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**Pharmacotherapy in Autism Spectrum Disorders, Including Promising Older Drugs
Warranting Trials**

Pharmacotherapy in ASD

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Abstract

Available pharmacotherapies for autism spectrum disorders (ASD) are reviewed based on clinical and research experience, highlighting some older drugs with emerging evidence. Several medications show efficacy in ASD, though controlled studies in ASD are largely lacking. Only risperidone and aripiprazole have Federal Drug Administration (FDA) approval in the USA. Methylphenidate studies showed lower efficacy and tolerability for attention deficit hyperactivity disorder (ADHD) than in the typically developing (TD) population; atomoxetine demonstrated lower efficacy but comparable tolerability to TD outcomes. Guanfacine improved hyperactivity in ASD comparably to TD. Dextroamphetamine promises greater efficacy than methylphenidate in ASD. ADHD medications reduce impulsive aggression in youth, and may also be key for this in adults. Controlled trials of the selective serotonin reuptake inhibitors citalopram and fluoxetine demonstrated poor tolerability and lack of efficacy for repetitive behaviors. Trials of antiseizure medications in ASD remain inconclusive, however clinical trials may be warranted in severely disabled individuals showing bizarre behaviors. No identified drugs treat ASD core symptom; oxytocin lacked efficacy. Amitriptyline and loxapine however, show promise. Loxapine at 5-10 mg daily resembled an atypical antipsychotic in positron emission tomography (PET) studies, but may be weight-sparing. Amitriptyline at approximately 1mg/kg/day used cautiously, shows efficacy for sleep, anxiety, impulsivity and ADHD, repetitive behaviors, and enuresis. Both drugs have promising neurotrophic properties.

Key Words: Autism; Pharmacotherapy; Dextroamphetamine; Loxapine; Amitriptyline; Minimally verbal; Neurotrophic

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Core Tip: Most prescribing in ASD is off-label; only risperidone and aripiprazole are FDA-approved in ASD, for irritability. Atypical antipsychotics are associated with metabolic side effects. Loxapine at 5-10mg/day resembled an atypical antipsychotic in PET studies; preliminary studies and clinical experience in ASD suggest efficacy and a promising metabolic profile. Controlled ADHD medication trials in ASD youth include methylphenidate, atomoxetine and guanfacine. The author recommends dextroamphetamine as an important treatment option for ADHD in ASD. Amitriptyline often improves impulsive aggression, self-injury, sleep, anxiety and enuresis. This article suggests additional older drug trials in ASD: dextroamphetamine, amitriptyline, loxapine, and lamotrigine for likely seizures.

INTRODUCTION

Autism spectrum disorder (ASD) is diagnosed using criteria of significant deficits in social communication and interaction, together with at least two types of restricted and repetitive interests and behaviors (RRBs)(1). ASD develops prenatally and during early childhood. There is no longer an age cut-off for diagnosis, though it is often evident by age 1-3 years. The prevalence of ASD has risen globally since 2000. Two separate USA studies using the 2016 National Survey of Children's Health reported ASD prevalence of 1 in 40 children (2, 3). After decades there is still no definitive medication treatment for the core features of autism likely due to the heterogeneity of ASD, including various genetic causes. Recent studies with negative findings for core symptoms include oxytocin, bumetanide and SSRIs fluoxetine and citalopram for restrictive and repetitive behaviors (RRBs) (4). A meta-analysis confirmed there are still no treatments with efficacy for RRBs (5).

In addition to core ASD disabilities, the majority of these individuals have other serious challenges affecting them. Approximately 30-50% also have intellectual disability (ID) (6). Those more severely affected for example by birth injuries may have hydrocephalus and cerebral palsy, along with varying degrees of motor paralysis. Although there is a tendency worldwide to diagnose ASD in high-functioning, milder

cases, an estimated quarter of individuals with ASD have less than 20 words of expressive language and are thus minimally verbal (7). Approximately 20-40% of those with ASD also have epilepsy, with greater rates in the more severely affected (8), which includes minimally verbal individuals.

In addition, psychiatric illness occurs several times more commonly in those with ASD than in the general population (9, 10). Common presenting problems include hyperactivity, impulsive aggression, property destruction and self-injury, which are not Diagnostic and Statistical Manual-fifth edition- Text Revised (DSM-5-TR) diagnoses. A study of 1,380 youth with ASD found that over two thirds (68%) manifested aggression towards a caregiver, and almost half (49%) showed aggression towards non-caregivers (11). Psychiatrist training in the field of developmental disabilities is seriously lacking in most universities worldwide, and has marginally improved in the USA in the past 5 years (12, 13). Individuals with ASD and their caregivers have great difficulty identifying a provider in their geographical area who will treat them. The field still suffers from a serious lack of clinical trials to guide treatment of psychiatric comorbidity. Those providers who treat such patients must rely on the few ASD clinical trials published, experience gained by different medication trials, and extrapolation from studies in typically developing individuals.

An analysis of 33,565 children with ASD, found that 35% received 2 or more psychotropic medications, while 15% received 3 or more (14). Polypharmacy especially with antipsychotics is even greater in adults, when many non-psychiatric medications are also prescribed apart from psychotropic medications (15). The lack of evidence base results inevitably in exposure of these individuals to repeated medication trials, an unnecessary burden of side effects, and attrition from care (16). Individuals with ASD often have one or more comorbid DSM-5-TR diagnoses. Working DSM-5-TR diagnoses are important guides for selecting classes of medications. Diagnostic symptoms of DSM-5-TR diagnoses may be more difficult to recognize in those more severely affected, including the minimally verbal. The Diagnostic Manual of Intellectual Disabilities-2 (DM-ID2) (17) is a useful crosswalk for applying DSM-5 criteria to



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of ADHD in 63 tertiary-referred adults with ASD screened for psychiatric comorbidity, notably 68% for lifetime prevalence of ADHD (9). Additionally, ADHD is less likely to improve after adolescence in youth with ASD than in the general population with ADHD. In the community, inattentive-type ADHD is the most common subtype found in ASD/ID, however it is often untreated.

The hyperactive-impulsive subtype of ADHD has poorer outcomes in individuals with ASD, related to the more disruptive nature of hyperactivity as well as a greater likelihood of impulsive aggression, self-injury and property destruction (19). Affect dysregulation, the inability to properly regulate and modulate emotions, was not included in DSM-5 as a diagnostic feature of ADHD, but is emphasized in DMID-2 as an important feature in individuals with developmental disabilities including ASD. The authors of the DSM-5 ADHD criteria later published an article emphasizing affect dysregulation as an important part of ADHD (21). ADHD-associated mood fluctuations present an important source of impairment especially in those with developmental disabilities and ADHD. Especially in adults with ASD, the ADHD diagnosis may be overlooked, resulting in a bipolar or borderline personality disorder misdiagnosis.

ADHD medications are important for improving learning, speech and language, and executive functions including inhibitory self-control. These medications improve affect dysregulation in ASD, which often manifests as impulsive aggression when the person is frustrated. Response inhibition of affective fluctuations such as laughing or crying is impaired in ADHD, related to executive function deficits. A meta-analysis of executive function in ASD found that broad executive function deficits remain stable and do not improve across development in such individuals (22). Obsessive compulsive disorder (OCD) is very commonly associated as well in ASD, and could complicate treatment of ADHD with stimulants since the latter may increase anxiety in a dose-related manner (23). On the other hand, non-stimulant ADHD medications may help reduce OCD and repetitive behaviors in ASD, although studies are still needed.

Medications for ADHD can be divided into stimulant and non-stimulant drug categories.

When to Try Stimulants in ASD?

Stimulants are more likely to show efficacy and tolerability in higher-functioning individuals with ASD who have predominantly ADHD symptoms in contrast to cases with OCD symptoms, prominent repetitive behaviors or self-injury. In the latter group, non-stimulant medications may be a more tolerable choice. Young children with ASD often begin their first ADHD medication trials when their disruptive behavior interferes with education of themselves and others in the classroom. As with typically developing (TD) young children with ADHD, the first drug tried is usually the stimulant methylphenidate (MPH), in divided doses three times a day, up to 1mg/kg/day or less; individual responses vary.

Dextroamphetamine (DEX) immediate release (ir) merits study in ASD, according to the author's decades-long experience. DEX has double the potency and duration of action as MPH, notably 4 to 6 h. A meta-analysis comparing efficacy of stimulants in 23 controlled studies for ADHD found a modest advantage of amphetamines over MPH for treating ADHD in pediatric patients (24). Divided doses given morning, lunch time, and a half-dose at 4pm if needed, totaling approximately 0.5mg/kg/day or less give good coverage, better than MPH. Overall, DEX ir produces less lunch-time appetite suppression, less anxiety and irritability than long-acting stimulants according to author experience. Despite the current low level of evidence for DEX in ASD, clinical trials are warranted, and patient trials in the office may be beneficial.

However, methylphenidate is the only stimulant studied so far in ASD, with findings of lower tolerability and lower efficacy than in typically developing youth. Large studies include a multisite study by the group Research Units of Pediatric Psychopharmacology (RUPP) (25), and a Cochrane database systematic review (26). The RUPP study of 72 children with ASD, aged 5 to 13 years, found all low doses studied were superior to placebo for hyperactivity and impulsivity. Subjects were pre-selected for ability to tolerate a test dose of MPH for a week. Total doses, each given for a week, were 0.125mg/kg, 0.25 mg/kg, and 0.5mg/kg and were deliberately low in

order to minimize side effects. However only 49% were responders, a rate much lower than the 75% response rate in TD children. Even the greatest effect size of 0.54 was significantly lower than that for ADHD response in TD children. Side effect rates were approximately double those found in TD children, and 18% exited the study early due to intolerable side effects. These included irritability, decreased appetite, and insomnia. Parent-rated lethargy, social withdrawal, and inappropriate speech increased significantly. There are also two small randomized, controlled trial (RCT) studies and one multisite study of methylphenidate for ADHD in ASD. Two small RCT studies of methylphenidate for aggression in ASD found benefit over placebo on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale (27, 28, 29). Intolerable side effects were common in the latter study also, including mood changes, agitation and abnormal movements.

The Cochrane systematic review (26) of MPH in children and adolescents with ASD included 4 crossover studies, totaling 113 children ages 5 to 13 years; most (83%) were boys. There was a significant benefit on teacher-rated inattention but insufficient data to perform an impulsivity-outcome meta-analysis. Treatment duration for each dose of MPH was 1 wk. High-dose MPH significantly improved hyperactivity as rated by teachers in 4 studies, 73 subjects, ($p < 0.001$) low quality evidence, and parents in 2 studies, 71 subjects ($P = 0.02$), low quality evidence. Ratings were on the hyperactivity subscale of the Aberrant Behavior Checklist. MPH clinical usefulness is also limited by its short half-life of 2-4 h.

Of the long-acting stimulants in ASD, only one small study has been published. This small study of 24 children, mean age 8.8 years, found significant benefit of MPH - extended release in ASD (30). However this was not a representative ASD sample, since the participants' mean IQ was 85.0 (SD=16.8). MPH-ER may be useful and more tolerable for example in high-functioning individuals with ASD. Comparative studies of long-acting stimulants are lacking in ASD, including for irritability (31). Long-acting stimulants were designed to take effect and wear off gradually, and to reduce side effects and rebound effects in the general population with ADHD. However, clinical

observations suggest that in ASD, long-acting stimulants may have even greater side effects than immediate-release preparations, including worsened anxiety, appetite suppression, self-injury, lip-licking, nail-picking, trichotillomania, and compulsive behaviors, in a dose-dependent manner. The more severe the ASD, the more of a problem such side effects present, although studies are needed. Therefore, non-stimulant ADHD medications may be preferable in these individuals.

When to Try Non-stimulant ADHD Medications in ASD?

As stated, non-stimulant ADHD medications are preferable to stimulants for individuals who have more severe ASD, and those who also have prominent OCD, RRBs and self-injury. These include atomoxetine (ATX), alpha agonists and tricyclic antidepressants (TCAs). Clinical experience in ASD suggests that these medications can be added to low-dose stimulants that are partially helpful if the person is unable to tolerate stimulant dose increases due to side effects. Several clinical trials in TD individuals have found efficacy and tolerability of ATX in combination with stimulants, although such combinations are not FDA-approved (32). A recent review compared responses between MPH, ATX and guanfacine in 9 controlled studies of 430 children with ASD (33). MPH and ATX were superior to placebo for ADHD. Poorer response was found in more cognitively disabled individuals.

Atomoxetine

Atomoxetine is a noradrenergic reuptake inhibitor shown to produce improvements in inhibitory control as part of executive functions. Importantly, acute ATX administration increased behavioral inhibition as measured by a stop-signal task in adult ADHD not accompanied by ASD (34) as well as in normal adults without either ADHD or ASD (35). Author experience confirms that atomoxetine may be a good choice for impulsive aggression in ASD including in adults and minimally verbal individuals, and for poor focus and disorganization in higher-functioning individuals. A randomized, multisite 10-week double-blind placebo-controlled trial of atomoxetine, with or without parent training, was performed for ADHD in 128 children aged 5 to 14 years with ASD. Atomoxetine showed greatest efficacy together with parent- training,

but also the drug alone was superior to placebo (36). Overall, tolerability was good, to a maximum dose of 1.8mg/kg/day; mean dose was 1.4mg/kg/day. Dosing was divided into twice-daily doses, to reduce side effects. The most common side effects were nausea, decreased appetite, early morning wakening and fatigue. Suicidal ideation and QTc changes were not found, in contrast to findings in children without ASD (37). In addition, another acute RCT study of 97 youths with ASD treated with atomoxetine, including open long-term follow-up, showed moderately improved ADHD symptoms and side effects similar to those found in studies of atomoxetine in youth with ADHD but no ASD (38, 39).

Atomoxetine trials are warranted in ADHD in adults with ASD, especially for impulsive aggression, based on author experience. The strategy is to “start low and go slow’ while response is observed for, using divided doses of twice a day to improve tolerability and coverage. A recent retrospective study disputes the need for extra caution however and found similar responses to ADHD treatments in adults with ADHD and ASD to those found in a comparison group with ADHD but no ASD (40). The therapeutic window may be narrower in minimally verbal and lower-functioning individuals with more severe degrees of ASD, according to clinical experience. Should behavioral worsening occur after an atomoxetine dose increase, the beneficial response is usually recaptured by dose reduction.

Amitriptyline

Amitriptyline in low doses may be especially useful if used with caution, in comparison with other available non-stimulant medications, despite a lack of comparative studies. Tricyclic antidepressants (TCAs) including amitriptyline are second only to stimulants in ADHD efficacy, although most evidence for their use in ADHD is from studies of the second-generation TCA desipramine in youth without ASD. An advantage over stimulants according to this author’s experience is that amitriptyline may benefit ADHD, anxiety, OCD, gastrointestinal pain, headaches, enuresis and insomnia (15). Though currently there is a low level of published evidence, prospective studies are warranted, in the author’s opinion. A retrospective chart review

on amitriptyline (41) published by the author's group examined 50 tertiary-referred children and adolescents with ASD, ADHD and high rates of aggression and self-injury, who received low dose AMI (mean dose 1.3 +/- 0.6 mg/kg/day) with mean trough blood level of 114.1 +/- 50.5 ng/mL. Response occurred clinically in 60% of patients at the final visit, and in 82% of patients for at least 50% of follow-up visits. Importantly, 30% had failed atomoxetine, and 40% had failed 3 or more other ADHD medication trials. Amitriptyline was used in combination with stimulants, most often low dose dextroamphetamine i.r., and also low dose risperidone or aripiprazole. In the low doses used amitriptyline did not cause complaints of constipation or urinary retention. Side effects included QTc increase on routine EKG, which did not halt treatment except in 3 cases with QTc >440, behavioral activation and worsening of aggression. Prospective, randomized controlled studies of amitriptyline in ASD are warranted.

While a 2014 Cochrane review (42) of TCAs in TD youth showed no serious adverse events associated with taking TCAs, mild increases in pulse rates and diastolic blood pressure occurred. Of note is that the overdose risk with TCAs is lower in individuals with ASD since most individuals including adults with ASD do not self-administer their medications. TCAs should not be prescribed for use in chaotic households or in those with a risk of overdose by a family member.

Alpha Agonists

The class of alpha-agonist drugs is FDA-approved for ADHD in typically developing children but not in ASD. Since these drugs may benefit tics and Tourette disorder, they are usually a first-line treatment choice in such individuals. This drug class includes guanfacine, clonidine, long-acting guanfacine (Intuniv TM) and long-acting clonidine XR (Kapvay TM). An 8-week multisite study of extended-release guanfacine in 62 children with ASD and ADHD, mean age 8.5 years, found a significant improvement in comparison with placebo. Modal guanfacine ER dose was 3mg/day (range 1-4mg/day) (43). The most common side effects were fatigue, drowsiness and decreased appetite. For subjects on guanfacine, blood pressure dropped in the initial 4 wk, but returned almost to baseline by week 8. Pulse rate also dropped but remained

lower than baseline at week 8. A small study of clonidine (44) examined response of 8 male children with autistic disorder in a double-blind, placebo-controlled crossover design for ADHD symptoms. While parent-rated Conner's questionnaire ADHD ratings improved significantly during clonidine treatment, teacher ratings were not significantly improved except for oppositional behavior. Side effects included drowsiness and decreased activity. Due to their short half-lives, the immediate-release preparations of clonidine and guanfacine should be dosed 3 times a day. Dosing is built up gradually while monitoring for dizziness, hypotension and bradycardia. Other side effects include weight gain, sedation and irritability.

Although alpha agonists improve attention, studies in otherwise TD youth with ADHD have shown their combination use with a stimulant medication produces greater attentional improvement than does either alone. Combination treatments of alpha agonists and stimulants are FDA-approved for ADHD in the non-ASD population, but not in ASD. Clinical experience suggests however that alpha agonists may be less helpful for ADHD symptoms in adults with ASD.

Thus in the author's opinion, DEX, ATX and amitriptyline may be useful additions to treatment options for ADHD comorbid with ASD, including in adults.

EXISTING ANTIPSYCHOTIC STUDIES, AND EMERGING EVIDENCE FOR OTHER ANTIPSYCHOTICS

Antipsychotics are used to treat psychosis as well as irritability in ASD, and are classified into two classes: atypical/ novel antipsychotics and typical/ classical antipsychotics. ASD core symptoms including odd, stereotyped talk on unusual restricted topics of interest are still often misdiagnosed as schizophrenia symptoms in everyday practice. Psychosis can also be confused with bizarre behavior related to subclinical seizures, in which case antiseizure medications may help. Psychotic disorders can be comorbid with ASD, including schizophrenia, delusional disorder, unspecified psychosis, or as a component of a major mood disorder such as bipolar disorder, major depressive disorder or schizoaffective disorder (45).

Typical Antipsychotics

Typical antipsychotics block dopamine D2 receptors to alleviate psychosis or mania, but produce motor ¹side effects including acute dystonias, extrapyramidal side effects (EPS), tardive dyskinesia and more rarely, neuroleptic malignant syndrome which can be fatal. Haloperidol was studied in early trials by Campbell and colleagues, in young children, but found to produce tardive withdrawal movements (46, 47) and further studies were halted. According to clinical experience, typical antipsychotics often have a lag time to onset of response in individuals with ASD, and increasing the dose early in treatment especially of high potency antipsychotics like haloperidol may result in extremely severe EPS and dysphagia after a while, especially more severely disabled individuals, with resulting joint contractures. (16). Low potency typical antipsychotics including chlorpromazine produce hypotension, slowing, cognitive dulling and weight gain in those with developmental disabilities as well as in the general population. Thioridazine produced QTc prolongation and is no longer marketed.

The medium-potency, typical antipsychotic loxapine blocks serotonin as well as dopamine, and in low doses resembles an atypical antipsychotic in positron emission tomography (PET) studies, but with less or no weight gain (48, 49, 50) which will be discussed in more detail below. Atypical antipsychotics were designed to overcome these motor side effects of typical antipsychotics by a different mechanism of action, notably by blocking serotonin as well as dopamine receptors, amongst others. However an unanticipated side effect of the atypical antipsychotics turned out to be weight gain, Type II diabetes and multiple other medical side effects (51), which is more severe in those with developmental disabilities. Atypical antipsychotics also produce possible motor side effects including neuroleptic malignant syndrome and tardive dyskinesia in the general population but also in ASD.

Atypical Antipsychotics

Only two antipsychotics are FDA-approved in ASD, for children ages 6 years and older with irritability, notably risperidone and aripiprazole. The RUPP multisite 8-

week risperidone RCT study of 101 children and adolescents, mean age 8.8 years, found significant efficacy of risperidone *vs* placebo for irritability ¹ on the Clinical Global Impressions-Improvement subscale (52), and the Aberrant Behavior Checklist-Irritability subscale (29) at a mean dose of 1.8mg/day. Effect size was 1.2. Side effects included significant weight gain, appetite increase in 73%, fatigue in 59%, and drowsiness in 49%, as well as prolactin elevation. The greatest benefits reported by parents were for self-injury and aggression. Another larger multisite RCT study of risperidone and parent training in 124 children and adolescents ages 4 through 13 found that parent training could lessen the dose of risperidone needed (53). Risperidone doses were a mean of 2.26mg/day or 0.071 mg/kg in the risperidone-only group, *vs* 1.98mg/day or 0.066 mg/kg ($p=.04$, two-sided test) in the combination group of risperidone plus parent training.

Weight gain associated with risperidone treatment was marked, especially in some individuals in a double-blind crossover study performed by the author's group, of risperidone *vs* placebo for challenging behaviors in participants aged 6 to 65 with ID and ASD (54). In a subset of 19 subjects over approximately a year, weight gain was as follows: children ($n = 5$) ages 8 to 12 years gained 8.2kg on average, adolescents ($n = 6$) aged 13 to 16 years gained 8.4kg on average, and adults gained 5.4kg on average (55). Prolactin elevation is greater with risperidone than with other atypical antipsychotics. Breast development, galactorrhea and amenorrhea should be monitored (56). It is important to monitor for weight gain and metabolic syndrome abnormalities, notably hypertension, glucose elevation, midline obesity, and triglyceride elevations. These are important predisposing factors to diabetes, stroke, myocardial infarction, and cognitive dysfunction and brain abnormalities (55). In the author's experience, keeping risperidone doses low at or below 2mg/day total, and splitting dosing to three times a day can help minimize weight gain. Importantly, clinical experience suggests that risperidone may be the most effective antipsychotic for self-injurious behavior.

⁶ A multisite RCT of aripiprazole in 218 children and adolescents with ASD, aged 6-17 years, mean age 9.3 years, found significant improvement in irritability in the

aripiprazole *vs* the placebo group. Doses were 5, 10 or 15mg/day in this 8-week, parallel groups study. However, there was no protection against long-term relapse, the author agrees with this finding based on clinical practice, meaning that the efficacy may decrease over time, and increasing the dose may not recapture the initial good response. Side effects included sedation, the most common side effect leading to discontinuation, and significant weight gain (57). Mean weight increases at week 8 were 0.3kg for placebo, 1.3kg for 5mg/day, 1.3kg for 10mg/day and 1.5kg for 15mg/day groups, all $p < .05$ *vs* placebo. Importantly, aripiprazole in a low dose of 1mg/day normalizes prolactin for example in an individual responding to risperidone who has elevated prolactin producing gynecomastia (58). One small open pilot study compared olanzapine with haloperidol in children with autistic disorder (59) and one studied ziprasidone *vs* placebo (60) in ASD. Metformin for weight gain treatment with atypical antipsychotics was studied in a 16-week, 4-center multisite RCT of 60 children. Metformin was associated with reductions in future weight gain, notably BMI z-scores decreased significantly more from baseline to week 16 than in the placebo group ($p=.003$). However metformin did not alter lipid abnormalities, and gastrointestinal side effects identified included abdominal discomfort, abdominal pains and diarrhea (61), (in contrast to loxapine substitution discussed below).

Loxapine Resembles An Atypical Antipsychotic at 5-10mg/day

Loxapine shows promise clinically in adolescents and adults with ASD according to preliminary studies, and RCTs are warranted. This antipsychotic is a dibenzoxazepine tricyclic structure classified in the medium potency group of the typical antipsychotic class. Loxapine was designed in the 1980s to resemble clozapine but without the clozapine molecular component causing agranulocytosis. Loxapine has a history of extensive use in schizophrenia, usually at 40 to 80mg/day (maximum dose of 200mg/day) and may lack the marked weight gain and metabolic side effects of clozapine and other atypical antipsychotics (62). A case report of a 10 year old female with autistic disorder who responded to loxapine 15mg/day described its efficacy for treatment-resistant aggression and self-injurious behavior (63). In low doses of 5 to 10

mg/day, loxapine resembles an atypical antipsychotic on PET brain studies, but lacks the weight gain and metabolic side effects (64, 65). A prospective 12-week open trial of loxapine for irritability and aggression in 16 adolescents and adults with ASD (48), demonstrated that loxapine in low doses of 5 to 10 mg per day significantly improved irritability ratings on the ABC-I, with large pre- to post- treatment effect sizes on 4 subscales, $d=1.0-1.1$. Fourteen of 16 subjects completed the study, all of whom had Clinical Global Impressions-Improvement scale ratings of Very Much Improved or Much Improved at week 12. Larger clinical trials are warranted.

A retrospective loxapine chart review, also by the author's group, of 15 outpatient adolescents and adults with ASD and irritability, illustrates the strategy of adding loxapine 5-10 mg/day, followed by extremely gradual taper of offending antipsychotics reversed weight gain, metabolic syndrome and insulin resistance including diabetes (49). All those in the series had gained weight and manifested at least one other metabolic abnormality since starting on the baseline antipsychotic. Fourteen of the subjects were being treated with atypical antipsychotics and one received chlorpromazine, prior to addition of loxapine 5 to 10 mg daily, followed by behavioral improvement and then taper of the offending antipsychotic. Final loxapine dose in 12 subjects was 5 mg/day, and 10mg/day in 2 subjects. At the time of chart review, all but one subject (93%) were Very Much Improved or Much Improved on CGI-I. Mean weight loss after an average of 17 mo (range 7 to 26 mo) on loxapine was - 5.7kg, with BMI reduction averaging -1.9. Mean reduction in triglycerides was - 33.7mg/dL ($P = 0.03$). Two subjects were tapered off metformin by their endocrinologists, and one person's insulin for Type II diabetes was discontinued. Weight loss did not differ in those already receiving metformin at the time of loxapine add-on ($n = 4$) though the numbers are small and the reader is therefore cautioned.

In a long-term outcomes chart review study, of 34 children, adolescents and adults with ASD, mean age 23.4 years (range 8 to 32 years), long-term low-dose loxapine at a mean dose of 8.9mg/day (range 5 to 30mg) was associated with lower rates of tardive dyskinesia and EPS than expected for a typical antipsychotic, mean

treatment duration was 4.2 years (50). Stahl (62) describes the addition of low doses of a classical antipsychotic to an atypical antipsychotic to “lead in” or “top up” the effect. Using loxapine add-on at 5-10mg/day, the author has been able to minimize dose increases above 1.5-2mg a day total of risperidone and appears weight-sparing.

Dysphagia and Bowel Obstruction Associated With Antipsychotics

A clinical word of caution is important regarding minimally verbal and neurologically impaired individuals treated with antipsychotics. Dysphagia is a common but often overlooked side effect of antipsychotics, predisposing to aspiration pneumonia and initiation of parenteral feeding after surgical insertion of gastrostomy tubes, which may then be life-long if the antipsychotic medications are not changed. Aspiration pneumonia is more common in those with severe developmental disabilities and minimally verbal individuals and those with cerebral palsy or quadriplegia treated with even moderate doses of antipsychotics, especially if the individual also receives concomitant cytochrome P450 2D6 (CYP2D6)-inhibiting selective serotonin reuptake inhibitors (SSRIs) (66).

Substitution of the antipsychotic with other medications if needed, and gradual dose taper may allow swallowing improvement and normal eating reinstatement provided a repeat video swallow study is normal. A large study in non-psychiatric inpatients without ASD receiving antipsychotics mostly for delirium control found a significant association with aspiration pneumonia in comparison with a non-antipsychotic exposed group (67). The association magnitude was similar for typical and atypical antipsychotics. Also repeated ED and medical visits are commonly needed for ostomy revisions and infections. In clinical practice the problem is often magnified in individuals with spasticity by high dose anticholinergics such as baclofen or tizanidine. SSRIs that inhibit CYP2D6 may increase the effective dose of antipsychotics and other medications such that small-appearing doses actually are effectively much larger. In addition, such prescribing practices often lead to severe constipation, paralytic ileus, bowel obstruction and resection in individuals with severe disabilities. The author

avoids using loxapine in individuals with severe disabilities and uses low dose risperidone in divided doses instead, due to the elevated dysphagia and EPS risks.

SELECTIVE SEROTONIN REUPTAKE INHIBITOR STUDIES IN ASD; AND WHAT OTHER DRUGS MAY HELP RRBs?

SSRI Studies Have Not Demonstrated Efficacy for RRBs

While SSRIs may initially appear to help anxiety, depression and compulsive behaviors they may later worsen problems significantly and produce behavioral activation, especially in higher doses, in a dose-related manner. A 12-week RCT study of 149 youth aged 5 to 17 years with ASD treated with citalopram, dosed up to 20 mg daily (mean dose 16mg/day) for RRBs in ASD, was negative (68). Overall there was no change in repetitive behavior but also significant side effects occurred. These included impulsiveness, increased energy level, hyperactivity, decreased concentration, increased RRBs, insomnia, diarrhea and skin dryness and itching.

A 14-week RCT study of 158 youth aged 5 to 17 years with ASD, treated with fluoxetine found no differences from placebo for RRBs as rated on the Child Yale-Brown Obsessive Compulsive Scale- Pervasive Developmental Disorders version (69). Another fluoxetine RCT was also negative; Australian investigators randomized 146 youth aged 7.5 to 18 years with ASD to fluoxetine (20mg/day if <40kg or 30mg/day if >=40kg) or placebo. Any differences favoring fluoxetine were statistically nonsignificant after variables of gender, verbal abilities and baseline differences were controlled for. There was also no significant trend toward improvement on secondary outcome measures of RRBs, irritability, anxiety or global change (70). An older, smaller RCT study of 39 youths aged 5-16 years found that a mean dose of 9.9mg/day of fluoxetine was superior to placebo (71), however this has not been replicated. Some individual case studies and a case series suggested fluoxetine response however (72).

⁸ Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed drugs in ASD (4), although their use is not backed by study evidence. In the author's experience they may be helpful in high-functioning individuals with ASD, for anxiety or depression. The Cochrane collaboration literature review of SSRIs in autism

found no overall benefit in ASD, weighing positive and negative studies against each other (73). In the author's experience, non-stimulant ADHD medications rather than SSRIs can help OCD and repetitive behaviors, including atomoxetine and amitriptyline, anecdotal evidence but could be worth a try in the clinic. Many times the patient is presenting on an antipsychotic already. RRBs may relate also to ADHD symptoms, notably impulsivity, as part of a common cognitive impairment of executive function ("putting the breaks on") ie non-specific response inhibition (74). These investigators found significant associations between repetitive speech and impulsive speech, between stereotyped behavior and overactivity, and between restricted preferences and impulsivity. This study further justifies the argument for studying non-stimulant ADHD medications for RRBs.

The TCA Clomipramine Reduced RRBs in One Small Study

Two TCAs typically targeting OCD, repetitive behaviors and hyperactivity, notably clomipramine and desipramine were compared with placebo in one double-blind study (75). The investigators compared clomipramine to placebo in 12 subjects with autism using a crossover design, together with 12 different subjects completing a parallel trial of clomipramine *vs* desipramine. Clomipramine was superior to placebo and desipramine in reducing ratings on stereotypies, compulsive ritualized behaviors ($p < .05$) and anger, while desipramine was no different from placebo except in reducing hyperactivity. However in the author's experience substitution of amitriptyline for clomipramine in patients who present on clomipramine has produced greater global clinical improvements. This was an empirical observation made by the author's team in the 1990s that appears valid still today (41).

In a small cross-over study, 5 of 18 children (28%) treated with low dose fluvoxamine responded (76). Fluvoxamine was found to benefit RRBs, maladaptive behavior, aggression and language in a small 12-week RCT of 30 adults with autistic disorder (77). Treatment studies of SSRIs or other classes of agents for depression and for suicidal behavior in ASD are lacking. For anxiety disorders in general in ASD, some smaller studies suggest the efficacy of citalopram, and some were positive for

buspirone. One buspirone study in ASD found worsening of aggression and self-injury (78).

Maintenance benzodiazepines are avoided as a general principle in individuals with developmental disabilities, except for insomnia and as pre-sedation for blood tests and other procedures including dental work. Downsides include disinhibition effects, cognitive slowing and impairment, clumsiness, falls and injuries associated with benzodiazepine treatment.

HOW TO APPROACH ANTISEIZURE MEDICATIONS?

The therapeutic behavioral effects of antiseizure medications in ASD for use other than seizures are inconclusive, according to available evidence. An RCT by the author's team of valproic acid for aggressive behavior in youth with ASD was negative, although some subjects appeared to benefit from it, likely related to the heterogeneity within ASD (79). Another study found valproic acid to be beneficial for RRBs in ASD, however this finding has not been replicated. Worsening of behavior occurred in 4 of 13 cases (80). Divalproex was effective for controlling irritability associated with fluoxetine treatment in ASD (81).

Clinical experience suggests a trial of antiseizure medication such as valproic acid or lamotrigine may be beneficial especially if seizures are known or suspected, and the presentation of behavior problems is bizarre or atypical. This pertains especially to minimally verbal individuals with severe ASD, who have very high rates of seizures, and those with a known history of traumatic brain injury.

For Mood Disorders

Apart from ADHD, bipolar disorder is another, much less common cause of impulsive aggression in ASD. A 25% lifetime prevalence for bipolar disorder *vs* 68% for ADHD was found in a tertiary-referred population of high-functioning adults with ASD (9). Minimally verbal individuals may also present with bipolar-like illness however studies of this portion of the ASD spectrum are still needed. Although lithium may be helpful, antiseizure medications are a first line of treatment for bipolar disorder in individuals with developmental disabilities.

Divalproex and Carbamazepine

Mood-stabilizing antiseizure medications including divalproex and carbamazepine are the first-line treatments for mania, mixed or rapid cycling bipolar disorder in the general population (82) as well as in individuals with developmental disabilities. Valproate/divalproex is FDA-approved for bipolar mania but not for acute bipolar depression in the general population. Divalproex can also be effective for acute mixed bipolar disorder (83). Side effects include weight gain, polycystic ovarian syndrome, low blood platelets, alopecia, elevated liver enzymes and less often pancreatitis. In addition, divalproex can cause ASD if taken in early pregnancy (84). Weight gain, hepatic enzymes and blood cell counts require monitoring.

Both divalproex and carbamazepine are available in extended-release formulations. Carbamazepine is weight-neutral but side effects may include nausea, vomiting, dizziness, drowsiness, dry mouth, constipation and unsteadiness. A rare but extremely serious potential side effect of carbamazepine is Stevens-Johnson syndrome, which may start as an influenza-like illness but progress to a blistering skin rash, skin peeling and death.

Lamotrigine

Lamotrigine is the mood- stabilizing antiseizure medication of choice for bipolar depression treatment as well as prophylaxis. Apart from the vigilance needed for a serious skin rash again associated with Stevens-Johnson syndrome, and the need to start lamotrigine slowly to try and prevent this, the longer-term profile of lamotrigine (LTG) is favorable in comparison with other antiseizure medications. Another important use for consideration in psychiatry, according to author experience, is for suspected seizures including spells of eye-blinking, mouth movements or disorientation episodes accompanied by bizarre behavior presentations in ASD, as mentioned above.

Evidence for lamotrigine is weaker for acute bipolar depression and rapid cycling bipolar disorder in the general population. Lamotrigine must be started extremely slowly by adding a low dose every 1 to 2 wk, and even more gradually if the

individual is receiving divalproex (adding 25mg every 2 wk), to avoid a potentially life-threatening skin rash that begins on the upper chest region. Skin rash signs include skin peeling, blistering, hives, itching and painful sores in the mouth or around the eyes. Other lamotrigine side effects include blurred or double vision, poor motor coordination, headache, drowsiness, and difficulty thinking or speaking.

Gabapentin

Gabapentin is an add-on antiseizure medication often prescribed off-label in psychiatry for various indications despite negative RCTs including for bipolar disorder. Rather than acting on gamma-amino butyric acid (GABA), gabapentin likely acts on calcium channels in the brain and spinal cord, and has few drug interactions since it is renally excreted. Gabapentin add-on to valproic acid and low dose antipsychotic was helpful in an open study by the author, in adults with developmental disabilities (86). Gabapentin in divided doses 3 times a day, totaling 900 to 1800 mg a day were effective as add-on to valproic acid and low dose antipsychotic, and also in a subset replaced lithium and thus eliminated lithium side effects. Gabapentin side effects included dizziness and clumsiness; to prevent these it was started at 100mg daily and increased slowly by only 100-200 mg per week, although prospective RCT studies are needed.

While lithium is still used in ASD, the side effects are often worse in those with developmental disabilities, and include polydipsia and polyuria (excessive thirst, drinking and enuresis) and tremor. Acute toxicity is a medical emergency requiring dialysis and ICU treatment, and is a greater risk in individuals with disabilities. Vomiting, diarrhea, failure to drink fluids for any reason, and certain medications including the angiotensin-converting enzyme (ACE) inhibitor losartan predispose to toxicity (86).

Insomnia is very common in ASD and should not be interpreted as mania-related illness unless accompanied by other observable mania features. Another pitfall is that loud, rapid speech and outgoing personality may not be due to bipolar disorder but an enduring personality trait with a life-long history.

Antiseizure Medication- Related Behavioral Side Effects

Importantly, several antiseizure medications while benefitting seizures may produce adverse behavioral effects. The latter may not have been considered by the neurologist especially if the seizures are adequately controlled. Therefore identification of such side effects by the psychiatrist is essential. Barbiturate-based antiseizure medications including phenobarbital and phenytoin, and benzodiazepine-based medications, as well as vigabatrin often worsen behavior. Such medications may lead to an ADHD-like picture of affect dysregulation, hyperactivity, restlessness, impulsive aggression and self-injury (87). Carbamazepine, oxcarbazepine, levetiracetam and topiramate may also worsen hyperactivity, mood or psychotic symptoms or other behavior problems. Lamotrigine and divalproex may be less likely to have behavioral side effects in adults with ASD according to clinical experience.

DISCUSSION

Studies included followed a broad and thorough literature review of pharmacotherapy in ASD, in order to provide a clear overview of the topic as well as the author's expert opinion. Limitations of this opinion review include that aside from evidence-based guidelines, prescribing practices may be extremely variable, not only by country and region, but also by individual practitioners who may find other medications useful in ASD. The author has however attempted to provide a personal but balanced view overall. Regarding future drug treatments for core ASD symptoms, it may not be possible for one drug to target and treat all of the many subtypes of ASD, given the many genetic and other causes. Also of note is that while certain drugs such as atomoxetine may not be available in all countries, amitriptyline is approved in many countries and is available in generic forms.

CLINICAL PEARLS GLEANED OVER MANY DECADES of research and practice treating all ages with developmental disabilities

Environmental and emotional causes are more likely to respond to behavioral consultation: This can be key also in treatment resistance

It is important to emphasize that environmental and emotional causes of behavior problems will be more likely to respond to behavioral consultation and psychosocial

interventions. Of late, there has been greater recognition of environmental contributors to psychiatric illness in the field in general. Abuse of all types is also more likely in vulnerable individuals such as those with developmental disabilities. Taking a detailed longitudinal history is essential, regarding likely environmental stressors such as family deaths or job losses, moves and staff changes leading to frustration and severe “protest” behavior problems including aggression, before making psychiatric diagnoses and trying medication treatments. Protest behaviors and use of aggression as communication are more likely especially if the individual has demonstrated consistently good functioning over one or more periods of time in their past. A developmental and childhood psychiatric history is also essential to understanding of presenting problems. Irritability can result from many non-psychiatric causes, including medical illness, lack of sleep, general frustration or unhappiness with a living situation. Treating just dimensional behavior problems, such as irritability or hyperactivity with single medications may be feasible for milder cases. As in other branches of medicine, if the diagnosis is wrong then the treatment will unlikely help.

Closer examination for ADHD and trying ADHD treatments pays off, including in females and adults with severe disabilities.

This applies to ADHD wrongly diagnosed as bipolar disorder, since antipsychotics and mood stabilizers do not adequately treat ADHD-related impulsivity. This was a personal lesson the author learned early on in practice after specializing in treating this population. Females diagnosed with depression and recurrent suicidality may also respond to ADHD treatments, allowing for cautious taper off of antidepressants. Parents and caregivers often describe a person with ADHD person as “anxious” since they rarely sit still, and “moody” due to lack of affect regulation associated with easy crying or laughing spells.

3. Dextroamphetamine, atomoxetine and amitriptyline are useful for ADHD comorbid with ASD

Impulsive aggression such as cussing, hitting, kicking, biting, pinching and running off may respond to one or more ADHD treatments if the ADHD history and diagnosis

are elicited. Many adults already received treatment for ADHD as children but once transitioning services happens the ADHD diagnosis is overlooked. Although only studies in TD individuals are available as discussed above, a combination of low dose stimulant together with a non-stimulant ADHD medication such as atomoxetine, amitriptyline or guanfacine may be needed. Low dose risperidone may also be used in combination with the ADHD treatments, although again only one study in the TD participants is available regarding this (88).

Two ADHD medications may be needed (stimulant and non-stimulant) possibly also together with low dose antipsychotic such as risperidone in moderate-to -severe cases with aggression. In the author's experience, atomoxetine is frequently clinically useful for ADHD with impulsive aggression, including in more severely disabled individuals. The tolerable doses may be lower than in higher functioning individuals, although improvements may be regained if the dose is decreased again after behavioral worsening following a dose increase occurs. More studies are warranted. Amitriptyline in low doses can be extremely helpful for cases with insomnia, headaches, gastrointestinal issues, ADHD, impulsive aggression and OCD, used with caution and watching for drug interactions. Studies are warranted of amitriptyline for RRBs in ASD according to author experience.

Are RRBs part of the ADHD spectrum, and could they respond to ADHD treatments?

The study by Burbridge and coworkers (74) leading to the concept of RRBs as related to ADHD, in other words a type of motor impulsivity, may be key to guiding future studies for RRB etiology and treatments. One study found atomoxetine was somewhat effective for RRBs in youth with ASD, which is promising (39). No known treatment currently exists for core ASD features, likely due to the heterogeneity and many different genetic causes. Metformin, arbaclofen, lovastatin, trifinetide, 5-HT7 agonist ligands, flavonoids, cannabidiol, cannabis and the dietary supplement sulfurophane amongst others, are still being studied (4).

Risperidone Remains Useful in youth with severe irritability and may be helpful for self-injury; dose at $\leq 2\text{mg/day}$ in divided doses

Dosing risperidone at or below 2mg/day given in divided doses may mitigate weight gain and metabolic side effects, though individuals vary. Another author observation is that risperidone may be the most effective medication for self-injurious behaviors including self-biting, head-banging, self-hitting and others. Weight gain and metabolic side effects require monitoring.

Loxapine at 5-10mg/day resembles an atypical antipsychotic but likely with emerging safety evidence of a more favorable metabolic profile

Loxapine is one of the main antipsychotics now used in practice by the author and several colleagues in other regions, for adolescents and adults with ASD, related to an empirical finding made over 2 decades ago and then the preliminary published studies discussed above. Addition of 5-10mg/day of loxapine often produces significant clinical improvement in irritability and aggression, which if needed then allows very gradual taper of other antipsychotics which have caused excessive weight gain or produced to little response. While a common practice may be to follow schizophrenia guidelines and convert a treatment-resistant person to a depo antipsychotic, hoping for improved aggression control, adding loxapine in my experience produces superior results overall. However loxapine is likely not suitable for more severely disabled individuals due to its potent dopamine blocking action that may cause dysphagia in them; low dose risperidone may be preferable in this setting. Olanzapine is another cause of dysphagia in those with more severe disabilities, according to clinical experience.

Gabapentin may be a useful add-on to divalproex and low dose antipsychotic if lithium is not a good choice for the individual patient

Published preliminary evidence on gabapentin add-on to valproate and low dose antipsychotic in ASD may be useful when lithium is not tolerated due to side effects, or if lithium toxicity has already occurred once or more. Studies are needed.

SSRIs may be helpful in higher-functioning ASD for anxiety or depression, but not for RRBs

SSRIs remain the most widely prescribed drug class in ASD in the USA overall. Recent negative studies of citalopram and fluoxetine for RRBs in youth with ASD are

helpful in this clarification. In many cases, high dose SSRIs worsen OCD and agitation, while gradual SSRI taper may lead to clinical improvements. Also, in cases involving SSRIs increasing the effective antipsychotic dose due to CYP2D6 inhibition, swallowing impairment and bowel motility problems may be reversed by gradual SSRI taper and medication revisions.

CONCLUSION

Existing studies in ASD are useful guides for clinical practice, but many more are still needed. Most prescribing in individuals with developmental disabilities is of clinical necessity off-label. Some older psychotropic medications with emerging evidence may extend and improve possible successful treatment options for clinicians serving individuals of all ages with ASD and severe behavior problems. Until controlled studies of these drugs become available, cautious clinical use starting with low doses and minding drug interactions may be justified. Another important focus should be alerts regarding possible ADHD with impulsive aggression, especially in females and in adults with ASD. The older medications worth trying include, but are clearly not limited to, dextroamphetamine, atomoxetine and amitriptyline for individuals with ADHD associated with impulsive aggression.

For irritability and psychotic comorbidity in adolescents and adults with ASD, preliminary published evidence and clinical experience point to loxapine in doses of 5-10mg/day having atypical antipsychotic properties but likely with lower metabolic risk associated. For likely seizure activity associated with bizarre behaviors that is unable to be worked up *via* electroencephalogram (EEG) due to lack of cooperation, lamotrigine may be considered, especially in those with severe disabilities since they have higher rates of seizures. No medications have been identified and replicated so far to treat the core symptoms of autism, including RRBs, and may never be, related to the vast heterogeneity of ASD causes, both genetic and others. Drugs without demonstrated benefit for core symptoms include risperidone, oxytocin, bumetanide, buspirone, citalopram, fluoxetine, fluvoxamine and N-acetyl cysteine. While SSRIs are the most

commonly prescribed drugs in ASD and may help individual patients, recent RCT studies did not show significant efficacy for RRBs in ASD, but rather a significant side effect burden including behavioral activation. Clinical trials of the older drugs we discussed are warranted. All medications should be used in conjunction with other multimodal therapies including behavioral consultation, and selected for the individual patient.

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