gain in the first few weeks after receiving antipsychotics. In the following several months, the rate will gradually decrease and flatten.

Summary. The side effects for antipsychotic medications are common and can be severe. Although atypical antipsychotics are less likely to result in extrapyramidal side effects than are typical antipsychotics, these forms of motor movements can still occur, especially when the medication is used for a long period of time. Monitoring of drug effectiveness and side effects for sedation and weight gain is a critical aspect of prescribing atypical antipsychotics. These side effects are more likely than not for most atypical antipsychotics, but can be managed if anticipated and identified.

Issues in Prescribing and Managing Atypical Antipsychotics

Dosage and titration. Any change in the dosage of atypical antipsychotics is to be made carefully (Almandil & Wong, 2011). The adage of "start low and go slow" applies. There is some evidence that higher doses increase the possibility of extrapyramidal effects (Pierre, 2005). However, this research is based on studies of adults diagnosed with schizophrenia and is not entirely consistent in the findings. The strongest dose-specific effects are related to fatigue. Incidences of parent-reported fatigue for children aged 6–17 years with ASD and aripiprazole are: placebo 0%; 5 mg 3.8%; 10 mg 22.0%; and 15 mg 18.5% (Hirsch & Pringsheim, 2016; Marcus et al., 2011). Dose-related effects have not been a major focus of research for atypical antipsychotics and reliance on general principles and caution is supported (Lake et al., 2017).

Drug interactions. People with ASD are at risk for a host of issues in addition to irritability and aggression. Some of those issues such as ADHD, seizure disorder, movement disorders, and other psychiatric issues may require medications. There are several medications that should not be taken with atypical antipsychotics: antidepressants (both selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors), anxiolytics, anti-seizure medications, and lithium. Hypotensive and other anticholinergic agents are contraindicated. Tobacco and marijuana smoking and alcohol can also be dangerous.

Withdrawal symptoms. Discontinuation of atypical antipsychotics requires a specific protocol of gradual reductions of dosage. The specific period of gradual withdrawal is dependent on the specific medication. However, withdrawal requires a minimum of 15 days to reduce from the therapeutic dose to entirely discontinuing the medication. Most commonly, 30–60 days of weaning the person with ASD from the medication is recommended. Withdrawal symptoms commonly include nausea and vomiting, increased blood pressure, and sleep disturbances (i.e., commonly delayed sleep onset and rarely night terrors (Wright et al., 2014). Increasing or

returning psychotic symptoms have been reported for persons with schizophrenia, but hallucinations and delusions have not been reported for those with ASD. Dizziness, muscle pain, and numbness in extremities are less common and usually resolve over two or three weeks after discontinuation. The most significant problems occur when the medications are rapidly withdrawn without a gradual reduction of dosage. This most typically occurs when the caregiver notices some side effect and withdraws the medication immediately without consulting with the prescribing medical professional.

Communication of medication to educators and parents. Although all medication and therapeutic treatments require communication among prescribers, patients, caregivers, therapists, educators, and other professionals; communication is a major issue in the treatment of irritability and aggression. Caregivers are especially important because they are typically the first to notice side effects that can be severe and permanent if not addressed. Moreover, caregivers must be warned that should they notice signs of side effects, that immediate and sudden withdraw could lead to exacerbated or new neurological side effects. Frequent communication with specific action plans for a variety of plausible scenarios (e.g., dramatic change of behavior, rapid weight gain, unusual motor movements, regression of skills, change in language or socialization) will assist in maximizing the effectiveness of treatment.

Future research and practice agenda. As the incidence and prevalence of ASD continues to increase and about 20% of children and adolescents experience severe irritability and aggression, there will be increasing prescriptions of atypical antipsychotic medication. Given that it is possible that young children could be prescribed this class of medication for a longer period than has been studied before, longitudinal studies are required. Developmental response to medications is not entirely clear. Dose is not entirely weight dependent and there is mixed evidence of dosage responses. Research for providing evidence-based guidelines dosage recommendations and issues related to polypharmacology is required. For clinicians, an important factor is the possibly complementary role that atypical antipsychotics and behavioral interventions can have. Because educators, psychologists, and other therapists tend to use behavioral approaches; and developmental pediatricians, psychiatrists, and pediatric neurologists tend to prescribe medications there is a strong clinical need to coordinate the best aspects of each approach to improve the overall outcomes for people with ASD. There a vast potential number of research and practice agendas on this topic. However, multi- and inter-disciplinary agendas have the greatest potential to advance the quality of life for people with ASD.

Conclusions

There is evidence that the use of antipsychotic medication can reduce the frequency and severity of irritable and aggressive behaviors. Evidence of positive changes in cognitive, social, and linguistic functioning is not strong and should not be used for these issues. Behavioral interventions are also effective for addressing frequency

and severity of irritable and aggressive behaviors. However, behavioral interventions require a great deal of time, consistency, and expertise. Many families and educational systems do not have the coordination among parties to implement this form of treatment with integrity. As such, the benefits of atypical antipsychotics may outweigh the substantial risk factors. Although side effects can be severe and are documented for children with ASD, the relative ease of implementation and reliance on medical professionals is an important treatment option for many.

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