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ARTICLE

Psychopharmacological Treatments in Children with Fetal Alcohol Spectrum Disorders: A Review

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Abstract

Psychiatric symptoms in children with Fetal Alcohol Spectrum Disorders (FASD) present with high prevalence and morbidity, often across symptom domains, e.g. ADHD-like symptoms, emotional dysregulation and sleep problems. Polypharmacy is often used, but no empirically-based guidelines exist regarding optimal treatment for these children. Moreover, stimulant use in these children is controversial as their responsiveness may be different due to altered neural circuitry associated with prenatal alcohol exposure. The objective of this review is to give an overview of existing data on pharmacological treatments of neurobehavioral symptoms in FASD. Our literature review yielded limited and conflicting clinical data on the effectiveness of pharmacological treatments for psychiatric symptoms in children with FASD, with some symptom domains lacking data altogether. We emphasize the need for clinical trials to guide pharmacological treatments in this complex population.

Keywords Fetal alcohol spectrum disorder (FASD) · Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE) · Psychopharmacology · Psychostimulants

Introduction

Fetal alcohol spectrum disorder (FASD) affects an estimated 1–5% of the population [1, 2]. The toxic neurodevelopmental sequelae of prenatal alcohol exposure, combined with the high frequencies of psychosocial risk factors in exposed children including abuse, neglect, and multiple home placements, put these children at high risk for psychiatric symptoms and disorders [3, 4]. The neurobehavioral consequences of prenatal alcohol exposure have been well characterized in children and common symptoms include inattention, hyperactivity, impulsivity, emotional dysregulation, sleep problems, disruptive behavior, and mood problems, often affecting academic and social functioning [3, 5, 6].

Attention deficit hyperactivity disorder (ADHD) is the most commonly identified comorbid psychiatric disorder in this population, with the majority of FASD-affected children meeting criteria for this disorder [7–9]. For example, Fryer et al. [8] compared a group of 39 children prenatally exposed to alcohol to 30 non-exposed controls and used the Kiddie Schedule for Affective Disorders and Schizophrenia and the Computerized Diagnostic Interview Schedule for Children to determine rates of psychiatric disorders. They diagnosed 95% of the exposed children with ADHD, compared to 30% of controls. These authors also found high rates of oppositional defiant disorder (38% in exposed children versus 17% in controls), as well as high rates of depressive disorders (18% in exposed vs 0% in non-exposed) and anxiety disorders. The elevated risk for conduct problems was highlighted in a study by D'Onofrio et al., who in a sample of 8621 children found rates of mother-reported conduct problems to be 0.35 standard deviations higher in children exposed to alcohol prenatally versus non-exposed children. Although prevalence of specific psychiatric disorders varies largely between studies, there is general agreement that the prevalence of both externalizing and internalizing problems is high in children with FASD (for review, see [3]).

DSM-5 now recognizes the neurobehavioral syndrome associated with prenatal alcohol exposure as Neurodevelopmental Disorder associated with Prenatal Alcohol Exposure (ND-PAE), both as a condition for further study, and as a disorder that can be coded for under Other Specified

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Neurodevelopmental Disorder [10]. ND-PAE can be diagnosed if a child with more than minimal prenatal alcohol exposure presents with impaired neurocognitive functioning (IQ, executive functioning, learning, memory, and/or visuo-spatial reasoning), impaired self-regulation (mood, behavior, attention, and/or impulse control), and at least two impairments in adaptive functioning (language, social communications, daily living skills, and/or social skills) [11, 12].

Many children with FASD require psychopharmacological interventions in addition to behavioral and educational interventions; however, no guidelines exist regarding optimal psychopharmacological treatments in this complex population. The symptom domains where pharmacological treatments may have the most impact are those pertaining to impairments in self-regulation (mood, behavior, attention, and/or impulse control). Stimulants are very effective medications for treatment of idiopathic ADHD [13] and given the high occurrence of ADHD-like symptoms in children with FASD, stimulants would be a logical first-line treatment for these children. However, research points towards a distinct neurocognitive and behavioral deficit profile of FASD-affected children compared to children with idiopathic ADHD [14]. In addition, data regarding stimulant responsiveness is limited and mixed. Consequentially, the use of stimulants in this population is controversial. Other treatments that have shown to be effective for idiopathic ADHD include the selective norepinephrine reuptake inhibitor atomoxetine and the alpha-2 agonists guanfacine and clonidine, but efficacy of these treatments in children with FASD is not known. Similarly, although depressive and anxiety disorders are commonly diagnosed in individuals with prenatal alcohol exposures [3, 8, 15], the selective serotonin reuptake inhibitors shown to be effective in the general population may have differential effects in children with FASD, especially given distinctive neurodevelopmental fetal alcohol effects on the serotonin and dopamine systems [16, 17]. Furthermore, antipsychotics including risperidone and aripiprazole, which have been well studied and FDA approved for aggression and irritability in autism spectrum disorders, remain understudied in FASD. Finally, mood stabilizers, frequently used for disruptive disorders and mood disorders in children (with only lithium having FDA approval in children for bipolar disorder), have unknown efficacy and safety profiles in children with FASD. The goal of this review is to provide an overview of existing data on psychopharmacological treatments for neurobehavioral symptoms of FASD/ND-PAE and highlight the need for clinical trials in this population.

Methods

Studies for inclusion in the review were identified from the following electronic databases: PubMed/Medline, Embase, Google Scholar, Scopus, and Cochrane Library. Search terms were ["fetal alcohol spectrum disorder" OR "fetal alcohol syndrome" OR "alcohol related neurodevelopmental disorder"] AND ["pharmacological treatment"]. Both clinical and preclinical studies were considered for inclusion in the review if the article (1) studied a target population of children aged 0–17 with a fetal alcohol spectrum disorder, including individuals with a diagnosis of Fetal Alcohol Syndrome (FAS), partial FAS, neurodevelopmental disorder associated with prenatal alcohol exposure (ND-PAE), alcohol-related neurodevelopmental disorder (ARND) or studied an animal model of FASD; and (2) studied a pharmacological intervention or pharmacological interaction focused on improving symptoms related to neurobehavioral manifestations of FASD.

Prenatal interventions to ameliorate the impact of PAE were excluded, as these articles are beyond the scope of this article and are not pertinent to psychiatric care of affected individuals. Review articles were excluded but were used to identify additional references. For Google Scholar, only the 200 most relevant search results were screened. Articles in languages other than English were excluded. There was no limitation on time period for inclusion. Our initial search was conducted in 2019, and an updated search was conducted on December 15, 2020. Our search yielded a combined 891 results. The title of each study was screened for relevance and, if relevant, the abstract was subsequently screened. Fifteen studies met full inclusion criteria and were reviewed completely. Given the heterogeneity of the study interventions and the study designs, a meta-analysis could not be conducted, and the narrative synthesis method was used instead to display results. Preclinical and clinical studies were grouped and narrated separately. Figure 1 displays a flow diagram of the screening and selection process.

Results

Preclinical Studies

To our knowledge, seven animal studies have reported on the effects of psychopharmacological treatments on neurobehavioral symptomatology associated with FASD/ND-PAE. All of these studies used a rat model of prenatal alcohol exposure and six studies focused on treatments with psychostimulants for ADHD-like symptoms with one study additionally including atomoxetine in their treatment paradigm. One study investigated Agmatine to ameliorate depression- and anxiety-like behaviors and cognitive functioning. In these studies, locomotor activity was assessed as a proxy for ADHD symptomatology. Locomotor activity in rats is typically studied using open field locomotion tests. In open field locomotion, the rats are placed in a gridded "open field" (e.g. 60 × 60 cm field with 10 cm grid squares) and in a

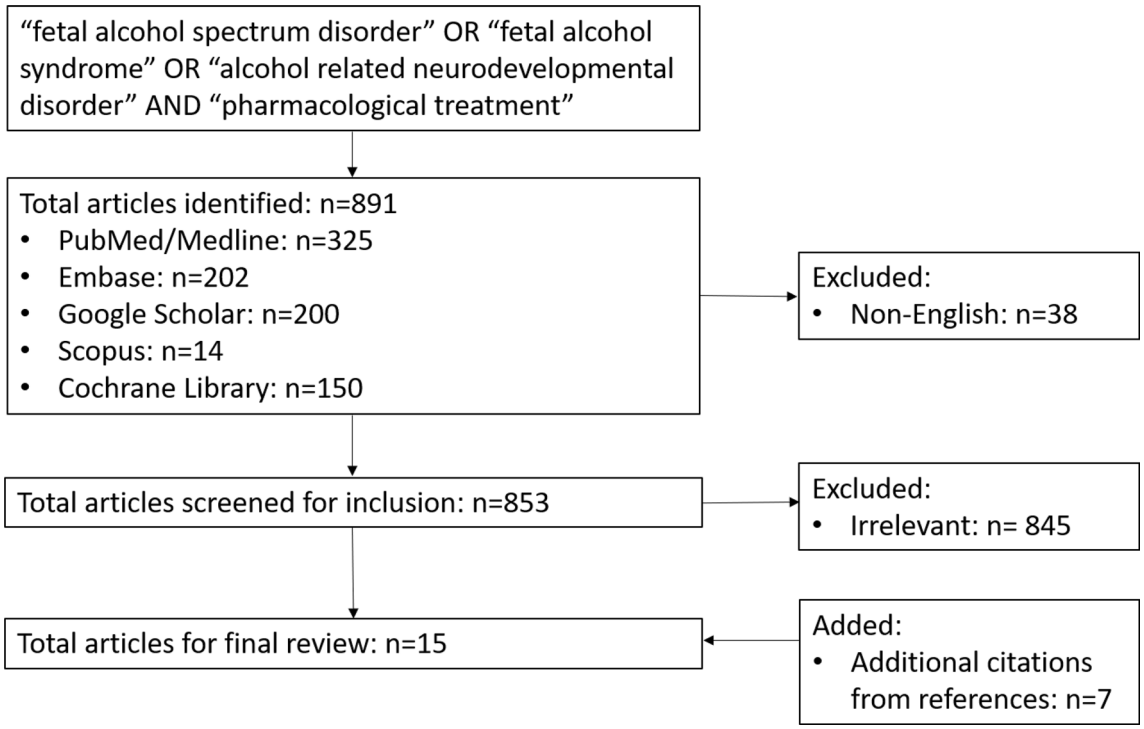

Fig. 1 Flow diagram of screening and selection of studies

predefined time-period (usually between 5 and 20 min), the total duration of ambulation activity is measured. In addition, total grid line crossings are recorded. Alternatively, an automated home cage-type activity monitor may be used.

Ulug and Riley [18], in a rat model of FASD, tested the effects of low dose and high dose methylphenidate on locomotor activity using an automated home cage-type activity monitor (San Diego Instruments, Inc) and found that low dose methylphenidate had no effects on locomotor activity, while high dose methylphenidate worsened locomotor activity. Similarly, Means and colleagues [19] found worsening of hyperactivity in the open field after treatment with methylphenidate in both young and adult offspring prenatally exposed to alcohol in their rat model of FASD. Chronic amphetamine administration also showed worsening of locomotor hyperactivity in male and female rats [20]. Similarly, Randall and Hannigan in their 1999 study on the effects of methylphenidate found dose-dependent increases in locomotor activity with methylphenidate administration [21]. However, their model was limited by the lack of observed baseline increases in locomotor activity in rats with prenatal alcohol exposure.

Juarez and Alvarez in 2015 tested both methylphenidate and atomoxetine in their rat model of FASD and included paradigms to assess for hyperactivity as well as for impulsivity [22]. They found methylphenidate to be mildly effective for impulsivity, and in contrast to the previous studies, found no effect on locomotor activity. Furthermore, their results showed that atomoxetine was able to ameliorate both hyperactivity and impulsivity as tested by open field locomotion and a delay-discounting test [22]. Further evidence for the differential effects of psychostimulants in brains prenatally exposed to alcohol compared to control brains originates from Shen and Choon's electrophysiological studies [23]. In their rat model, they showed that the excessive excitability of dopamine neurons in the ventral tegmental area found after prenatal alcohol exposure was decreased by methylphenidate treatment, while rats without prenatal alcohol exposure showed increased excitability of these neurons after methylphenidate treatment.

Overall, the preclinical data on stimulant medications for FASD is discouraging at worst and conflicting at best, with four studies showing worsening locomotor activity after psychostimulant administration, one study showing no effect, and electrophysiological data showing improvements. Atomoxetine, in contrast, shows improvements of both hyperactivity and impulsivity, but this has not (yet) been replicated.

A recent study on the NMDA receptor modulator Agmatine investigated the effects of Agmatine administration to rats prenatally exposed to alcohol on anxiety- and depression-like behaviors and spatial memory using the elevated plus maze, and Morris's water maze, respectively [24]. Increased entries and time spent into the open arms of the elevated plus maze was seen, which is considered indicative

of a reduction in anxiety-like behaviors. Similarly, during the forced swim test, decreased immobility time (i.e. time spent floating in a water tank without struggling) and decreased time to reach the platform was seen, which is considered suggestive of amelioration of depression-like behaviors. The authors also observed improved spatial memory using Morris's water maze. They did not observe differences in open-field locomotor at baseline in their fetal alcohol syndrome model, nor changes in locomotor activity after treatment with Agmatine. Table 1 summarizes the available preclinical data on psychopharmacological treatments for FASD.

Clinical Studies

To our knowledge, eight clinical studies have previously reported on pharmacological treatments for children with FASD, ranging in sample size from n = 4 to 77. Six articles studied the effects of stimulants [25–30]; two of these in addition reported on the effects of neuroleptics and/or mood stabilizers [25, 30].

Randomized Controlled Clinical Trials

Snyder et al. [29] conducted a double-blinded crossover randomized controlled trial including 11 children recruited from an outpatient treatment center, had a diagnosis consistent with FASD as well as ADHD and were reported to be on a stimulant medication and responsive to their stimulant medication. Treatment arms consisted of their own type and dose of medication (Methylphenidate, n = 8; Pemoline, n = 2; Dexedrine, n = 1) versus a color-matched placebo control in a crossover design and a 1-day washout period. Outcomes included a computerized vigilance test to test for attention, the Underlining Test to test for impulsivity and the parent-reported Conners' Abbreviated Symptom Questionnaire to test for hyperactivity. No differences were found between stimulant treatment and placebo treatment for the attention and impulsivity test, but children showed significant improvements in blinded parent-reported hyperactivity while on stimulants compared to on placebo (T score of 68.36 (SD 17.4) on stimulant compared to T score of 84.4 (SD 14.0); repeated-measures analysis of variance (ANOVA), $F = 8.66$, $p = 0.016$). Despite improvements, the hyperactivity remained in the clinical range while on stimulants. This study was limited by its small sample size. In addition, the attention and impulsivity tests did not include age-corrected data, such that a treatment effect may have been masked by an age effect. Furthermore, the sample only included children that had already shown subjective treatment responsiveness, which likely overestimated the effect of stimulants on hyperactivity and limits generalizability of the study.

Oesterheld et al. [26] also conducted a double-blinded cross-over randomized controlled trial of methylphenidate in children with FASD and ADHD, using a sample of four treatment-naive children recruited from a Native American long-term residential school. In addition to the methylphenidate arm (0.6 mg/kg TID), two placebo arms were included as well as a 2-day washout period prior to each treatment arm. Outcomes included the Conners' Parent Rating Scale (CPRS) Hyperactivity-Impulsivity domain and the Conners' Teacher Rating Scale (CTRS) Hyperactivity-Impulsivity domain, both of which showed significant improvements from clinical range to normal range (repeated measures ANOVA, $F = 4.34$, $p < 0.05$ for CPRS; repeated-measures ANOVA, $F = 6.42$, $p < 0.02$ for CTRS). In addition, the CTRS Daydreaming-Attention domain was obtained, which showed no significant improvements in the methylphenidate treatment arm compared to the placebo arms (repeated-measures ANOVA, $F = 1.429$, $p = 0.289$). Reported side effects in the stimulant arm included poor appetite (n = 3), headaches (n = 2), mild stomach aches (n = 2), and weight loss (n = 1). Limitations of the study include its small sample size, limited external validity (institutionalized children, Native American children only, and exclusion of children with seizure disorders). Furthermore, the instruments used were subjective, and maintenance of blinding may have been compromised due to side effects. These two studies represent the only randomized clinical trials reporting on stimulant use in children with FASD.

Choline supplementation was shown to be feasible in one randomized, double-blinded, placebo-controlled phase 1 trial with preschoolers [31], and showed improvements on the elicited imitation memory paradigm (secondary outcome) in the younger subgroup after controlling for age ($t(83.1) = -2.21$, $p = 0.030$) but did not show improvements in the primary outcome measure of the Mullen Scale of Early Learning. Another randomized, double-blinded, placebo-controlled phase 2 trial in school-aged children showed no effect of choline supplementation on neuropsychological measures of memory (Paired Associates Learning test, $p = 0.73$), executive function (Design Fluency, $p = 0.31$; Spatial Working Memory, $p = 0.31$; Spatial Working Memory strategy, $p = 0.32$), attention (Quotient ADHD System, $p = 0.72$) and hyperactivity (Grooved Pegboard, $p = 0.92$) [32]. Reported p-values are for group x time interaction in a repeated-measures mixed-effects model. Two additional trials on pediatric choline supplementation are currently underway, and two atomoxetine trials have recently been completed per clinicaltrials.gov registries.

Archival Record Review

O'Malley and colleagues [27] conducted an archival record review of 30 children with symptoms of prenatal alcohol exposure. Observations included increased clinical responsiveness to amphetamines compared to methylphenidate

Table 1 Animal studies on psychopharmacological treatments for prenatal alcohol exposure

Reference	Drug; dosing	Animal model; outcome	Conclusion
Ulug and Riley [18]	MPH Exp 1: 0, 0.5, 1 mg/kg Exp 2: 0, 2, 8.6 mg/kg	Long evans rats Locomotor activity measured by open field test	Low dose MPH had no effect on overactivity. High dose MPH worsened overactivity
Means et al. [19]	MPH Exp 1: 0, 1, 2, 4 mg/kg (young offspring) Exp 2: 0,2,4,8 (adult offspring)	Long Evans rats Locomotor activity measured by open field test	MPH treatment increased the frequency of ambulation in both young and adult rats with PAE
Hannigan and Pilati [20]	D-amphetamine: 0, 2, 10 mg/kg	Long Evans rats Locomotor activity measured by open field test	Chronic amphetamine administration produced exaggerated increases in locomotor activity in male and female rats with PAE
Randall and Hannigan [21]	MPH: 0, 4, 8 mg/kg	Long Evans rats Locomotor activity measured by automated home cage-type activity monitor	MPH resulted in dose-dependent increases in locomotor activity. However, no PAE effect on locomotion in offspring adults
Shen and Choong [23]	MPH: 1 mg/kg	Sprague-Dawley rats Electrical activity of VTA dopamine neurons measured by electrophysiological recordings	MPH treatment produced a decrease in excessive excitability of VTA dopamine neurons in alcohol exposed rats versus increased excitability in control rats
Juarez and Alvarez [22]	MPH: 3 mg/kg Atomoxetine: 2 mg/kg	Wistar rats Locomotor activity measured by open field locomotion test. Impulsivity measured by a delay-discounting task	MPH treatment had no effect on motor activity and mildly improved impulsivity. Atomoxetine improved both motor activity and impulsivity
Aglawe et al. [24]	Agmatine: 20–80 mg/kg	Sprague Dawley rats Anxiety-like behaviors measured with EPM; depression-like behaviors measured by FST; learning and memory measured by MWM; locomotor activity measured by open field test	Agmatine improved anxiety- and depression-like behaviors, improved learning and memory and had no effect on locomotion in rats with PAE

MPH methylphenidate, *PAE* prenatal alcohol exposure, *VTA* ventral tegmental area, *EPM* elevated plus maze, *FST* forced swim test, *MWM* Morris's water maze

(22% response rate versus 79% response rate) [27], but no specific information was provided on how clinical responsiveness was measured and no statistical information was provided in this study. Coe and colleagues [30] also conducted an archival record review and analyzed 22 children that had a total of 66 medication trials, which were grouped into six medication categories: mood stabilizers/anticonvulsants (carbamazepine, valproic acid and lithium), neuroleptics (risperidone, loxitane, thioridazine), stimulants (methylphenidate, dextroamphetamine, pemoline, Adderall), alpha-2 agonists (guanfacine and clonidine), SSRI's (fluoxetine, sertraline, fluvoxamine, and buspirone and bupropion were grouped in this category as well), and tricyclics (TCA; imipramine). Clinical responsiveness for the symptoms that each medication trial targeted was derived from physician-reports and/or family-report. In addition to psychiatric target symptoms, seizures were included as a target symptom for the mood stabilizers. They reported high response rates for mood stabilizers (eight trials with an 88% response rate), with hyperactivity (n = 1) and sedation (n = 1) noted as side effects. Neuroleptics (with target symptom aggression in 83% of cases) showed an 83% response rate in six trials, with excessive sedation noted as a reason for discontinuation in one case. Stimulant responsiveness was seen in 63% of the 27 stimulant trials, and side effects were reported in eight trials and included poor appetite, insomnia, hyperactivity, and mood lability. Additionally, an 82% response rate was reported for eleven trials of SSRI's (given for moodiness, depression or aggression), although three of these trials were discontinued due to appearance of manic symptoms. A 44% response rate was reported in the nine alpha-2 agonist trials, which were used to target symptoms of impulsivity and hyperactivity (44%) or aggression (33%), and these medications were discontinued in two cases due to sedation. Finally, four trials of tricyclic antidepressants (for target symptom of inattentiveness) showed no positive effects.

Doig et al. also conducted a medical record review of ADHD medications in children with FASD and included children that were referred to their clinic for further evaluation of ADHD symptom, consideration of start of a medication trial, or evaluation of a current medication trial [28]. 27 children were included in their analysis and the Texas Children's Medication Algorithm Project was used to guide start and change of medications. The change between baseline and best ADHD rating scale (SNAP-IV) scores was used as the primary outcome and the researchers reported improvements in all three domains. Specifically, the hyperactivity/impulsivity domain showed a mean score change of 0.5 ($t = 5.2$, $p < 0.01$, effect size Cohen's $d = 1.3$), the inattention domain showed a mean score change of 0.8 ($t = 6.3$, $p < 0.01$, Cohen's $d = 1.8$), and the oppositionality/defiance domain showed a mean score change of 0.5 ($t = 5.1$, $p < 0.01$, Cohen's $d = 0.7$). The authors note that hyperactivity/impulsivity and oppositionality/defiance symptoms were more responsive to stimulant medications than inattention symptoms as more children reached normalized scores on hyperactivity/impulsivity (66.7%) and oppositionality/defiance domains (70.4%) than on the inattention domain (33.3%; $\chi 2 = 6.0$, $p < 0.05$, $\chi 2 = 7.4$, $p < 0.01$, respectively). They further note that many children were on methylphenidate when they achieved their best scores. Limitations of this study include the small sample size, lack of a comparison group and inclusion of mostly children with mild FASD.

Frankel and colleagues conducted an observational study of pharmacological treatments in the setting of an RCT on a social skill intervention [25]. More specifically, they studied the effect of social skills training on children with FASD and hypothesized that currently prescribed psychotropic medications act as a moderator of the outcome [25]. 77 children were included; 28 children were taking stimulants and 13 children were taking neuroleptics. The primary outcome was the parent and teacher 55-item Social Skills Rating System, which includes items related to assertion, self-control, and problem behaviors. They showed that children prescribed neuroleptics demonstrated greater improvement on parent-reported Self-control (mean difference + 4.5, $F(1,73) = 10.52$, $p < 0.005$), parent-reported Assertion (mean difference + 3.8, $F(1,73) = 8.79$, $p < 0.005$), parent-reported Problem Behaviors (mean difference + 5.2, $F(1,73) = 4.36$, $p < 0.05$), teacher-reported Self-control (mean difference + 2.9, $F(1,73) = 6.66$, $p < 0.05$), teacher-reported Assertion (mean difference + 1.5, $F(1,73) = 3.81$, $p = 0.05$) when compared to those who did not receive neuroleptics. In contrast, children who were prescribed stimulants showed no improvement on parent-reported scores nor on teacher-reported Assertion and Self-Control and showed poorer outcomes on teacher-reported Problem Behavior (mean difference −0.6, $F(1,73) = 5.72$, $p < 0.05$) [25]. The results from these archival record reviews should be interpreted with care given the nonexperimental nature of these reports, i.e. lack of comparison groups, lack of randomization and lack of blinding.

To our knowledge, no clinical studies exist on the effectiveness of sleep medications, despite frequent use of sleep medications in this population. Similarly, data on the effectiveness of antidepressants to address anxiety in this population is lacking. Table 2 summarizes the published literature on pharmacological treatments for children with FASD.

Discussion

Initial pre-clinical studies suggested no effect or even worsening of hyperactivity with stimulant treatment in models of FASD [18–22] and mild improvements on impulsivity [22]. There are several factors limiting the interpretation of data

Table 2 Clinical studies on psychopharmacological treatments in children with prenatal alcohol exposure

Reference	Sample size; drug	Study type; outcome	Conclusion
Snyder et al. [29]	N = 11 MPH/Dexedrine/ Pemoline vs PBO	Blinded crossover RCT; Computerized attention task, underling test for impulsivity, parent rating scale for hyperactivity	Stimulants improved hyperactivity but not attention or impulsivity
Oesterheld et al. [26]	N = 4 MPH vs PBO	Blinded crossover RCT; parent and teacher ratings scales for inattention, impulsivity hyperactivity	MPH improved hyperactivity and impulsivity but not attention
O'Malley et al. [27]	N = 30 MPH, amphetamines	Archival clinical record review; subjective parent and treating MD report of ADHD symptomatology	More children responded to amphetamine (79%) than to MPH (22%)
Coe et al. [30]	N = 22 PAE Stimulants, antipsychotics, mood stabilizers, SSRIs	Archival clinical record review; subjective clinical response to broad range of symptoms	Positive response to stimulants: 63%. Positive response to mood stabilizers: 88%. Positive response to antipsychotics: 83%. Positive response to SSRI: 82%
Doig et al. [28]	N = 27 MPH, amphetamines	Archival clinical record review; SNAP-IV scales	MPH and amphetamines improved hyperactivity/impulsivity and oppositionality more than inattention
Frankel et al. [25]	N = 77 No meds vs. Neuroleptics vs. Stimulants	Medications were evaluated as moderator for social skills intervention effect	Kids on stimulants showed no/poorer response to social skills intervention; good response to social skills intervention on neuroleptics
Wozniak et al. [31]	N = 60 Choline supplement vs. PBO	Double-blinded RCT; Mullen Scales of Early Learning and the elicited imitation memory paradigm	Choline may improve memory in preschoolers but not global cognitive ability
Nguyen et al. [32]	N = 55 Choline vs. PBO	Double-blinded RCT; Neuropsychological measurements of memory, executive function, attention, hyperactivity	Choline is not effective in school-aged children

MPH methylphenidate, *PBO* placebo, *RCT* randomized controlled trial

from these preclinical studies. First, neurobehavioral symptoms associated with prenatal alcohol exposure are difficult to model in rodents and even when successful in finding a rodent proxy for a human symptom, given the profound differences in executive functioning circuitries between rodents and humans, underlying mechanisms of modeled symptoms are likely to differ between rodents and humans. Although most of these studies were able to model hyperactivity associated with prenatal alcohol exposure, Randall and Hannigan did not find such hyperactivity associated with prenatal alcohol exposure [21], nor did Aglawe et al. [24]. Furthermore, a behavioral paradigm to test for impulsivity was only included in one study [22]. The effects of psychotropic medications on other neurobehavioral symptomatology of FASD/ND-PAE, including impaired sustained attention, temper tantrums and mood symptoms may be particularly difficult to model in animals. Additional limitations of the reported preclinical data include the lack of rigor in reporting that has become the standard for clinical studies, including but not limited to the lack of reporting of blinding, lack of reporting of a power analysis, and the lack of accounting for repeated testing when determining alpha level for accepting statistical significance.

Clinical data remains limited and shows mixed results. For providers, it may be difficult to decide on starting or changing medications in this complicated group of patients with severe comorbidity and frequent look-alike symptoms.

Symptoms of impairments in executive functioning can be conceptualized in different domains, including sustained attention, inhibitory control, and emotional dysregulation. Given the robust effectiveness of stimulants in the general population, a logical first line of pharmacological treatment for difficulties with sustained attention and inhibitory control are stimulants, and based on previous data, an improvement in these domains can be expected in some children. However, some children will remain in the clinical range despite improvements, and other children will not improve or may even worsen on stimulants. No data exists regarding the treatment of emotional dysregulation in FASD. Emotional dysregulation, although often closely correlated with inattention and impaired inhibitory control, may be better addressed with an alpha-2 agonist as a first line of pharmacological treatment, given favorable reports for this indication in non-FASD pediatric populations [33]. However, the data available from FASD studies is very limited with only one archival study [30] analyzing responsiveness to alpha-2 agonists, with a reported 44% response rate reported in nine trials, in a mix of target symptoms. Therefore, no overall conclusions can be drawn regarding the effectiveness of alpha-2 agonists. Antipsychotics like risperidone could be considered for emotional outbursts, but given the side effect profile of antipsychotics, these medications should in our opinion be reserved for children whose tantrums lead to unsafe situations (harming self or others) and in which other treatment options have failed.

It is also important to pay close attention to the other comorbidities that often exist in this population. Sleep problems occur frequently, with multi-factorial causes that likely include sleep-arousal dysregulation [34]. Although no evidence exists regarding efficacious sleep treatments in this population, after general non-pharmacological treatment options have failed, it may be helpful to consider an alpha-2 agonist given the frequent comorbid emotional dysregulation, hyperactivity and impulsivity which may also benefit from this class of medication, thereby minimizing polypharmacy.

Symptoms of impaired mood and anxiety are also common in this population. If first-line treatment with psychotherapy is not effective or feasible, traditional mood and anxiety medications, starting with a trial of SSRI, may be considered, although data regarding efficacy or side effect profile is very limited. In fact, the only study we found that included analysis of SSRI's was the archival study by Coe et al.[30], and given the very limited sample size of 11 trials of SSRI medications (some of which with target symptom of aggression rather than depression), overall conclusions cannot be drawn. For symptoms in the psychosis domain, although rare, antipsychotics may be the logical first-line treatment, but for this domain as well, data is lacking in the FASD population.

Guidelines for practitioners are sparse [35], and there is no practice consensus among providers. Clearly, there is a need for larger efficacy and effectiveness studies in children who are alcohol and drug exposed to better inform care. In addition to psychiatric symptoms, children with in utero exposures often have learning disabilities, intellectual functioning in the low-average range, and impaired adaptive functioning including impaired social functioning. It is therefore imperative that these children receive adequate educational support in the form of an individualized education plan, specific accommodations, and therapy as indicated, which will often consist of speech, occupational, social skills, behavioral, and family therapy.

Little is known about pharmacological interventions in children prenatally exposed to drugs other than alcohol. Commonly, children with prenatal alcohol exposure have also been prenatally exposed to other drugs and, reversely, reports of prenatal alcohol exposure are common in children with other prenatal drug exposures, even when a formal FASD diagnosis cannot be made.

In conclusion, although traditional treatments for ADHD-like symptoms in children prenatally exposed to alcohol and drugs can be effective, the effectiveness is likely not as robust as in the general population. Clearly, clinical trials are needed to assess the efficacy and safety of existing and novel psychotropic medications to target the myriad of symptoms

seen in children with in utero alcohol/drug exposures. Given frequent comorbid symptoms in this population, it is imperative to take a comprehensive approach to treatment when evaluating and treating the different symptom domains. Medications will rarely result in complete symptom resolution in this population, and it is imperative that timely referrals be made for adjunctive behavioral, cognitive, and educational services.

Summary

Our literature search for reports on psychopharmacological treatments for children with FASD/ND-PAE yielded seven preclinical and eight clinical studies, the latter ranging in size from n = 4 to 77. 6 clinical studies reported on the effects of stimulants; 2 of these in addition reported on the effects of neuroleptics, mood stabilizers; 1 in addition reported on alpha-2 agonists and antidepressants. The results ranged from negative or no effects to partial or positive effects of stimulants. Other observations included increased responsiveness to amphetamines compared to methylphenidate, and good response to mood stabilizers and neuroleptics. Overall, stimulants appear effective in at least a subset of children with FASD/ND-PAE and are safe. Response rates are likely not as high as in idiopathic ADHD. Furthermore, choline supplementation is not effective for neurobehavioral symptomatology in children with FASD. No clinical studies were found on the effectiveness of sleep medications, despite frequent sleep problems in this population. Similarly, data on the effectiveness of SSRIs to address depression and anxiety in this population is very limited. Given that epidemiological studies have indicated that this condition occurs in 1–5% of the population, there is clearly a need for clinical trials studying the efficacy of psychotropic medications in children with FASD/ND-PAE.

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