Curr Treat Options Peds (2017) 3:57–68
DOI 10.1007/s40746-017-0081-0

Mental Health (WF Njoroge and TD Benton, Section Editors)

Pediatric Psychopharmacology: a Primer for the Treatment of Common Mental Health Conditions

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Published online: 11 May 2017

This article is part of the Topical Collection on *Mental Health*

Keywords Pediatrics · Psychopharmacology · Mental health

Opinion statement

The purpose of the review is to provide an overview of psychopharmacologic agents commonly used in pediatric practice. Stimulants, alpha-2-agonists, and SSRIs have empirically supported efficacy and have safety profiles that allow them to be prescribed and managed in the pediatric primary care setting. Pediatric primary care providers, independently or in collaboration, are integral components of a functioning pediatric mental health system of care.

Introduction

About 7–10% children and adolescents receive prescriptions for psychopharmacologic medications and most pediatric mental health care is provided by pediatricians or family practice physicians [1, 2]. This paper will review the common medications used in pediatric primary care settings as well as provide a less detailed overview of medications that children seen in pediatric primary care settings may take.

Support for pediatric practice

Many pediatric providers do not feel confident in their ability to address the mental health needs of their patients. To support primary care pediatricians, the American Academy of Pediatrics (AAP) and other have developed tool kits addressing practical aspects and content aspects of this work, including assessment, practice transformation, and advocacy tip [3]. Additionally, innovative service delivery models offer collaborative care for youth with mental health needs, including phone consultation support, co-located mental health professionals, and educational approaches [4, 5].

Common themes across medication classes

Pediatric psychopharmacology approaches share some common principles [6]. First, treatment should follow

an assessment that clarifies the diagnosis being treated. Family education about the diagnosis, expected course, and range of treatment options are important to enhance adherence. Basic behavioral strategies, such as positive parenting approaches or teaching relaxation skills can be helpful in alleviating distress, in many situations, while other treatment is being initiated [7]. Resources like the parentsmedguide.org, Healthychildren.org, and Facts for Families (aacap.org) can be helpful adjuncts to the conversation. Effective communication approaches can improve clinical outcomes as well [8]. The American Academy of Pediatrics (AAP)'s "HELP" pneumonic encourages intentional effective communication strategies including use of hope, empathy, loyalty, patient's language (words as well as actual language), actively partnering with patients/families, asking permission to address sensitive topics and move forward, collaborative planning. Finally, with respect to medication trials, parents and patients deserve explicit informed consent/assent procedures regarding the level of evidence guiding the recommendation for the child's age, likelihood of efficacy, potential adverse effects, and regulatory status of the medication in children [9]. Especially because primary care evaluations is necessarily more limited in scope than a specialty mental health assessment, apparent treatment failures should prompt a review of the diagnostic formulation in addition to consideration of alternative approaches [10].

Stimulants

Stimulants are the most commonly prescribed class of medications used for children and adolescents [2]. In pediatrics, stimulants are nearly exclusively used to treat attention deficit hyperactivity disorder (ADHD), for which they carry an FDA indication. Immediate release amphetamines have FDA indications for children as young as age 3, although limited research supports their use preschoolers [11]. Methylphenidate, which has been studied in preschoolers, is approved for children 6 and up, as are most extended release formulations [12, 13]. Stimulants can also decrease aggression, generally considered when non-pharmacologic interventions have been ineffective.

Formulations

The two classes of stimulants, methylphenidates and amphetamines, are available in a wide variety of formulations, presented in Table 1, differing by mode of administration and duration, including immediate release and extended release pills and liquid formulations. Methylphenidate-OROS (Concerta) which uses an osmotic pump to deliver a sustained administration through 12 hours, was developed to reduce high peak levels that might contribute to abuse. Lisdexamphetamine was developed to reduce the risk of abuse by binding a lysine molecule to d-amphetamine. The lysine is cleaved off in the acidic gastric environment is intended to reduce the potential of abuse.

Clinical uses

The AAP recommends the use of stimulants as first line treatment in conjunction with behavioral supports for children and adolescents with ADHD 6 years of age and older [14]. Most treatment guidelines recommend either class of stimulants [14–16]. Family preferences, family history of positive or adverse effects of a particular class of medication, or specific formulation needs may all influence the

Table 1. Stimulant formulations

	Formulations	Brand names
Methylphenidate	Liquid	Methylin, Quillivant XR
	Tablet (immediate release)	Ritalin
	Chewable tablet (IR)	Methylin
	Tablet (extended release)	Ritalin SR
	Capsules (extended release in order of estimated duration of action)	Ritalin LA < Metadate ER < Metadate CD < Concerta = Aptensio XR
	Transdermal patch	Daytrana
Dexmethylphenidate	Tablet	Focalin
	Capsule	Focalin XR
Mixed amphetamine salts	Orally dissolving tablet	Adenzys XR (d:l ratio: 3:1)
	Tablet	Adderall (d:l ratio 3:1), Evekeo (d:l ratio: 1:1)
	Capsule	Adderall XR
	Liquid suspension	Dynavel XR (d:l ratio 3.2:1)
d-amphetamine	Tablet	Dexedrine
	Spansules	Dexedrine spansules
	Liquid	Procentra
Lisdexamphetamine	Capsule	Vyvanse

choice. Stimulants can be titrated up relatively quickly, starting with the lowest available formulation and increasing to a target dose each week if a parent is able to report reliably on adverse effects and clinical outcomes. Community care is associated with poorer outcomes compared to research interventions, with notable differences in frequency of appointments and maximum dosage [17]. Thus, close follow-up and adequate dosing seem warranted to avoid this pattern.

Monitoring

Using validated measures of ADHD symptoms, such as the Vanderbilt ADHD Rating Scales, for teachers as well as parents and older youth is helpful for tracking symptoms. The most common adverse effects of stimulants are decreased appetite, abdominal pain, headaches, and sleep disturbance. Growth velocity may be slowed, but a recent study suggests that overall adult height is not significantly affected [18, 19]. Heart rate (HR) and blood pressure (BP) should be monitored, though changes are rarely clinically significant [20].

All controlled substances offer a potential for diversion or misuse. A recent national study suggested the majority of 10–18 year olds had obtained medications outside of the physician-patient relationship and/or sold or given away a prescription and clinical awareness of

this potential is appropriate [21]. The associations among substance use and stimulants suggest ADHD treatment appears to protect against cigarette smoking and does not increase other substance use risk [22, 23].

Central Alpha-2-agonists

Alpha-2-agonists, clonidine and guanfacine, are commonly used in pediatrics as treatment for ADHD, aggression, tics, and sleep [24]. The immediate release formulations of both medications carry FDA indications for hypertension with no age restriction. Extended-release formulations of both alpha-2-agonists are approved for ADHD starting at 6 years old.

Formulation

Alpha-2-agonists are available in immediate release tablet form and in extended release [24]. Clonidine is also available in a once-weekly transdermal patch.

Clinical uses

Alpha-2-agonists are commonly used for ADHD as second-line treatment, for children with stimulant contraindication, or if parent declines to consent for a stimulant. Although comparative effectiveness studies are lacking, meta-analytic data suggest lower effect size than for stimulants [25]. Alpha-2-agonists have long been used as adjunctive treatment to stimulants to supplement the effects of the stimulants without adding to the stimulant adverse effect profile, such as anorexia [25].

Clonidine is also used as a sleep agent, especially in children with ADHD. Despite common usage, a recent systematic review identified only one systematic published report of this use, with an overall positive outcome [26, 27]. Guanfacine, a more selective alpha-2 agonist, causes less sedation, but is also sometimes used at bedtime if a child is already taking it during the day.

Alpha-2-agonists can be effective for tic disorders and carry a relatively benign side effect profile compared to antipsychotic agents, which are also used for tic disorders [28].

Monitoring

Important potential adverse effects of both agents in this class include somnolence, hypotension, and fatigue. Most decreases in HR and BP are not clinically significant [29]. Severe adverse effects, sometimes related to accidental or intentional overdosing, include syncope, hypotension, or death [30]. Abrupt discontinuation of immediate release alpha-2-

agonists being used in multiple doses per day can result in rebound hypertension.

Atomoxetine

Atomoxetine is a second-line alternative treatment for pediatric ADHD. As a non-stimulant, it offers a different side effect profile including a lack of an abuse potential [31]. Atomoxetine is FDA approved for the treatment of ADHD in children over 6 [12]. Formulation: Atomoxetine is available in a capsule.

Clinical uses

Atomoxetine is generally used to treat ADHD as a second line agent or in children with a contraindication for stimulants. Over 25 randomized-controlled studies establish atomoxetine's benefit in reducing signs of ADHD in children and adolescents by both parent and teacher reports, with similar effects for inattention and hyperactivity/impulsivity [32]. Atomoxetine can also reduce signs of oppositional defiant disorder and may also improve overall quality of life, although less so than signs of ADHD. Atomoxetine's effects are slower to emerge than other ADHD medications, with effects starting at 2–4 weeks with a lower effect size than stimulants [33]. Atomoxetine has also been considered as a treatment for youth with anxiety comorbid with their ADHD for which there is limited, but promising evidence [34].

Other targets of treatment, including autism spectrum disorders, tics, and mood disorders have not been studied or have yielded negative or inconclusive findings.

Monitoring

The most common adverse effects of atomoxetine are generally mild and include GI symptoms, somnolence, and irritability [35]. Atomoxetine carries a block box warning related to suicidality because of its structural association with anti-depressants, but a 2016 study examined suicidality in over 500,000 patients and found no increase compared to stimulants [35, 36]. Case reports suggest a very low risk of treatment-emergent hypomania when starting atomoxetine or increasing the dose [37]. A very small number of cases of hepatic failure have been reported on atomoxetine [38]. No baseline testing is required, but family education for signs of potential hepatic failure is warranted Ref: FDA.gov (2010) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021411s035lbl.pdf Accessed 4/24/2017.

Cardiovascular effects most commonly reported with atomoxetine are usually small increments in systolic BP and HR, but can be more significant [12]. Shortened QTc interval has also been described in

meta-analysis, suggesting that children with risk factors should be assessed prior to initiation and/or monitored [32].

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs, especially fluoxetine, sertraline, and citalopram and escitalopram, are used in pediatric psychiatry to address a range of anxiety and mood problems. Rates of prescribing increased until 2004 when an FDA black box was applied and the rates of prescribing in primary care declined substantially after that time [39].

Regulatory

The lower age limit of approvals are as follows: Sertraline (Major depressive disorder (MDD)): 6 yo; escitalopram 12 yo (MDD), and fluoxetine (obsessive compulsive disorder (OCD): 8 [12].

Formulation

Most SSRIs are available in tablet or capsule form. Fluoxetine, sertraline, and citalopram are available in suspension. Fluoxetine's 90-mg capsules offer weekly administration options.

Clinical uses

SSRI's in pediatrics are used clinically to address depression, anxiety, and OCD.

Depression

Most guidelines recommend non-pharmacologic treatment for mild depression in children and adolescents [40]. Recommendations to treat moderate-severe depression or mild depression not responsive to supportive approaches are based upon a literature in which fluoxetine is supported by the most robust data for treatment of pediatric (predominantly adolescent) depression, with limited support for other SSRIs. Fluoxetine was the medication in the Treatment of Adolescent Depression (TADS) landmark study which demonstrated that the combination of fluoxetine and cognitive behavioral treatment (CBT) offered the fastest recovery and a lower rate of suicidal ideations compared to CBT or medication alone [41]. The American Academy of Child and Adolescent Psychiatry and Guidelines for Adolescent Depression in Primary Care (GLAD-PC) program recommend consideration of sertraline and (es) citalopram as reasonable alternatives to fluoxetine given their empirical support [42, 43]. Very limited data has shown safety or efficacy of SSRI's in treating depression in children under 12 and most guidelines commonly recommend consultation with or referral to specialty mental health providers [43].

Psychopharmacologic treatment for pediatric depression generally should be continued at least 9 months to minimize relapse risk, with discontinuation trial in the summer when possible [44].

Anxiety

SSRIs are commonly used for pediatric anxiety. A recent meta-analysis reported an overall moderate effect size for SSRIs and selective norepinephrine reuptake inhibitors for treating non-OCD anxiety disorders [45]. Although each SSRI has not been tested for each of the specific types of anxiety disorders, such as separation anxiety, social anxiety, and generalized anxiety, clinical guidelines recommend selecting SSRIs using factors like half-life, family history of response to medication as well as published empiric literature [46]. Starting with the best studied pediatric medications, fluoxetine and sertraline, may be warranted in pediatric settings. The other anti-depressants have less data supporting their use in anxiety, have lower effect sizes, or higher rates of adverse effects (reviewed in [47]). For children with moderate-severe anxiety, a combination of an SSRI and CBT is more effective than monotherapy in short- and long-term follow-up (e.g., approximately 80% response rate vs. 55–60% at 12 weeks) [48]. These findings highlight the importance of advocating for combined treatment for youth taking an SSRI for anxiety.

A substantial literature demonstrates the effectiveness of SSRIs, specifically fluoxetine, fluvoxamine, and sertraline in treating moderate-severe pediatric OCD [49]. For OCD, combination with CBT is more effective than monotherapy.

SSRIs have not been shown to provide clinical benefit in posttraumatic stress disorder, as monotherapy or in addition to CBT [50, 51].

Monitoring

Prior to initiating an SSRI, screening for a history of bipolar disorder in the family is warranted, as this history suggests an increased risk of mania associated with an SSRI [46]. Monitoring of anti-depressants requires tracking of symptoms in a systematic way, including with validated paper and pencil measures. Non-proprietary measures that are easy to use in primary care include the Pediatric Symptom Checklist-17 for general symptom monitoring, the Patient Health Questionnaire-9 for depression, and the Screen for Child Anxiety Related Disorders for anxiety [52–54] . A more extensive list is available on the AAP's Mental Health Toolkit [3]. Treatment effects are generally expected in 3–6 weeks, with somewhat faster responses for anxiety disorders. Lack of clinical response after titration to target dose warrant reevaluation of the diagnosis and trial of alternative treatment. Common adverse effects of SSRI's include GI symptoms, headaches, and changes in sleep. "Activation," which involves elevated energy without mood change, is not uncommonly seen in children on anti-depressants. Mania is a potentially dangerous adverse effects related to SSRIs and occurs in approximately 5% of children with depression. SSRIs can be

associated with sexual side effects in adolescents and these warrant explicit monitoring because of reluctance to spontaneously report.
Black box: In 2004, the Food and Drug Administration placed a black box warning on anti-depressants, indicating a higher risk of suicidal behaviors in youth, with a guideline for weekly monitoring in the first month of treatment and every 2 weeks in the following week, as well as the same pattern with dose changes [55]. The link between increased suicidal thoughts and behaviors, but not completed suicide, has been established, with a doubling of rates from 2% on placebo to 4% (as reviewed in [55]). It should be noted that the black box was followed by a substantial decline in diagnosis and treatment of youth with depression and associated higher suicide rates. Thus, pediatricians are encouraged to continue to use indicated treatment and careful monitoring rather than avoid diagnosis and treatment.

Other medications that primary care providers may co-manage

Other classes of medications are best initiated by or in collaboration with a specialty mental health provider because of the seriousness of the disorders they treat or the complexity of adverse effects or monitoring [56]. Atypical antipsychotic agents, including risperidone, olanzapine, aripirazole, quetiapine, and ziprasidone, have FDA indications to treat bipolar disorder, psychotic illnesses, and tic disorders. Risperidone and aripirazole are also indicated treatments for irritability and aggression in children with autism [12, 57]. Some medications in this class have been shown to be effective in addressing severe aggression and are commonly used for this purpose [58]. Their use is limited by the potential for significant metabolic effects, including metabolic syndrome, hyperprolactinemia, the potential for extrapyramidal side effects, and the need to follow labs, vital signs, and growth parameters on a regular basis [59].

Benzodiazepines can be effective for short-term anxiolysis, but the lack of evidence and potential for adversity including dependence make them generally only adjunctive medications as part of a more complex treatment plan [46]. Buspirone has few reported side effects, but no published evidence supporting its efficacy in children for anxiety although a promising pilot suggests it may be helpful in addressing repetitive behaviors in autism [60].

Lithium can be helpful medications in mania, but requires vigilant monitoring of effects and the narrow therapeutic window. Carbamazepine and lamotrigine, have minimal to no rigorous evidence supporting their use in pediatric psychiatric disorders and carry with them substantial risks of adversity.

Conclusions

Pediatric providers can play important roles in the care of youth with psychiatric disorders, especially ADHD, depression, and anxiety, using stimulants, alpha-2-agonists, atomoxetine, and SSRIs. Monitoring of these medications requires regular visits with attention to clinical effects,

psychiatric and physical adverse effects, all of which is feasible in the pediatric setting. Pediatric providers have a range of training and expertise in pediatric psychopharmacologic treatment, as well as a range of access to specialists. Collaboration with non-prescribing therapists can be helpful in sharing ideas about diagnostic formulation and treatment progress. Innovative collaborative approaches allow pediatric providers to work with specialty mental health providers to care for children whose clinical needs are outside the scope of training and practice of the pediatric provider. With some support, the medications described in this paper have the efficacy and safety profile to be used within the pediatric primary care setting. Pediatric providers should consider referral if (1) they are not sure about the diagnosis or diagnostic formulation, (2) patient has not responded to first- or second-line trials of medication reviewed in this chapter prescribed in typical doses, (3) they are considering more than two concurrent medications (e.g., more than stimulant plus SSRI, or stimulant plus alpha agonist), and (3) if they are unsure of next steps,. As with all treatments, effective communication, a therapeutic alliance, and use of motivational strategies are likely to enhance the treatment plan.

Compliance with Ethical Standards

Conflict of Interest

Mary Margaret Gleason reports grants from Baptist Community Ministries, Louisiana Office of Public Health, Klingenstein Third Generation Family Foundation, and Zero to Three.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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