Journal of Population Therapeutics & Clinical Pharmacology

Original Article
DOI: 10.15586/jptcp.v27i3.681

Treatment algorithm for the use of psychopharmacological agents in individuals prenatally exposed to alcohol and/or with diagnosis of fetal alcohol spectrum disorder (FASD)

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Submitted: 18 May 2020. Accepted: 19 May 2020. Published: 16 July 2020.

ABSTRACT

Psychotropic medication treatment of individuals who have experienced prenatal alcohol exposure (PAE) has lagged behind psychosocial interventions. Multiple psychotropic medications are often prescribed for those diagnosed with a range of neurodevelopmental disabilities and impairments of PAE

(neurodevelopmental disorder associated with prenatal alcohol exposure and/or fetal alcohol spectrum disorder [ND-PAE/FASD]). Despite the diverse comorbid mental disorders, there are no specific guidelines for psychotropic medications for individuals with ND-PAE/FASD. When prescribed, concerned family members and caregivers of individuals with ND-PAE/FASD reported that polypharmacy, which was typical and adverse effects render the psychotropic medications ineffective. The objective of this work was to generate a treatment algorithm for the use of psychopharmacological agents specifically for individuals with ND-PAE/FASD. The development of decision tree for use to prescribe psychotropic medications incorporated findings from previous research and the collective clinical experience of a multidisciplinary and international panel of experts who work with individuals with ND-PAE/FASD, including an algorithm specialist. After multiple meetings and discussions, the experts reached consensus on how best to streamline prescribing along neurodevelopmental clusters. These were subdivided into four ligand-specific, receptor-acting medication targets (hyperarousal, emotional dysregulation, hyperactive/neurocognitive, and cognitive inflexibility). Each cluster is represented by a list of common symptoms. The experts recommended that prescribers first ensure adequate psychosocial and environmental, including sufficient dietary, exercise, and sleep support before prescribing psychotropic medications. Treatment then progresses through three steps of psychotropic medications for each cluster. To support established treatment goals, the most function impairing clusters are targeted first.

Keywords: *fetal alcohol spectrum disorder, prenatal alcohol exposure, medication algorithm, psychiatric medication, psychopharmacological agents*

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) represents the complex range of neurodevelopmental disabilities and impairments associated with prenatal alcohol exposure (PAE).[1] Neurodevelopmental disorder associated with prenatal alcohol exposure (ND-PAE) is a mental disorder (International Classification of Diseases, Tenth Revision code F88) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[2] Individuals with ND-PAE/FASD display a complex array of neuropsychological, neurological, and neurodevelopmental features arising from the interplay between the neuroanatomical/neurophysiological effects of PAE and other neurobiological and psychosocial challenges (i.e., the compounding effects of toxic stress, neglect, trauma, adolescent substance use, nutrition, etc.). The terminology ND-PAE/FASD has been selected by consensus of the expert panel of authors to indicate the population to which this article addresses and for which the forthcoming algorithm is meant to apply. The older the patient the more difficult it is to confirm PAE. These guidelines are intended to apply to adults with a history of PAE and associated neurodevelopmental dysfunction. For those under 18 years of age, the experts recommend these guidelines only apply when a multidisciplinary team-based ND-PAE/FASD diagnosis is confirmed.

Compared to effective psychosocial approaches, specific research on effective psychotropic medications for individuals with ND-PAE/FASD is lagging, with mixed results from two systematic reviews.[3,4] Clinicians treating individuals with ND-PAE/FASD are challenged by the complex disorder and high rates of comorbid disorders. When clinicians prescribe multiple medications targeting various comorbid disorders, they can increase the risk of overmedication and unwanted side effects. Indeed, the rates of prescribed psychotropic medications among those with ND-PAE/FASD is high, and overmedication often results in unpredictable side effects.[5,6]

Treatment algorithms are indicated in neurodevelopmental and mental disorders to minimize polypharmacy, reduce side effects, improve patient outcomes, and fill gaps where treatment guidelines are missing.

CanFASD is a national FASD research network in Canada (https://canfasd.ca/) that values the contributions of their Family Advisory Committee (FAC), a group representing families of individuals with ND-PAE/FASD. Concerns about indications and outcomes of psychotropic medications were raised by the FAC, which led a multidisciplinary panel of physicians experienced with treating ND-PAE/FASD to convene in order to develop a psychotropic medication decision-tree algorithm for the treatment of ND-PAE/FASD.

The aims of this article are to describe the development of a treatment algorithm for ND-PAE/FASD across the lifespan, based on existing research evidence and multidisciplinary expert panel consensus, to highlight considerations for younger patients, and to recommend areas for future research.

METHODS

This study is an expert review, which incorporated findings from a previous systematic review of studies related to psychotropic medication use in ND-PAE/FASD published by a number of the authors of this article.[4] Of the 329 participants with ND-PAE/FASD included in that systematic review of 25 studies, data on study type, design, sample size, dose, medication names, route of administration, side effects, benefits, mechanism of action, and recommendations were extracted and summarized.[4] These results were then provided to the expert panel, which consisted of a child and adolescent psychiatrist with expertise in neurodevelopment; adult psychiatrists, including one with expertise in neurodevelopmental disorders; developmental pediatricians; a pediatrician; a pharmacologist; and a family physician. An algorithm development expert and a FAC member were also part of the panel. The expert panel reviewed all relevant articles initially used in the systematic review and was instructed to recommend treatment decisions that aligned their expertise with existing evidence. The panel met four times (2016–2018) with substantive communications between meetings. By the second meeting, experts individually wrote a 500-word summary of their approach to using psychotropic medications with those with ND-PAE/FASD and individually constructed a version of an algorithm. Discussion summaries were transcribed, and recommendations were developed taking into account different age groups, including preschool children. Given the dearth of evidence, the panel sought an approximate conceptual framework of domain deficits (Figure 1) to connect the possible mechanisms of psychotropic medications with treatment clusters.[7] Panel members reached consensus on the final algorithm in May 2018 after three revisions, with input from the fully engaged FAC representative and algorithm development expert, and recommended an update after 2 years of use.

RESULTS

The panel of experts endorsed the FAC's concerns that individuals with ND-PAE/FASD, and their caregivers, experience inordinate stress from complications of high dose multiple psychotropic medications.[5,8] Noting the positive role of psychosocial interventions in other neurodevelopmental conditions,[9] experts recommended the rational use of psychotropic medications *after* first establishing family, psychosocial, and community supports. In recommending an ND-PAE/FASD-specific treatment algorithm, the experts reasoned that individuals with ND-PAE/FASD compared to neurotypical patients have neuronal wiring challenges that respond differently to psychotropic medications, many of which are based on ligand-specific receptors. For example, those with ND-PAE/FASD who did not respond to

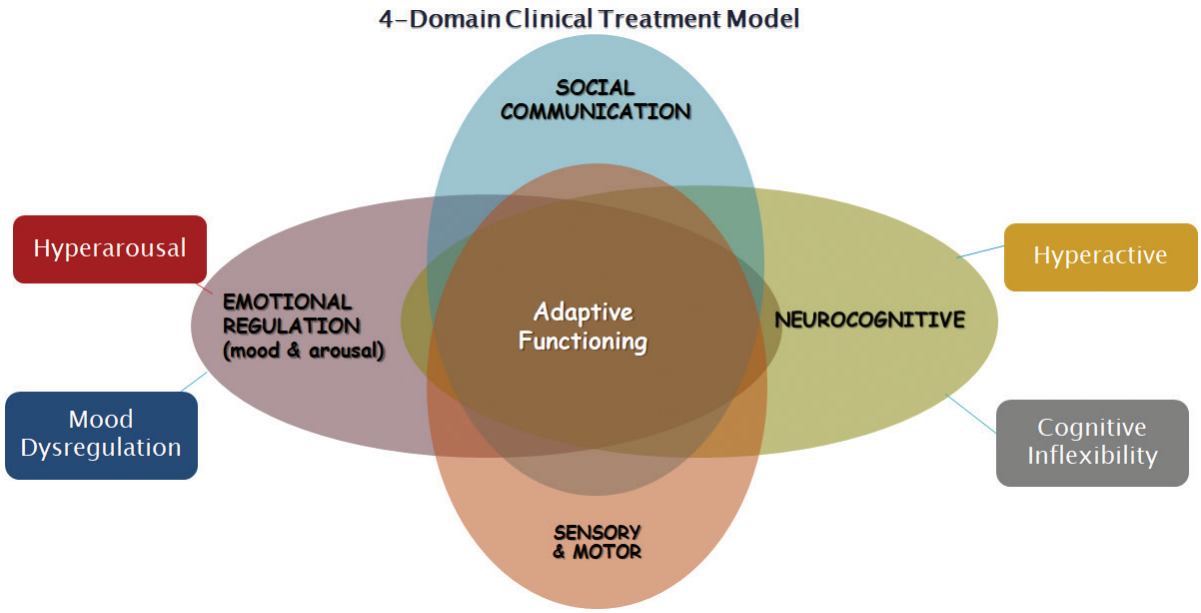

FIG 1. Neurodevelopmental Domains of ND-PAE/FASD. Adapted from O'Malley and Rich (2013).[7]

TABLE 1. Pharmacological Intervention Steps in Management of ND-PAE/FASD

Clinical Intervention Steps	Intervention
Step 1	Diagnosis and nonpharmacological interventions
Step 2	**First line of algorithm:** Domain-specific pharmacological intervention
Step 3	**Second line of algorithm:** Domain-specific pharmacological intervention plus primary and secondary domain-specific intervention (maximum four medications in adults; two in children)
Step 4	Traditional treatment algorithms published for comorbid conditions (depressive disorder, Attention deficit hyperactivity disorder (ADHD), anxiety disorder, etc.)
Step 5	Consider medications under the adjunctive pharmacotherapy section (for adults only, this step does not apply to children)

ND-PAE/FASD, neurodevelopmental disorder associated with prenatal alcohol exposure and/or fetal alcohol spectrum disorder.
Note: The primary diagnosis is ND-PAE/FASD and *the most prominent* presentations are the target of treatment.

methylphenidate showed an unexpectedly higher response to amphetamine.[10] ND-PAE/FASD-induced sensory processing deficits occurs alongside comorbid, socialization, attention, and thought problems which may contribute to some of the variances in response.[11,12] Table 1 describes the experts' recommended intervention steps. Step 4 exists because current evidence does not support or refute the use of traditional algorithms for mental disorders in those with

ND-PAE/FASD. Other factors considered were complexity,[13] side effects, and reported over-prescription.[5,11] The new and emerging section of the algorithm was based on anecdotal and unpublished experiences of the experts.

Recognizing the genetic and neuroanatomical wiring associated with ND-PAE/FASD as fundamental abnormalities, four clusters were selected by expert consensus as potential clinical targets amenable to psychotropic medications: (1) autonomic hyperarousal, (2) hyperactive/neurocognitive, (3) cognitive flexibility, and (4) emotional regulation.[7,14,15] Although not etiological, the selected clusters align with two DSM-5 neurocognitive domains and the conceptual neurodevelopmental framework of O'Malley and Rich[7] (Figure 1).

DISCUSSION

This treatment algorithm, grouped in pharmacologically responsive clusters, was based on both collective expert experience and existing research evidence for ND-PAE/FASD treatment. The major novelty of the algorithm is its opportunity for clinicians to aid decision making and to streamline treatments when using psychotropic medications with ND-PAE/FASD patients. This is achieved when treatment targets identical features comprised of functional clusters. By targeting one of the four clusters of autonomic hyperarousal, hyperactive/neurocognitive, cognitive flexibility, or emotional dysregulation, therapists using the algorithm should aim to reduce symptoms that are most debilitating and thus optimize functional improvement. The clusters are not mutually exclusive, such as when hyperactivity coexists with hyperarousal; however, an informed cluster selection can more specifically guide treatment choices. A similar approach to treatment selection for ADHD has demonstrated good outcomes for clinicians, patients, and their families.[16] The ADHD patients treated in that study using a six-step treatment algorithm had improved functioning and reduced polypharmacy compared to the treatment as usual group.[16]

Guided by the principles of psychopharmacological interventions for intellectual and neurodevelopmental disorders, we recognize current psychotropic algorithms in use for other mental disorders that co-occur with ND-PAE/FASD. Some of these algorithms are available under the American Psychiatric Association treatment guidelines (https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines). The guidelines are also available for the treatment of psychiatric symptoms in children (https://www.jaacap.org).[17] One of the authors (D.O.) has previously led numerous algorithm development projects and continues to develop and publish medication algorithms for adults with mental disorders (see http://www.psychopharm.mobi/). Although traditional algorithms have their role, specific considerations are required for complex and often refractory disorders like ND-PAE/FASD.

Premedication Nonpharmacological Therapeutic Interventions

The experts recommended that clinicians first use nonpharmacological interventions, including functional behavior analysis, behavioral management, and environmental modifications, before pharmacotherapy. Such comprehensive psychosocial interventions have the potential to reduce stress, improve adaptive functions, and provide meaningful participation in school and work-related activities.[6] Adopting psychosocial interventions first targets, the neurodevelopmental functional clusters considered are deficits in cognition, language, academic achievement, memory, attention, executive function, affect dysregulation, adaptive functioning, and motor skills. To promote compliance and appropriate use, as well as to optimize psychotropic medications, we recommend that clinicians establish baseline biopsychosocial parameters, set specific treatment goals, and thoroughly discuss psychotropic medication use

with patients and families. Consultation with the relevant clinicians is critical. Furthermore, when prescribing psychotropic medications, clinicians should regularly assess drug effects or benefits, negative side effects, and, when necessary, decrease or withdraw offending medications. Prescribing for ND-PAE/FASD is based on the risk-benefit ratio of the medication rather than target dosing (adhering to a specific recommended dose).[6] Open communication with pharmacists is encouraged to reinforce appropriate dosing while minimizing/eliminating unwanted side effects.[6]

We recommend the following prior to using the treatment algorithm: (1) review prior multiple psychotropic medications, noting any difficulty with dose adjustment or drug interactions, (2) optimize current medications, and (3) safely discontinue dispensable medications, while ensuring stable mental state and functioning.

Description of the Treatment Algorithm

The treatment algorithm is summarized in Figure 2. We recommend that clinicians identify and address the most debilitating cluster, which can be defined as one that most directly and negatively impacts established treatment goals. The four clusters (which could overlap clinically) are based on region-specific changes in the central nervous system.

Hyperarousal

Brain stem, midbrain, and limbic subcortical areas affected in ND-PAE/FASD contribute to disordered sleep, which in turn exacerbate mood dysregulation and emotion-based executive function, especially when individuals have experienced trauma. Symptoms include disordered sleep symptoms such as shortened sleep duration, increased bedtime resistance, sleep anxiety, and, specifically in children, night awakenings and parasomnias. Similar to the physiology of neurodevelopmental disorders, the circadian release of melatonin is disturbed in individuals with ND-PAE/FASD.[18] Further, disordered sleep symptoms can be compounded by features of psychological trauma[14] prevalent in this patient population,[19] such as vigilance, resistance, defiance/anger, and aggression. These features of trauma relate to noradrenergic stimulation of the hypothalamic-pituitary-adrenal (HPA)-axis and alterations of brain serotonergic pathways.[20] Nevertheless, there are a number of available treatment options to address disordered sleep symptoms. For instance, increased sleep efficiency can often be achieved by nonpharmacological approaches and hypnotics such as melatonin and zopiclone.[5,18,21] Clonidine and guanfacine are first recommended as alpha-2 adrenergic agonists effective in REM behavior disorder and sleep hyperhidrosis, respectively.[21] The second line of treatment for adults include selective serotonin reuptake inhibitors (SSRIs), followed by adjunct treatment (see section, "New and Emerging Areas"). Buspirone (serotonin receptor partial Agonist (5HT-1A)) acts to reduce anxiety and tension.[7,22]

Emotional dysregulation

Prenatal alcohol exposure negatively impacts the hippocampus, amygdala, HPA axis, and prefrontal cortex, which can cause dysregulated emotions, social behavior, sexual behavior, empathy, and flight and fight responses.[23] Increased irritability, depressed mood, anxiety, mood swings, and aggressiveness are common features and treatment foci in ND-PAE/FASD. Mood stabilizers (carbamazepine, lamotrigine, and valproate for adults) are the first line of treatment because they stabilize the basis of ND-PAE/FASD's mood problems, glutamate signaling, and brain-derived neurotrophic factor abnormalities.[11,24,25] Clinicians must be very cautious elevating lamotrigine doses to avoid Stevens–Johnson Syndrome.[6] Selective serotonin reuptake inhibitors (citalopram, fluoxetine, escitalopram, and sertraline; note citalopram's black box warning) are recommended as second-line treatment, especially where depression is prominent.

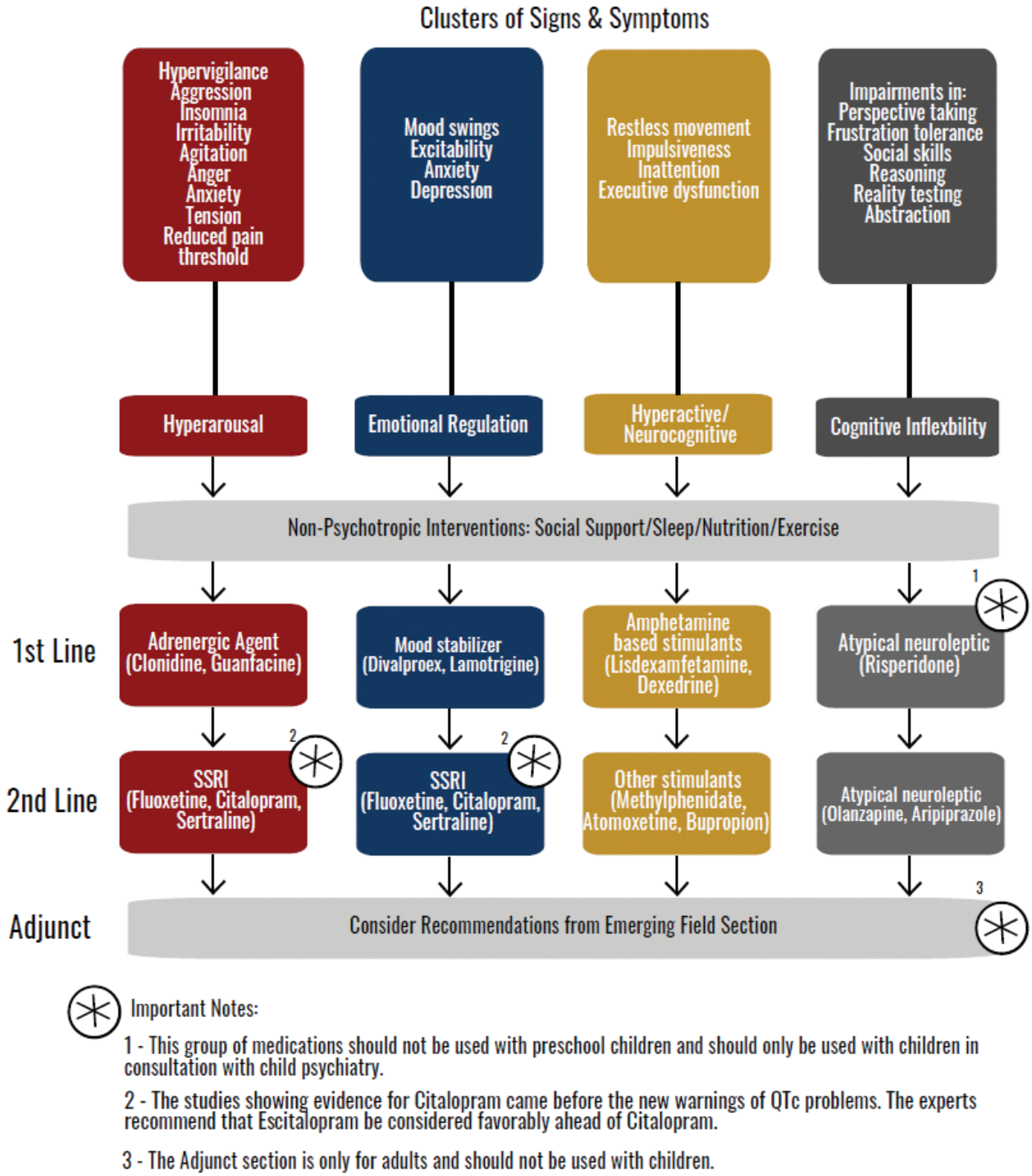

FIG 2. Proposed Psychotropic Medication Algorithm (*See Discussion section for full instructions on administering the algorithm, and special considerations for children and adolescents).

Hyperactive/neurocognitive

Individuals with ND-PAE/FASD often exhibit downregulation in dopaminergic and noradrenergic systems. Therefore, stimulants are listed as first-line medications for prominent hyperactivity and impulse control symptoms.[3] Existing guidelines for the treatment of ADHD address how to treat impulsiveness and executive dysfunction.[26] Some researchers have reported that ND-PAE/FASD-related inattentiveness can be treated using amphetamine-based stimulants.[27] Lisdexamphetamine and dextroamphetamine are recommended as first-line options. Methylphenidate, atomoxetine, and bupropion are second-line options, depending on the age and response to first-line treatment.[4,15,28]

Cognitive inflexibility

Dorsolateral or orbitofrontal lobe function control cognitive flexibility.[29,30] The concreteness and poor adaptive functioning features of this cluster can predispose individuals to delusions, poor reality testing, and aggression.[28] Therefore, atypical antipsychotics (risperidone and olanzapine) are recommended as the first-line medications *in adults* with ND-PAE/FASD.[29] Aripiprazole, lurasidone, and quetiapine are second-line options. In difficult to manage or noncompliant adults, injectable zuclopenthixol decanoate and clozapine are also recommended.[29,31]

Specifics of Psychotropic Interventions Guided by the Treatment Algorithm in Children and Adolescents

In children and adolescents, psychotropic medications should be used to augment multidisciplinary psychosocial treatment planning and medical interventions. Most researchers have used patient samples between the ages of 6 and 16.[3–5,10] The experts recommend that, except in extreme situations of risk of harm to self or others, psychotropic medications should be considered only for patients over the age of 7. Therefore, additional recommendations include consulting with subspecialists, initiating more frequent reviews, and tapering off the medications as environmental adaptation and social support improve functioning. Sleep stabilization and nonmedication approaches are recommended before using the first-line treatment to address the most debilitating function. Sleep hygiene with melatonin added as needed is recommended to address disordered sleep symptoms. Neurocognitive/hyperactive cluster interrupts academic and family functioning and exerts the most disruption in younger patients. Experts endorsed the following.

Stimulants

Current evidence places stimulants as the first-line pharmacological treatment for ADHD-type symptoms, with methylphenidate shown to effectively reduce hyperactivity[32] and dextroamphetamine effective in 79% of children unresponsive to methylphenidate.[10] Despite the differential response, clinicians should use existing ADHD treatment guidelines in children with ND-PAE/FASD.[10,16] Almost 80% of children with ND-PAE/FASD are on stimulants.[28] Nonresponse to stimulants has been suggested as a "red flag" for clinicians to consider ND-PAE/FASD diagnosis and to explore other treatment considerations.[33] Clinicians should closely monitor and manage possible side effects of stimulants in children.

Atypical antipsychotics

Agitation and aggression can be effectively reduced by atypical antipsychotics, which are antagonists of central monoamine receptors (D2, 5-HT2A). Previous researchers found that risperidone was effective in 80% of ND-PAE/FASD children with disruptive behavior,[28] and reduced aggression and conduct disorder.[28,29] Alternatives to risperidone in ADHD treatment augmentation include olanzapine and aripiprazole.[34] Dopamine agonists (e.g., stimulants) and antagonists (e.g., neuroleptics) are commonly used medications that directly impact executive dysfunction

in children and adolescents.[29,35] In contrast, atypical antipsychotics, with more acceptable side effects profiles, are preferentially recommended. Olanzapine has significant metabolic side effects.

Mood stabilizers

Emotion dysregulation, anxiety, and mood disorders with or without seizures are amenable to mood stabilizers in ND-PAE/FASD.[11] Previous researchers found that mood stabilizers produced an 88% success rate in 6–17-year-olds by reducing moodiness, seizures, and aggression, and protecting against the manic switch.[11] Valproic acid, buspirone, and lamotrigine help mood regulation, while clonidine and melatonin help initiate and maintain sleep efficiency. Sleep disturbance was identified in 85% of those with ND-PAE/FASD.[36] These agents must be used with caution until more evidence is available to support their use in children.

Antidepressants and anxiolytics

Selective serotonin reuptake inhibitors (sertraline, fluoxetine, and citalopram) were effective in reducing symptoms,[3] but only fluoxetine is recommended in children.[15]

New and Emerging Areas

We recognize that it is difficult to make wide-reaching recommendations based on the relatively limited evidence presented in this research. Although this section is based more on anecdotal individual practice, we hope that it will stimulate research and obtain feedback on the algorithm developed here. Firstly, practitioners should consider the known effect and mechanism of action of the drug, use only in adults and complete adequate trial of first and second-line recommended treatment before the medications in this section. To examine the effectiveness of the psychotropic medications, prescribers should contribute to refining this algorithm by providing feedback to the authors. Family Advisory Committee is interested in the evaluation of the algorithm.

Nutritional supplementation

Offspring displayed fewer symptoms of ND-PAE/FASD when women who used alcohol prenatally were given nutritional supplementation.[37] Antioxidant treatment utilizing glutathione and lipoic acid has been suggested to partially reduce the onset of the ethanol-dependent developmental malformations with lipoic acid having more potent protecting ability; neither had an effect on the amount of cell death.[38] This is the basis for the use of glutamine, which was found to mitigate alcohol-induced acid-base imbalances and alterations in fetal regional brain blood flow. Experts recommend, based on theoretical but still emerging evidence in the literature, that individuals with ND-PAE/FASD should take omega-3, choline, iron, and glutamine to reverse oxidative stress. The effectiveness of these supplements may be due to reductions in oxidative stress and enhancing antioxidant supply.[39]

Experts recommend mirtazapine, trazodone, and tryptophan as options to treat adults with ND-PAE/FASD experiencing various forms of insomnia. The mechanism of action of these medications align with Gamma aminobutyric acid (GABA), serotonin, and adrenergic mechanisms described in ND-PAE/FASD.

Cannabidiol (CBD) may be useful and effective in treating adults with seizures and complex disorders such as ND-PAE/FASD. Cannabidiol has been useful in anxiety and depression in preclinical treatment studies.[40] Its use as an anxiolytic and antipsychotic aligns with its antioxidant theoretical mechanism. In a case report of a patient with adverse childhood experiences similar to those often experienced by individuals with ND-PAE/FASD, cannabidiol effectively reduced anxiety and insomnia.[41]

Based on the experts' clinical experience, lamotrigine (mood), aripiprazole (psychosis and agitation), vortioxetine (mood), and minocycline and bupropion (cognition and hyperactivity) were recommended for treating adults with ND-PAE/FASD. Minocycline's immune-mediated positive

effects have been demonstrated in animal models of ND-PAE/FASD.[42] Vortioxetine enhances cognitive abilities, and bupropion improves attention and motivation but should be monitored in light of its ability to reduce the seizure threshold. Lamotrigine and minocycline respectively act on ion junction transport and neuroimmune factors such as cytokines.[43] Prazosin and propranolol were recommended for their reduction of hyperarousal symptoms, which are common in individuals with ND-PAE/FASD who have experienced trauma.[44]

We request feedback from future users of this algorithm to further refine the above emerging areas. Feedback will allow algorithm developers to more precisely identify correct medications for a specific clinical need. Some recent research embraces the role of neuroinflammation and over-activation of the stress hormone cortisol and the HPA axis in the development of mental disorders. Researchers who have investigated laboratory animals, as well as individuals with ND-PAE/FASD and sleep disorders, suggest the need for iron/ferritin level determinations and replacement, if deficient.[5]

LIMITATIONS

The available evidence, including evidence from systematic reviews, was of insufficient power to confidently base the recommendations. The experts, whose experiences were factored in the development of the algorithm, have their own unique practice styles that may depend on a variety of untested conclusions. The algorithm has not been validated and its use in children is likely to be limited.

CONCLUSION

This article presents a treatment algorithm to address the complex symptoms experienced by individuals with ND-PAE/FASD. Clusters of ND-PAE/FASD individually or in combination, current evidence on psychotropic medications should guide the selection of appropriate medications. We believe that this stepwise decision tree should reduce polypharmacy and result in functional improvements. The algorithm is limited by the absence of specific experiments that inform ND-PAE/FASD-related clusters, as well as clinical trials that support the efficacy of the selected medications. Moving forward, we expect that this algorithm will be evaluated and refined on an ongoing basis through clinical trials. We request feedback on the utility of this algorithm in order to facilitate development and refinement and to increase the effectiveness of psychotropic medications. Ultimately, the algorithm should simplify and improve the pharmacological treatment of individuals with ND-PAE/FASD by reducing side effects and medication noncompliance.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

FUNDING

Some financial support for this project has been provided by Canada FASD Research Network, Saskatchewan Health Research Foundation Research Connections Fund, Lakeland Centre for FASD, and the University of Saskatchewan, College of Medicine and Department of Psychiatry.

DATA AVAILABILITY STATEMENT

None.

COMPLIANCE WITH ETHICAL STANDARDS

I am not sure if this statement is required for the manuscript. No human or animal participants were involved in the study. Please advise if there is any information you need from us.

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