*Handbook of Clinical Neurology,* Vol. 165 (3rd series)
*Psychopharmacology of Neurologic Disease*
V.I. Reus and D. Lindqvist, Editors
https://doi.org/10.1016/B978-0-444-64012-3.00023-X


Chapter 23

# Psychopharmacology of neurobehavioral disorders

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**Abstract**

At times psychotropic drug use is required to address behavioral and other interfering symptoms that accompany neurobehavioral disorders. We review such prescribing practice in autism spectrum disorder, fragile X syndrome, and Prader–Willi syndrome.

In this chapter we discuss both well-established and recent psychopharmacologic advances in autism spectrum disorder and two other neurodevelopmental disorders, fragile X syndrome (FXS) and Prader–Willi syndrome (PWS). In recent years, several new medications have been highlighted as effective with some even targeting the social deficits and seemingly "core symptoms" of these disorders. Often drug treatment in neurobehavioral disorders targets interfering symptoms and behaviors that are refractory to other therapeutic interventions and impair quality of life.

## AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social interaction, verbal and nonverbal communication deficits, and repetitive behaviors (American Psychiatric Association, 2013). Among individuals with ASD, there is extensive variability in degree of impairment within these domains. Often, ASD is also associated with mild to severe intellectual disability, motor coordination difficulties, and physical health issues; however, social impairment in ASD is distinctive and not explainable solely by cognitive delay. From a very young age, children with ASD experience social and communicative difficulties including absence of or diminished babbling, failure to respond to their name, and delayed pointing to express interest (for review see Martin and Volkmar, 1996; Sperdin and Schaer, 2016). The impairments associated with ASD are pervasive, although we do not fully understand the trajectory of the disorder. Deficits in social interaction do change somewhat throughout the lifespan but remain an area of great disability even among the highest functioning adults with autism (reviewed in Martin and Volkmar, 1996).

While these aspects are considered to be the "core symptoms" of ASD, there are still other subsets of symptoms that have been addressed via pharmacology. Given that many persons with ASD also exhibit symptoms severe enough to qualify for additional comorbid psychiatric diagnoses, the bodies of literature describing the general psychopharmacology of mental illness can at times be informative to ASD prescribing practice (McClellan et al., 2016). We review here the psychopharmacology of ASD by target symptom.

### ADHD and attention problems

Reports are mixed as to whether children with ASD can also fit the criteria for attention deficit hyperactivity disorder (ADHD). Pearson et al. (2013) reported that between 14% and 75% are reported to have symptoms consistent with ADHD. This wide range is the result of much debate over what designates "diagnosable symptoms." However, there is some consensus regarding the use of stimulants to address the symptoms of inattention, hyperactivity, and impulsivity. With extensive affirmation that stimulants (particularly methylphenidate) are effective in traditional ADHD, attention issues in ASD and related disorders should experience similar effects. However, in addition to those common

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effects, it has also been discovered that stimulants have a positive effect on the social aspect of ASD. The affective state and joint attention initiatives of children are better regulated with methylphenidate use (Jahromi et al., 2009).

With current stimulants now in "extended-release" formulas, one study conducted using methylphenidate chose the following method to closely mirror typical clinical usage. A within-subjects crossover design was employed so that each child would receive a high, medium, and low dose of methylphenidate in addition to a placebo. Using several validated parent and teacher report measures, it was found that overall ADHD symptoms improved with methylphenidate use. Improvements were seen across all treatment conditions within the areas of impulsivity, hyperactivity, irritability, social skills, and oppositional behavior (Pearson et al., 2013).

In addition to stimulant use, or when stimulants fail, antiadrenergics such as clonidine or guanfacine have been evaluated in ASD. In a double-blind, placebo-controlled crossover trial of guanfacine, significant improvement was observed in the hyperactivity of participants who were deemed "responders." By an analysis of the guanfacine versus placebo conditions it was noted that approximately 45% of participants responded positively to the guanfacine treatment (Handen et al., 2008). Therefore, while antiadrenergics may not be the first line of treatment in ASD they may still be valuable for hyperactivity in ASD. In a double-blind, placebo-controlled parallel groups short-term efficacy trial of guanfacine in 62 youth with ASD, Scahill et al. (2015) reported a significant positive effect of guanfacine (effect size = 1.67) targeting ADHD symptoms compared to placebo (Scahill et al., 2015). A similar overall guanfacine treatment response of 50% was noted.

Another option for treatment of ADHD symptoms in the context of ASD is atomoxetine, a selective inhibitor of noradrenaline that has efficacy comparable to methylphenidate for attention and hyperactivity concerns (Fernandez-Jaen et al., 2013). Several open label and double-blind, placebo-controlled trials have investigated atomoxetine with consistent findings of improved hyperactivity and inattention, overall less impairment, and limited adverse reactions in general ADHD (Harfterkamp et al., 2012; Fernandez-Jaen et al., 2013; Handen et al., 2015). One notable difference in terms of clinical value between atomoxetine and other treatments is a delay in improvement compared to the near immediate effect of stimulants and antiadrenergics (Handen et al., 2015). A 3-site 10-week placebo-controlled trial of 128 youths reported that atomoxetine alone and combined with parent training was well-tolerated and associated with reductions in noncompliance (Handen et al., 2015).

## Irritability and aggression

Irritability and aggression are common symptoms in individuals with ASD. Because of the severity of these symptoms, treatment options have been well investigated. Atypical antipsychotics are often the best method of treatment, with some more promising than others. Risperidone is the most frequently prescribed and was the first second-generation antipsychotic (SGA) approved by the FDA for treatment of irritability in ASD. A large placebo-controlled study in youth with ASD reported significant decreases in the irritability subscale of the Aberrant Behavior Checklist (ABC) by over 50%, compared to less than 15% in the placebo arm (McCracken et al., 2002). A second study found similar results: decreased ABC irritability subscale scoring by 64% compared to 31% on placebo. Few adverse effects were recorded during these trials, with weight gain being the most significant (Shea et al., 2004).

Aripiprazole is the second antipsychotic used in treating irritability and aggression in ASD to receive FDA approval. Very similar to risperidone, significant improvement was seen across several trials. In both fixed and flexible dosing settings, the short-term efficacy of aripiprazole in treating irritability has been established in two Phase III trials in youth with ASD (Marcus et al., 2009; Owen et al., 2009). A comparative analysis of risperidone and aripiprazole revealed that there are no significant differences in treatment efficacy and aggression/irritability reduction (Akhondzadeh et al., 2010; Wink et al., 2014). Both medications are very effective and promising for treatment, but the weight gain associated with each drug may be significant. Metformin is an FDA-approved medication used for treating type-2 diabetes in children. Wink et al. (2017) investigated the long-term effectiveness of metformin use targeting antipsychotic-associated weight gain in persons with ASD (Wink et al., 2017). In a 16-week short-term efficacy trial of metformin targeting antipsychotic-associated weight gain in 52 youth with ASD, metformin use was associated a significant reduction in weight gain compared to placebo (Anagnostou et al., 2016).

Other atypical antipsychotics including ziprasidone, olanzapine, quetiapine, paliperidone, and clozapine have open-label and small trial support showing potential in treating ASD-associated irritability. While none of these drugs are FDA approved for use in ASD, they do offer an alternative to risperidone and aripiprazole use when indicated (McClellan et al., 2016).

Finally, haloperidol, a first generation antipsychotic, has been established as effective for use in treating ASD-associated irritability. It is currently the only first-generation antipsychotic that has been evaluated

in placebo-controlled efficacy trials in ASD. Years ago, haloperidol was shown effective in reducing stereotypies and aggressive mannerisms in youth with ASD (Campbell et al., 1978; Hoshino et al., 1979; Perry et al., 1984). Haloperidol use is limited in ASD compared to second-generation antipsychotics, which are given in cases of higher rates of extrapyramidal symptoms, tardive dyskinesia, and withdrawal dyskinesia.

## Anxiety and mood regulation

While anxiety disorders and associated symptoms are heavily studied in typically developing populations, only a few treatment options have been explored in ASD despite being some of the most common symptoms experienced (Vasa et al., 2014). With the intention of reducing social deficits, selective serotonin reuptake inhibitors (SSRIs, particularly citalopram) and buspirone are the major methods of anxiety treatment in ASD. Vasa et al. (2014) conducted a systematic review of anxiety treatment in ASD and found 15 potentially informative studies with results focused on citalopram, fluvoxamine, and buspirone being the most rigorous.

Citalopram showed significant reduction in anxiety symptoms, aggression, stereotypies, and fixations. Via chart reviews, approximately 66% of children saw this response with citalopram use. Fluvoxamine showed significant side effects including major hyperactivity and was not found to be effective for treating generalized anxiety symptoms in ASD, though females were much more likely to respond than males in the same age range. Finally, Vasa et al. (2014) concluded that buspirone was the most effective treatment for anxiety in ASD. Nearly three quarters of participants saw improvements in anxious symptoms with minimal side effects. Anxiety is difficult to treat in ASD and much more research is needed to adequately address treatment concerns.

## Repetitive behaviors

Repetitive behaviors and obsessive compulsive mannerisms are one of the most characteristic symptoms of ASD (Ruzzano et al., 2015). These symptoms can be disruptive and troubling, so numerous treatment options have been explored. SSRIs have been thoroughly investigated in autism with mixed results. In adults, McDougle and colleagues found that fluvoxamine improved repetitive behavior, fixations, and other ASD-related symptoms. Approximately 53% of study participants responded to fluvoxamine treatment, making it a viable treatment option for repetitive behaviors in adults with ASD (McDougle et al., 1998).

In children, however, another study evaluating citalopram was not as promising. The placebo-controlled trial lasted 12 weeks and enrolled children between the ages of 5 and 17. No differences were found on any of the outcome measures and side effects were numerous (King et al., 2009). There is no evidence to indicate whether certain SSRIs may be effective within different age ranges.

Other than SSRIs, treatment for stereotypies is limited. Haloperidol is an additional drug that appears to be effective in treating adults with ASD but is not helpful in children (Campbell et al., 1978). Risperidone is the only medication with favorable data supporting its use in ASD for repetitive behaviors. In both adults and children, risperidone reduced stereotypies measured by the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) and the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS). The effect was consistent across both placebo-blind studies and open-label trials and increased over time (McDougle et al., 1998, 2005; McCracken et al., 2002).

## Core symptomology

There has been a lot of discussion regarding the core symptomology of ASD. It is difficult to address these major concerns because of the heterogeneity of ASD as a disorder. Several drugs, fenfluramine, secretin, and naltrexone, have been investigated with the hopes of addressing these concerns but have been found ineffective (du Verglas et al., 1988; Williams et al., 2012; Roy et al., 2015).

Oxytocin, however, is a powerful neurotransmitter-hormone that affects social cognition and attachment. Several studies have investigated the effects of intranasal oxytocin with mixed results. Several studies showed no significant effects (Anagnostou et al., 2012; Tachibana et al., 2013; Althaus et al., 2015). In one study, no differences were found between oxytocin and placebo on physiologic responses to empathy-centered social stimuli but split-analysis did indicate that individuals with ASD who were more distressed by images of others in stressful situations did react to oxytocin with increased social orientation (Althaus et al., 2015). Other studies reported improved caregiver-rated social, communication, and improved face processing (Domes et al., 2013; Yatawara et al., 2016). One study saw increased activity in the amygdala during facial processing tasks while taking oxytocin. Improved social orienting and processing may be the most promising outcome of oxytocin treatment (Domes et al., 2013).

Acamprosate is a novel medication that is very promising for ASD, using attenuation of *N*-methyl-D-aspartate and metabolic type 5 glutamate receptors.

A 12-week placebo-controlled trial investigated the efficacy of acamprosate on diminishing characteristic autistic symptoms. Children aged 5–17, with a clinical impairment referred to as "moderately ill" or greater using the CGI-S began treatment at 333 mg/day for 1 week. Regular increases in dosage were observed until ideal response occurred, measured by the CGI-I, or until intolerable adverse effects occurred. Across nearly all outcome measures, including those evaluating overall clinical impairment, hyperactivity, and social deficit, statistically significant improvement was noted (Erickson et al., 2013).

Similarly, several studies have established the efficacy of the antibiotic, D-cycloserine, as an effective clinical intervention for the core profile of ASD symptoms. Two conflicting studies by Posey and colleagues were conducted in 2004 and 2008. The 2004 single-blind study reports significant improvement with D-cycloserine use, specifically in terms of social engagement, repetitive behavior, and hyperactivity. At the highest dose, symptom severity decreased by nearly 60%. While not all measures showed significant improvement, higher doses of D-cycloserine showed the most improvement on the CGI-S and the ABC-SW (Posey et al., 2004). This is incredibly valuable as the social component of ASD is the most difficult to treat clinically. The 2008 follow-up study (Posey et al., 2008) and a separate study paired with social skills training showed no significant outcome differences (Minshawi et al., 2016).

## FRAGILE X SYNDROME

Genetic mutation of the *FMR1* gene is responsible for a variety of disabilities including cognitive deficits, attention-deficit/hyperactivity disorder, autism, and other socioemotional problems. Typically, the severity of the FXS impairment is correlated with the FMRP deficit, with more methylation indicative of greater impairment. Treatments for individuals with FXS full and premutation target several core areas.

### Inattention and hyperactivity

Stimulants are frequently prescribed for inattention and hyperactivity in FXS and are often the most prescribed drugs within the disorder (Hagerman, 1999; Amaria et al., 2001). One report emphasized by Berry-Kravis and Potanos (2004) noted that young boys with FXS performed better on stimulant medication than off, resulting in decreased motor activity and better academic grades (Roberts et al., 2002). Stimulants are not always effective in children under the age of 5 and can produce side effects such as anxiety and aggression, so they may not be suitable for all FXS patients (Berry-Kravis and Potanos, 2004).

Antiadrenergics such as guanfacine and clonidine have been found to be effective alternatives to stimulants in both younger children and those who did not respond well to stimulants. A parent survey indicated 63% of parents felt clonidine was clinically very helpful to their child (Hagerman et al., 1995). Guanfacine is helpful in FXS because it is longer lasting and does not often produce the drowsiness associated with clonidine (Hagerman et al., 2009).

Finally, L-acetylcarnitine is one more alternative to stimulant use. One major placebo-controlled study of L-acetylcarnitine proposed that the potential mood instability of methylphenidate and other stimulants makes L-acetylcarnitine the preferred choice for treating inattention and hyperactivity in FXS boys. In conjunction with increased academic and neuropsychiatric support, both the placebo and active treatment group saw improvements in hyperactivity as measured by their parents and teachers. However, the two groups did significantly differ, with the L-acetylcarnitine group showing more improvement from baseline than the placebo group (Torrioli et al., 2008). With this in mind, L-acetylcarnitine is a valuable alternative to the side effects often experienced with stimulants.

### Anxiety

Individuals with the FXS full-mutation, as well as mothers with the premutation gene, are highly susceptible to anxiety. This intensified anxious state can contribute to aggressive and self-injurious behavior, which is discussed later in this section. Outside of severe behavior, anxiety is debilitating and exacerbates other medical and psychiatric needs. SSRIs are particularly useful in the social anxiety and withdrawal aspect of FXS seen in females and higher functioning males and are used in approximately 50% of individuals with FXS. Between 50% and 60% of individuals with FXS responded well to fluoxetine in an open label trial (Berry-Kravis and Potanos, 2004). Selective mutism in a FXS female case study indicated improvement with fluoxetine as well (Hagerman et al., 1999). In a clinical chart review as well as a double-blind clinical trial, children benefited from a low-dosage of sertraline in such outcomes as improvement in social participation and motor and visual perceptual abilities as well as expressive and receptive language development (Indah Winarni et al., 2012; Greiss Hess et al., 2016). At this time, there are several different kinds of SSRI's available with unique side effects but the majority of the literature focuses on sertraline and fluoxetine. Some individuals experience increased hyperactivity on sertraline (Cohen and Iacono, 2002; Berry-Kravis et al., 2012).

### Aggression and self-injury

Some individuals with FXS also exhibit some problem behaviors such as irritability, aggression, self-injury, and perseveration. While these behaviors are less common, they do require treatment typically in the form of atypical antipsychotics. Approximately 80% of individuals respond to these medications in some way, but excessive weight gain or other side effects that lead to discontinuation may occur (Berry-Kravis and Potanos, 2004). Several atypical antipsychotics such as risperidone, aripiprazole, olanzapine, quetiapine, and ziprasidone are less sedating than first generation antipsychotics. Risperidone is the most frequently prescribed drug within this class, but no clinical trials have been held in the FXS population. Clinically, risperidone shows high response for aggressive behaviors in older males with FXS as well as younger males with ASD symptomology (Hagerman, 2010).

Aripiprazole is also heavily prescribed and presents a much lower risk of weight gain than risperidone. In an open label trial, individuals with FXS responded very well to aripiprazole and it also appears to treat hyperactivity and improve social behavior in addition to treating aggressive behavior (Erickson et al., 2011). Overall, atypical antipsychotics appear to be the best tool for treating aggression and self-injury in FXS but more blinded clinical trials are needed to validate the clinical and open-label evaluations that have been done.

## PRADER–WILLI SYNDROME

PWS is primarily caused by a disruption of the 15q11–q13 gene; however, PWS occurs as a result of the paternal gene. It is characterized primarily by infantile failure to thrive, hypogonadism, and hyperphagia. Individuals with PWS also tend to have developmental delays and characteristic behaviors including compulsiveness and temper outbursts. Psychiatric treatments tend to focus primarily on this behavioral profile, obsessive skin picking, and developmental delays (Goldstone, 2004).

### Skin picking and obsessive behaviors

A well-established and common symptom of PWS is self-injurious skin picking in which individuals compulsively pick or scratch at their skin, often creating open wounds or sores. The presence of any kind of skin disruption usually prompts or promotes the behavior and it can be difficult to redirect an individual fixated on this behavior (Cassidy and Driscoll, 2009).

Previously, treatments for skin picking focused on environment modification and behavior management. In a study specifically investigating treatment of skin picking, two individuals with severe self-mutilating skin picking were effectively treated with fluoxetine, an SSRI. One parent report indicated that skin picking was a compulsive behavior in one patient, which worsened when the patient was upset. Both patients saw diminished skin picking and healing of lesions after continued treatment with fluoxetine (Warnock and Kestenbaum, 1992).

As SSRIs are capable of exacerbating undesirable behaviors at times, alternatives such as topiramate have also been found effective for use in PWS. Antiepileptic drugs often reduce compulsive behavior but have known weight-gain side effects (Durst et al., 2000). Topiramate reportedly does not have the common weight-gain effects associated with most antiepileptics but is useful in managing self-injurious skin picking. In an open-label case study of three individuals with PWS, all three saw benefits with topiramate use.

### Behavioral outbursts

Children with PWS typically exhibit appetite suppression difficulties related to their inability to feel satiated, also called hyperphagia (Goldstone et al., 2012). This difficulty often results in severe behavioral concerns including food preoccupation, hoarding, anxiety around food, and emotional outbursts (Miller et al., 2011). All of these behaviors and processes are regulated in part by oxytocin in the brain. Notable oxytocin deficits have been identified in PWS (Swaab et al., 1995; Bittel et al., 2007). For this reason, intra-nasal oxytocin has been used as an effective treatment for PWS behavior problems. In comparison to placebo-control, Miller and colleagues found that short-term intra-nasal oxytocin treatment slightly decreased disruptive behaviors and caused no serious side effects (Miller et al., 2017).

## DOWN SYNDROME

Down syndrome (DS) is caused by Trisomy 21 or duplication of the 21st chromosome. DS is associated with developmental delay and risk for many medical concerns including hypothyroidism, sleep apnea, congenital heart defects, and increased risk of dementia in adulthood. These medical complexities present some challenges in the management of interfering behaviors and comorbid psychiatric conditions in this population with medication. Overall, psychotropic medication use in DS from the pre-pubertal age range with overall use of psychotropic drugs is estimated at 17% to a 25% use rate in adolescents with DS in a sample of 832 patients with DS (Downes et al., 2015).

### Anxiety and depression

SSRIs are the most common medication treatment for anxiety and depression in youth with DS with use of SSRI peaking in adolescents (Downes et al., 2015).

In a sample of 832 patients of 5–21 year olds with DS, SSRI use peaked from 10% to 15% of all patients taking a SSRI targeting depression and/or anxiety concerns in the 13–21 age range. This is consistent with the literature in DS noting a peak of internalizing symptoms in adolescent and young adulthood (Dykens et al., 2002).

### Irritability

In DS in youth, consistent with the autism literature, persons with DS commonly receive atypical or SGA treatment for interfering irritability marked by physical aggression, self-injurious behavior, and or severe tantrums. SGA treatment peaks in adolescence (9% receiving SGAs) and overall SGA use in DS is significantly increased in males compared to females (Downes et al., 2015). Given the concerns related to weight gain presented with SGA use, special care should be given to persons with DS given their preexisting medical risks such as sleep apnea and heart defects whose impact could be compounded by SGA-associated weight gain. Given this, use of more weight-neutral agents can be considered in the neurodevelopmental disorders field including use of ziprasidone or quetiapine (Yoon et al., 2016) for those with significant weight gain on risperidone or aripiprazole, for example.

## CONCLUSION

In the neurodevelopmental disorders field it is important to clearly define targets of psychiatric medication management to appropriately track and otherwise evaluate progress with treatment. Given there is no one or more than one drug indicated globally for a specific disorder or condition, all psychopharmacology is focused on targeting the symptom. Understanding the literature specific to various neurodevelopmental conditions can aid pharmacotherapy selection and enhance monitoring for potential adverse effects or tolerability concerns that may differ in persons with developmental disability compared to the general population. Clinicians must additionally be keenly aware of the challenges involved in evaluating both treatment response and tolerability in persons who may have limited communication skills. Despite clear potential needs for combined pharmacotherapy at times, the clear goal of psychotropic prescribing in these populations should be the least amount of medication needed at the lowest effective doses targeting clearly defined interfering symptoms and/or behaviors.

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