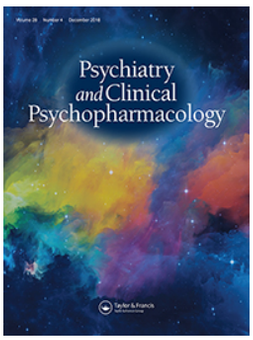

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The utility of psychotropic drugs on patients with Fetal Alcohol Spectrum Disorder (FASD): a systematic review

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ABSTRACT

BACKGROUND: Treatment of the complications arising from Prenatal Alcohol Exposure (PAE) has largely been focused on psychosocial and environmental approaches. Research on the use of medications, especially psychotropic medications, has lagged behind.

OBJECTIVES: This systematic review sought to investigate psychotropic medication related findings and outcomes in those diagnosed with Fetal Alcohol Spectrum Disorder (FASD).

METHODS: Comprehensive searches were conducted in seven major databases (Medline/PubMed, Scopus, Web of Knowledge, Embase, PsycINFO, Cochrane Library, and PsycARTICLES) up to February 2017. Key search terms with synonyms were mapped on these databases. There were no timeline restrictions and no grey literature searches. Two reviewers independently assessed 25 studies that met the inclusion criteria. Most studies were reviews of treatment and retrospective case series.

RESULTS: Two crossover randomized trials were reported, and the findings were not amenable to meta-analysis. Several conditions (depression, agitation, seizures, and outburst) combined with the most frequent presentation, ADHD, to represent the rationale for prescribing psychotropic medications. Second-generation antipsychotics were found to improve social skills, but the paucity of data limited the extent of clinical guidance necessary for the field.

CONCLUSIONS: The systematic review showed that there are some clinical evidence displaying the validity of psychopharmacological interventions in people with FASD, which varies across the spectrum of disease severity, age, and gender. There is a need for more clinical evidence-based studies in addition to clinical expert opinions to substantiate an optimal ground for individualized management of FASD.

The study protocol for this review was registered in PROSPERO with registration number CRD42016045703.

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KEYWORDS
Psychotropic medications; Fetal Alcohol Spectrum Disorder; Prenatal Alcohol Exposure; Fetal Alcohol Effects; partial Fetal Alcohol Syndrome; Alcohol-related Neurodevelopmental Disorder

List of abbreviations

5-HT	5-Hydroxytryptamine
ADD	Attention Deficit Disorder
ADHD	*Attention Deficit Hyperactivity Disorder*
ARND	Alcohol-Related Neurodevelopmental Disorder
ASD	Autism Spectrum Disorder
BZD	Benzodiazepine
CBA	Controlled before and after study
CBZ	Carbamazepine
CD	Conduct Disorder
CFT	Children's Friendship Training
CPRS-48	Conner's Parent Rating Scale-*48* items
EEG	Electroencephalogram
FAE	Fetal Alcohol Effects
FAS	Fetal Alcohol Syndrome
FASD	*Fetal Alcohol Spectrum Disorder*
FTA	Full-Text Article
FSIQ	Full Scale Intelligence Quotient
IQ	Intelligence Quotient
LMT	Lamotrigine (Lamictal)
MTA-SNAP-IV	Swanson, Nolan and Pelham Teacher and Parent Rating Scale
NEPSY	Developmental NEuroPSYchological Assessment
NRCT	Non-randomized Controlled Trial
NRI	Norepinephrine Reuptake Inhibitor
ODD	Oppositional Defiant Disorder
OxCBZ	Oxcarbamazepine
PAE	Prenatal Alcohol Exposure
PDE	Psychotropic Drug Exposure
PHT	Phenytoin
PB	Phenobarbital
PFAS	Partial Fetal Alcohol Syndrome
PIQ	Performance Intelligence Quotient
PSG	Polysomnogram
RCT	Randomized Controlled Trial
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SPSS	Statistical Package for Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tri-Cyclic Antidepressant
TPM	Topiramate
VIQ	Verbal Intelligence Quotient
VPA	Valproate

Introduction

Prenatal Alcohol Exposure (PAE) in utero causes impaired growth, central nervous system dysfunction, and may cause birth defects [1]. The spectrum of clinical presentations arising from the prenatal exposure to

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alcohol, Fetal Alcohol Syndrome (FAS), and Alcohol-Related Neurodevelopmental Disorder (ARND) is collectively diagnosed according to the second edition of the Canadian diagnostic guidelines as Fetal Alcohol Spectrum Disorders (FASD) [2]. FASD is the most common form of prenatally acquired brain injury and affects about 4% of the Canadian population [3]. FASD is characterized by a wide range of clinical features, including a reduced Intelligence Quotient (IQ) [4, 5], cognitive and learning disabilities, and severe behaviour challenges as well as impaired functioning [6, 7]. Attention problems are prevalent, with approximately 50–90% of children with FASD also clinically diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and/or Attention Deficit Disorder (ADD). Similarly, a large proportion of children with FASD are diagnosed with Oppositional Defiant/Conduct Disorder (ODD/CD), being the next most common disorder after ADHD [2, 8, 9]. Other areas of clinical focus often include difficulties in moral development, social judgment, and learning from previous experience [2, 10].

The utility of psychotropic drugs in FASD has been debated, especially among physicians and families supporting patients with FASD [3]. Adults living with FASD also have varying attitudes towards being prescribed these medications, which at times can influence compliance to the prescriptions. The disparate perspectives on psychotropic medication occur because of the limited progress in the development of evidence-based pharmacological interventions for FASD [2, 11]. This has been blamed on a lack of consensus among researchers and clinicians including a very common failure of clinicians to apply any evidence-based research when informing their practice in this area [2, 9, 11, 12]. Research evidence is gradually being accumulated to guide interventions. There has been a reliance on experiential knowledge from other fields such as interventions in intellectual disability disorders rather than research evidence specific to the field of FASD. Furthermore, the findings generated from human and animal studies on FASD have clear limitations, partly because of differences in methodologies [11]. Consequently, successes in animal model trials have not been readily translated into the development of interventions for humans [11]. The place of FASD as a global health problem meant less funding that the World Health Organization had been slow in recognizing the extent of sociopolitical and economic implications of FASD on a global scale [11]. Therefore, fewer resources have been allocated to the study of FASD compared with those devoted to the study of other neurodevelopmental disorders.

There is a slow emergence of evidence-based effective interventions among those with PAE/FASD [1, 13]. More recently, multi-component intervention provided to caregivers and families of children with FASD produced greater benefits on parenting and reducing children's disruptive behaviour [14]. Benefits include reduced long-term complications in those diagnosed. Caregiving skills were improved, and stress reduced when a range of regulatory, somatosensory, relational, and cognitive enrichments were administered in a child plus parents' psychotherapy session [15]. Lagging behind the psychosocial and education interventions, and supported by current evidence, is research on the use of psychotropic medications in those with PAE/FASD.

Individual variations in presentation are recognized in those with FASD as determined by unknown factors and mechanisms associated with the development of the deficits. Oxidative stress from decreased endogenous antioxidant levels, mitochondrial damage, lipid peroxidation, disrupted neuronal cell–cell adhesion, placental vasoconstriction, and inhibition of cofactors required for fetal growth and development are suspected to play a role in the etiology of FASD [16]. Other factors include differences in prenatal and postnatal exposures to other teratogens and substances of abuse as well alcohol having epigenetic effects. As such, simplistic approaches to medication treatment in FASD are lacking. Existing literature on psychopharmacological intervention and clinical responses in FASD and other comorbidities are based on case series and a handful of clinical trials [3, 6]. The field lacks a logical step-by-step process to guide the pharmacological management of FASD, based on clinical evidence and/or effectiveness of these pharmacological therapies. Although few clinical trials have been carried out to report the effectiveness of some psychopharmacological medications in FASD there is still a need to explore the levels of evidences on a larger sample scale, taking into consideration the pharmacodynamics, pharmacokinetics, dosages, and adverse effects of the pharmacological interventions applied in each study. We sought to systematically appraise peer-reviewed medical literature to identify and assess the evidence, utility, and efficacy of pharmacological interventions in the management of children and adults with FASD.

Methods

Registration

This systematic review protocol was registered in PROSPERO international prospective register of systematic reviews, on the 16th of August 2016, with the registration number CRD42016045703. Available from: http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID = CRD42016045703.

Research objective and eligibility criteria

The research team aimed to identify all literature evaluating pharmacological interventions for children and

young adults living with FASD, including any study design (RCTs, cohort, case series, etc.). All searched articles were limited to peer-reviewed journals only, and articles written in English. There were no timeline restrictions in the search strategy. The primary outcome of interest of this review was to identify evidence-based directives for managing FASD in clinical practice as this review combined with expert consensus will inform the development of a research-informed treatment algorithm for FASD in patients.

Data sources and search strategy

A data search was initiated on May 22, 2016, in seven electronic databases: MEDLINE/PubMed (biomedical sciences, 1946 to present), Sciverse Scopus (multidisciplinary; 1823 to present), ISI Web of Knowledge (multidisciplinary current awareness; 1998 to present), Embase (multidisciplinary; 1947 to present), PsycINFO (behavioural and social sciences; 1967 to present), Cochrane Library (Cochrane Database of Systematic Reviews; 2007 to present) and PsycARTICLES (behavioural and social sciences; 1967 to present). These databases were selected to cover a broad range of disciplines and provide an all-inclusive search. No limits were placed on date, and no grey literature was searched. A search query pre-identified by the authors was applied in each of the databases to identify articles for the review. The Medical Subject Heading (MeSH) included various expressions of FASD and classes of psychotropic medications such as anxiolytics, typical, and atypical antipsychotics. These terms were adapted for individual databases (see Table 1).

A reference list of 10 randomly selected relevant articles (Doig et al. [17]; Frankel et al. [4]; Hagerman [6]; Ipsiroglu et al. [3]; Kodituwakku [11]; Koren [2]; O'Malley and Nanson [9]; Ozsarfati and Koren [18]; Rowles and Findling [19]; Snyder et al. [20]) was manually hand-searched to identify any further article that may be relevant. A snowball technique was also adopted, where citations within articles were searched if they appeared relevant to the systematic review (Ji and Findling [21]; Huizink [7]). An update search of the seven bibliographic databases was conducted on February 04, 2017, to further identify any additional article published after the initial search.

Table 1. Keyword search syntax and search strategy for OVID MEDLINE.

1.	fetal alcohol spectrum disorder/
2.	f?etal alcohol spectrum disorder.ti.ab
3.	fetal alcohol syndrome/
4.	f?etal alcohol syndrome.ti.ab
5.	partial fetal alcohol syndrome/
6.	partial f?etal alcohol syndrome.ti.ab
7.	fetal alcohol effects/
8.	f?etal alcohol effects.ti.ab
9.	f?etal alcohol$.ti.ab
10.	(prenatal$ or prenatal$ adj3 (alcohol$ or exposure$)).ti.ab
11.	(alcohol$ adj3 neurodevelopment$ adj3 (disorder$ or defect$)).ti.ab
12.	or/1-11
13.	pharmacological therapy/
14.	pharmacotherapy.ti.ab
15.	(psychoactive$ or psychotropic$ or psychiatric$ adj3 (medication$ or drug$ or medicine$)).ti.ab
16.	(neuroleptic$ adj3 (medication$ or drug$ or medicine$)).ti.ab
17.	(antidepressant$ adj3 (medication$ or drug$ or medicine$)).ti.ab
18.	(antipsychotic$ adj3 (medication$ or drug$ or medicine$)).ti.ab
19.	(anziolytic$ adj3 (medication$ or drug$ or medicine$)).ti.ab
20.	(sedative$ adj3 (medication$ or drug$ or medicine$)).ti.ab
21.	(psychostimulant$ or stimulant$ adj3 (medication$ or drug$ or medicine$)).ti.ab
22.	or/13-21
23.	12 and 22

Same search terms were adapted for individual databases.

Citation management

All citations were collated and imported into Endnote x7 citation manager [22]. Duplicate citations were removed manually after assembling citations using Endnote, and further duplicates removed when found later in the process.

Study selection

The selections of studies to include in the review involved a two-level screening process. The first level consisted of screening only the title and abstracts to exclude citations that did not meet the eligibility criteria. A reviewer agreement scoring system was developed and reviewed by the authors. The scoring system rated articles with scores 0, 1, or 2 depending on the relevance of the article to the research question, i.e. no evidence of diagnosis and treatment, scored as 0, evidence of FASD diagnosis OR evidence of treatment, scored as 1, and evidence of FASD diagnosis AND evidence of pharmacological treatment scored as 2. The second level of screening involved pulling out Full-Text Articles (FTAs) of articles identified and scored as "1 or 2" in the first level for screening to identify relevance to the research question. For articles which could not be obtained through the institutional library database and/or holdings available to the authors were procured through contacts to source authors for assistance in procuring the articles.

Two review authors (UO and JE) independently screened title and abstracts of articles identified and reviewed the FTAs that fulfilled the eligibility criteria. These reviewers were not masked to author or journal names. Titles for which abstracts were unavailable were included for full-text article review. Conflicts between reviewers were resolved by a third reviewer (MM). The research team also met throughout this screening process to resolve other conflicts and discuss future directions of the review. The overall kappa between the two reviewers was 0.79. See Figure 1 for study selection process.

Data extraction

Three reviewers (UO, TA, and JE) independently extracted data from identified FTAs. Data were

compiled into a tabular spread sheet using Microsoft Excel 2015 [23] for validation and coding. The following title fields were entered for the selected review articles:

- Study characteristics: author(s), year of publication, title of publication, journal of publication, study type, study design
- Population characteristics: patients' age, gender, number of patients, country (setting)
- Intervention characteristics: psychotropic medications used, dosages, length of treatment, rationale for use, pharmacodynamics and pharmacokinetics identified, route of medication administration reported
- Outcome measures: evidence of improvement, alternative interventions, side effects and reason for discontinuation.

Data analysis

The data was exported into IBM Statistical Package for Social Sciences (SPSS), Statistics for Macintosh, Version 22.0 [24]. Descriptive statistics were calculated to summarize the data. Due to the paucity of relevant articles and small number of studies (especially RCTs), a meta-analysis could not be undertaken.

Critical appraisal and assessment of the methodological quality of included studies

We categorized the study designs in identified articles as follows: randomized control trials, qualitative, quantitative, or systematic review. Within these categories, the methodological quality of each included article was assessed independently by two reviewers (UO and JE), using a standardized critical appraisal form [25]. Due to the wide variety in study designs and methodologies, a qualitative assessment of the study quality of included articles was adopted. Differences in assessments were resolved by a third party (MM).

Risk of bias assessment for RCTs

For Randomized Controlled Trials (RCTs), Non-randomized Controlled Trials (NRCTs), and Controlled before and after studies (CBAs), we used the criteria recommended by the Cochrane EPOC group to assess risk of bias in studies with control groups [26, 27].

Results

Study selection

A total of 478 peer-reviewed articles were identified from the overall search. 463 were retrieved from the 7 bibliographical databases selected, and 15 from hand-searching of references and the snowball technique. Following deduplication and title and/or abstract screening, 105 articles were found to meet the eligibility criteria. All 105 FTAs were thereafter retrieved and reviewed for inclusion based on their respective reviewer agreement scores. Of the 105 FTAs read, 80 articles failed to meet these eligibility criteria, leaving a total of 25 peer-reviewed articles for inclusion into the final review (see Figure 1).

A total of 329 subjects with FASD were involved in the reported research on the use of psychotropic medications in treatment settings. The most common study design used in reviewed articles was a literature review analysis (13/25; 52%). They included narrative reviews, descriptive review summary, critical review analysis, or other types of literature review. Most of the studies applied a mixed qualitative and quantitative approach (11/25; 44%) with most of their data being secondary data (14/25; 56%).

The general characteristics of all included articles are summarized in Table 2.

Discussion

Apart from two controlled crossover studies of a small number of subjects, most medication studies were case series. About 329 subjects with FASD have been involved in reported research on the use of psychotropic medications in treatment settings, from our review findings. This systematic review found a significant deficit in evidence for the use of psychotropic medications in FASD compared to other neurodevelopmental disorders and disabilities [21]. Psychotropic drug use in patients with FASD can be often challenging in terms of the degree of effectiveness versus other concomitant realities, e.g. adverse effects. These difficulties are also, to a large extent, due to the complex interplay of the neurobiology of these patients and the psychosocial conditions they are faced with. The paucity of sufficient evidence on best psychotropic medication choice in the treatment of those with FASD is unsatisfactory, and with no guidance paints a vulnerable picture.

Understanding the pathophysiology of FASD may throw some light on the rationale for medication choices in managing FASD. The exact mechanisms leading to neuronal damage by alcohol during fetal life have not been fully elucidated, and many proposed mechanisms have been suggested based on experimental models [2]. It is well understood that alcohol commonly impairs the development of the dopaminergic, noradrenergic, serotonergic, cholinergic, glutamatergic, and histaminergic systems [6]. The dopamine D1 receptors of the meso-cortical system is the most impaired of the dopaminergic receptors [9]. Therefore, agents that facilitate dopaminergic transmission either by direct release of dopamine, as in the case with amphetamines, or prevent the reuptake of dopamine, offer a beneficial model for intervention [9]. This was the premise for a few clinical

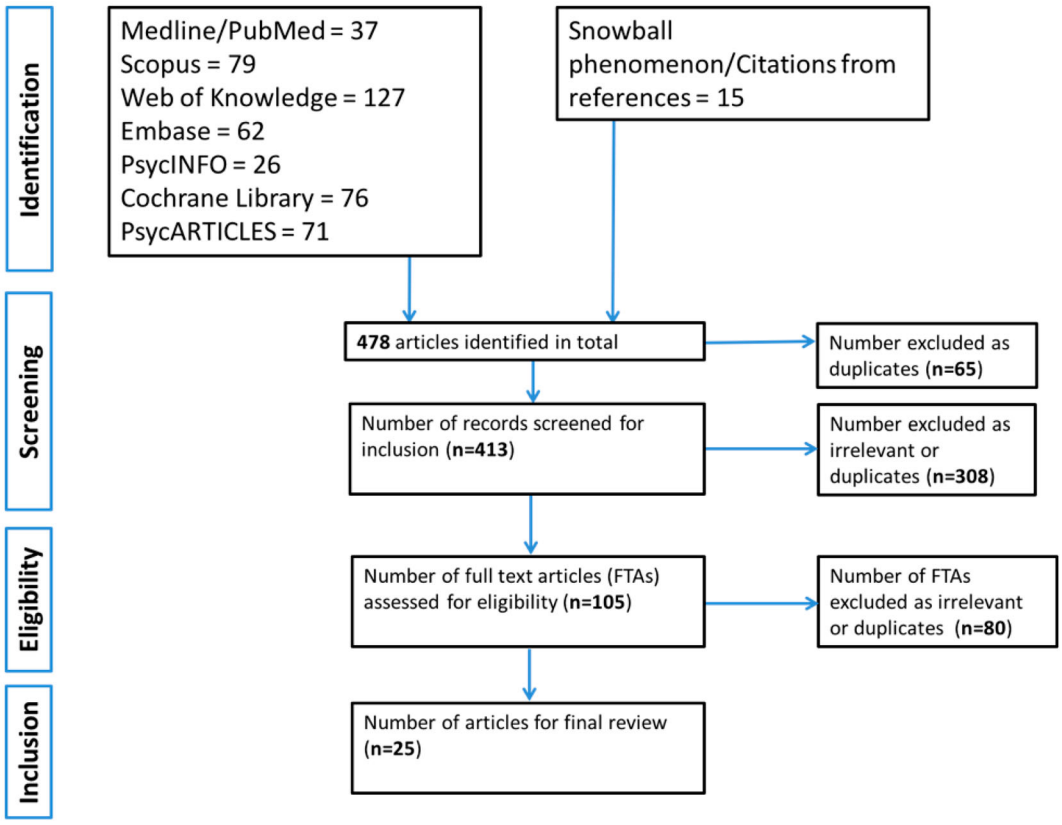

Figure 1. PRISMA [39] flowchart for study selection process.

studies using psychostimulant drugs like Dextroamphetamine and Methylphenidate for FASD, especially in cases of FASD and symptoms of hyperactivity and inattention. O'Malley et al. [8], Doig et al. [17], Infante et al. [31], Snyder et al. [20], and Oesterheld et al. [28] reported clinical studies to delineate the best stimulant therapy for FASD with symptoms of hyperactivity and inattention. The outcomes of these studies gave mixed yet uncertain verdicts for the use of these psychostimulants. In these studies, inattention was found to respond better to Dextroamphetamine than Methylphenidate, but a high adverse event profile induced discontinuation [17, 28]. Dextroamphetamine was deduced as preferred given its action on the D1 receptors. Conversely, in a study by Frankel et al. [4], stimulants were found to be less efficacious compared to second-generation neuroleptics, specifically in the domain of social skills. The use of stimulants in the latter study showed comparatively poor response both as monotherapy and in combination with neuroleptics [4].

The use of antipsychotics in FASD has also been debated in several reviews [2–6, 18, 21, 35]. Second-generation antipsychotics, which for the most part are serotonin-dopamine receptor antagonists, also possess anti-adrenergic and anti-histaminergic properties. These agents were used in the treatment of complications of seizure disorders associated with FASD [34], as adjunct therapy for Conduct Disorder [36], for disruptive behaviour in children with low IQ [5], and for secondary disabilities associated with FASD [6, 18]. The most common antipsychotic drug used in children with FASD is Risperidone, which in some research has demonstrated strong benefits in the treatment of short-term aggressiveness [18]. There are too few published controlled studies using Risperidone in FASD patients to draw any clinical conclusions. Frankel et al. [4] tried to compare outcomes involving social skills training among four study groups, which were stimulants only, neuroleptics only, stimulants and neuroleptic combinations, and no psychoactive medication group. Greater improvement on all outcome measures was found with Risperidone compared to those not prescribed neuroleptics [4]. Other benefits of Risperidone are the tendency to increase appetite which may be a favourable side effect for underweight children with FASD [4, 18, 36, 38]. However, there is a concern for long-term use because of the metabolic risk associated with most second-generation antipsychotics as well as having the potential for extrapyramidal symptoms and altering the dopaminergic system.

Antidepressants such as SSRI, SNRIs, NRIs, and TCAs are another class of medication prescribed for those diagnosed with FASD in the context of depression. From our review, SSRIs stood out as the most commonly prescribed of the class of antidepressants. It was reported as effective in treating ADHD symptoms when those coexist with behaviour problems such as outbursts, aggression, and compulsive behaviours in children with FASD [36]. There are limited published controlled studies of noradrenergic reuptake inhibitors

Table 2. Characteristics of included studies.

Author(s)	Study characteristics	Methods and methodology	Results and findings
Randomized control trials			
Oesterheld et al. [28]	Crossover RCT quantitative study. $n = 4$; 5–12 years FAS or pFAS and ADHD	– Test group given 0.6 mg/kg Methylphenidate – Control group given lactose or vitamin C as placebo – Placebo given three times a day for 5 days with a 2-day washout period	– Significant hyperactivity–impulsivity score on CPRS-48 with improvement in Methylphenidate group ($F = 4.34$, df = 2, $p < 0.05$) – Significant hyperactivity–impulsivity score on CTRS-39 with improvement in Methylphenidate group ($F = 6.42$, df = 2, $p < 0.02$) – No significant different on daydreaming-attention score on CTRS-39 ($F = 1.429$, df = 2, $p = 0.289$) Side effects reported: Decreased appetite (3 children), mild stomach aches (2 children), and headaches (2 children)
Snyder et al. [20]	RCT mixed study. $n = 12$, subjects aged 6–16 years with FASD and ADHD	– Subjects grouped into drug groups – Methylphenidate (8 children), pemoline (2 children) dexedrine (1 child), and a placebo (1 child) – Intervention given at regular doses for 3 days with a 1-day washout period	– No significant difference between groups for attention – Stimulant medication shown to improve hyperactivity scores compared with placebo
Systematic reviews			
Peadon et al. [1]	Explores clinical evidence for management of FASD in children	– Six electronic library databases searched evaluating early intervention programmes in participants aged below 18 years	– Limited evidence for pharmacological interventions for managing FASD – Cited evidences from Oesterheld et al. [28] and Snyder et al. [20]
Peadon et al. [29]	Evaluates the benefits and harms of pharmacological interventions for FASD in children	Keyword search for FASD or PAE across eight bibliographic databases	Results underway, yet to be published
Longitudinal studies			
Dalen et al. [30]	$N = 130$ (29 with FAS, 35 with FAE, and 66 with PDE	– Cognitive functioning tested using the Wechsler and NEPSY tests – No medications were used in this study	– VIQ results rated as 78, PIQ results rated 77, and FSIQ results rated as 75 in the FAS group – Values in FAS group showed significant difference compared with FAE and PDE groups
Frankel et al. [4]	$N = 77$ between ages 71 and 139 months and diagnosed with FASD followed longitudinally	– Interventions used includes (a) Stimulants, (b) Neuroleptics, (c) Antidepressants, and (d) parent-assisted Children's Friendship Training (CFT)	– CFT reports showed that children recorded greater improvement with neuroleptics on all outcomes than with controls – Children prescribed stimulant medications showed no improvement with stimulant medications
Infante et al. [31]	Children aged 7–15 and diagnosed with FASD and controls group with ADHD	– Stimulant medication used – Pre- and post-test carried with and without stimulant medications	– Control subjects with ADHD experienced greater improvement with stimulant medication than FASD subjects – FASD children subjects performed worse on several measures when tested on stimulant medication than when tested without a stimulant
Rangmar et al. [32]	30-year longitudinal study, $N = 79$ adults with FAS, mean age 32	– Assessed education, social adjustment, and mental health outcomes – Analysed and compared results with 3160 comparison individuals matched for age, gender, and place of birth	– FAS group had higher unemployment rates, lower social welfare, and higher mental health problems – Lower educational levels of subjects with FAS implicated as a possible reason for poor mental health and social outcomes
Rawat [33]	Study investigates the metabolic effects of ethanol and chlorpromazine during pregnancy and lactation	– *In vivo* and *in vitro* studies of rats and liver homogenates using chlorpromazine and ethanol – Drugs given to pregnant rats and followed till delivery and lactation	– Single dose of ethanol *in vivo* subjects led to 60% inhibition in the rate of chlorpromazine disappearance from the blood and 50% inhibition in *in vitro*

(*Continued*)

Table 2. Continued.

Author(s)	Study characteristics	Methods and methodology	Results and findings
Case series			
Bell and Hwang [34]	$N = 10$. FASD adolescents and adults exploring management of seizures in subjects	– Tests included: EEG recorded with sleep, overnight PSG – Medications used: LMT, CBZ, VPA, OxCBZ, TPM, PHT, PB, and BZDs	– LMT, CBZ, VPA, OxCBZ, and TPM produced significant response depending on seizure type – BZDs useful for breakthrough seizures and acute management of seizure disorder in FASD – PB and PHT used for status epilepticus in FASD
Calles Jr [35]	Overview of psychopharmacological interventions in children with ASD, Fragile X syndrome, and FASD	– Medications used: stimulants, antidepressants, antipsychotics, and mood stabilizers	– First-line treatment for ADHD in FASD is stimulants preferably Dextroamphetamine than Methylphenidate – Clonidine effective in sleep disorders in FASD, then Melatonin and Ramelteon, respectively – Risperidone eliminates aggression in FASD when others fail
O'Malley et al. [8]	$n = 30$ (22 males, 8 females), aged between 6 and 17 years with FAS or ARND and presented with ADHD	– Subjects received psychostimulant preparations (Methylphenidate and Dextroamphetamine) with comparable dosages	– 5/23 responded to Methylphenidate versus 16/19 treated with Dextroamphetamine – For those receiving both drugs, 8/12 did not respond to Methylphenidate but subsequently responded to Dextroamphetamine, while 1/12 did not respond to Dextroamphetamine but did respond to Methylphenidate – 3/12 did not respond to either drug
Review analyses			
Brown et al. [36]	An overview of psychopharmacological interventions in FASD	– Describes conduct-disordered adolescents with FASD and the neurocognitive deficits that affect emotional and behavioural self-control	– -Reported contrasting findings in the several studies for FASD – Cited results from O'Malley et al. [8], Coe et al. [37], Oesterheld et al. [28], Snyder et al. [20], and Frankel et al. [4]
Coe et al. [37]	$N = 22$, patients with FAS and partial FAS and ARND, aged between 3.5 and 17 years	– Chart reviews of subjects traced over previous 7 years – 66 medication trials on 22 subjects. Medication use: Stimulants, SSRIs, mood stabilizers/anticonvulsants, and antipsychotics	– Methylphenidate, Dextroamphetamine showed marked improvement out of 27 trials – Sertraline recorded marked improvement, out of 11 trials – Valproic acid and CBZ showed marked improvement out of 8 trials – Risperidone showed marked improvement, out of 6 trials
Doig et al. [17]	$N = 27$ children diagnosed with FASD, aged between 5.6 and 14.6 years	– 41 medication trials conducted to determine extent of change in ADHD symptoms as reported by teacher MTA-ANAP-IV scores – Medications used include stimulants and antidepressants	– 19 children obtained teacher MTA-SNAP-IV scores for opposition/defiance, 18 children obtained best scores for hyperactivity/impulsivity and 9 obtained for inattention across medication trials
Gralton [5]	Narrative analysis reporting evidence-based FASD pharmacotherapies	Medications reported in the analysis to be effective include stimulants, noradrenergic reuptake inhibitors, and antipsychotics	– Combining Methylphenidate and Atomoxetine improves response in children with refractory ADHD with significantly improved executive function – Reboxetine helpful for children with ADHD who are non-responders to Methylphenidate. Risperidone effective for disruptive behaviour disorders in children with low IQ
Hagerman [6]	A review analysis of psychopharmacological interventions in developmental disorders	Several studies reviewed to pull out evidence of pharmacological treatment of FASD. Notable ones included: Oesterheld et al. [28], Snyder et al. [20], O'Malley et al. [8], Coe et al. [37]	– Dextroamphetamine may be more effective than Methylphenidate for the treatment of ADHD in patients with FAS – Carbamazepine or valproate is usually helpful in mood disorders associated with FAS

(*Continued*)

Table 2. Continued.

Author(s)	Study characteristics	Methods and methodology	Results and findings
Huizink [7]	A narrative analysis describing evidence-based interventions targeting maternal substance use during pregnancy	Not mentioned	Recommendations to clinicians – Reduce maternal stigmatization to substance abuse and addiction – Reduce emphasis on the direct effect of addictive substance on children as it still holds unjustified scientific evidence? – Target correlated modifiable risk factors
Ipsiroglu et al. [3]	*N* = 17, age range 10–17 years' children with FASD/PAE	– 120 medication trials prescribed. Medications included: BZDs, stimulants, neuroleptics, SSRIs, anticonvulsants, TCAs, Propranolol, Lithium, and Gabapentin	– Establishment of functional sleep/wake behaviour assessment screening before starting medications could prove helpful in reducing polypharmacy or overmedication of children with FASD/PSE
Ji and Findling [21]	Critical review analysis of evidence-based pharmacotherapies for mental health problems in people with intellectual disability	Multiple studies reviewed. Medications reviewed include Antipsychotics, Stimulants, alpha agonists, mood stabilizers, anti-epileptics, antidepressants	– Risperidone effective in reducing behaviours associated with intellectual disability – Methylphenidate effective in ADHD symptoms – Atomoxetine and a-agonists beneficial also ADHD symptoms – Lithium effective in reducing aggression – Melatonin improves sleep in people with intellectual disability
Kodituwakku [11]	A review summary of published interventions for animal and human models with FASD	Medications reviewed: stimulants, neuroleptics, Bupirone, Ipsapirone, Aniracetam, Histamine	– Buspirone or Ipsapirone on mothers reduced the adverse effects of ethanol on the 5-hydroxytryptamine (5-HT) system in the offspring – Aniracetam was shown to reverse deficits in learning and memory in alcohol-exposed rodents
Koren [2]	A review analysis of evidence-based pharmacotherapies for disruptive behaviour in FASD	Medications reviewed: Antipsychotics, stimulants, antidepressants, anticonvulsants	– Risperidone + Methylphenidate + Amphetamine + Dextroamphetamine and Atomoxetine showed favourable responses to FASD and ADHD, ODD and CD comorbidities – Methylphenidate + Risperidone + Lamotrigine + Olanzapine showed favourable responses in female subjects with FASD + ODD and ADHD comorbidities aged 9.5 years
O'Malley and Nanson [9]	Literature review on the history of, and current evidence on, fetal FAS, FASD, and ADHD in children	Use of psychostimulants to decipher the link between FASD and ADHD as well as other comorbidities. Medications reported included Methylphenidate and Dextroamphetamine	– Evidence of clinical and neuropsychological link between FASD and ADHD which may explain the differential response to standard psychostimulants – Cited results in O'Malley et al. [8]
Ozsarfati and Koren [18]	A drug guide for the treatment of disruptive behaviour in children with FASD	Several medications reviewed for the treatment of comorbidities in FASD, including sleep problems ADHD, ODD, and CD	– Methylphenidate, amphetamine, Dextroamphetamine should be first-line drugs for FASD – SNRIs, Atomoxetine plus 2 selective alpha-2 adrenergic agonists should be second-line drugs for FASD
Rowles and Findling [19]	Reviews the efficacy of pharmacological interventions for children suffering from developmental disorders	Several reviewed interventions noted	– Methylphenidate at doses 0.3 and 0.6 mg/kg were associated with a positive response on the Conners Hyperactivity Index in 75% of cases. Also, improved hyperactivity in 49–62% of cases

(NRIs) like Atomoxetine specific to ADHD in FASD. However, Atomoxetine appears to be less effective than Methylphenidate in children with an IQ below 85 [5]. It may still be useful in the inattention domain of FASD due to its noradrenergic stimulation effect.

In paediatric patients living with FASD, a lot of medications used are "off label," as research in children is limited for ethical reasons [5, 11]. Also, the presentation of several neurodevelopmental disorders in children can at times require a careful chronological delineation of the symptoms and their progression in order to understand the diagnosis [11]. For example, sleep difficulties may present with irritability and behavioural issues, or features of inattention and learning challenges. Here, the choice of medication should be based on the most relevant diagnosis causing functional impairment or targeting two co-existing diagnoses [18]. ADHD symptoms which occur more in childhood can be treated with a stimulant such as Adderall or Dexedrine [6].

This systematic review provides an overview of the evidence for specific psychotropic medication use in patients with FASD. A potential limitation may have been the bias towards English language publications as our search was limited by language. Another limitation of our review was in the quality of the studies available for inclusion. For example, non-psychotropic medications such as choline were not included in the search. Also, the study designs may have appeared inadequate for the RCTs which failed to adequately elucidate the methods of randomization, allocation concealment, follow-up, and/or blinding. Furthermore, the sample sizes in these studies were very small rendering these studies underpowered or insufficiently powered. Several other included articles were retrospective review analysis or descriptive/narrative case series which showed weak evidence for medication use in FASD.

Conclusion and recommendations

More research and specific funding are required for more high-quality intervention research in FASD and specifically on the use of psychotropic medications since they are widely prescribed. An algorithm based on current evidence and input from expert in the field should be developed in order to facilitate a systematic approach to using medications. A means of feedback and evaluation of the algorithm should allow for improvement in the evolution of treatments. In addition to more controlled studies, such research-based algorithm use has been known to advance a field like FASD where the current evidence is insufficient.

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