Approaches to Treating Children With ADHD and Common Comorbidities

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OBJECTIVES

1. Identify comorbidities of ADHD in children.
2. Differentiate between ADHD medications with respect to specific co-occurring diagnoses.
3. Recognize knowledge gaps and potential areas of future research for treating patients with ADHD and comorbidities.

CE ACCREDITATION

Contact hours: 1.0.

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most common mental health disorder among children and adolescents, with a prevalence rate of 9.8% in children 3 to 17 years of age (Bitsko et al., 2022). The American Academy of Pediatrics (AAP) has published guidelines for treatment of ADHD in children and adolescents ages 4 to 17 years that address diagnosis, treatment and monitoring of ADHD (Wolraich et al., 2019). The AAP guidelines do not address treatment of children with comorbidities but identify the treatment of ADHD in children with comorbidities as an area for future research. To address this gap, a review of ADHD treatment in children with comorbidities including anxiety, depression, substance use disorder (SUD), epilepsy, tic disorders (TD), oppositional defiant disorder (ODD), learning disabilities (LD), autism

TABLE 1. Pharmacologic treatment of ADHD and comorbid conditions

Medication class	Common example(s)	Mechanism of action	Clinical effect
Stimulant	Methylphenidate, amphetamine	Blocks the reuptake of NE and dopamine into presynaptic neurons	Improvement of core ADHD symptoms
Alpha- agonist	Guanfacine, clonidine	Selective alpha-2 adrenoreceptor agonist; reduces sympathetic nerve impulses, diminishing sympathetic outflow, vasomotor tone, and heart rate; in ADHD, regulates subcortical activity in the prefrontal cortex	Affects working memory and behavioral inhibition, thereby improving symptoms associated with ADHD
SNRI	Atomoxetine	Selectively inhibits the reuptake of NE	Improvement of core ADHD symptoms and emotional lability
SSRI	Fluoxetine, escitalopram	Inhibits CNS neuron serotonin reuptake, increasing serotonin activity	Improvement of anxiety, depression
NDRI	Bupropion	Dual inhibition of norepinephrine and dopamine reuptake	Improvement of depression; smoking cessation
Hormone	Melatonin	Acts on melatonin receptors	Aids in regulation of the sleep-wake cycle

Abbreviations: SNRI, serotonin and norepinephrine reuptake inhbitor; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor.

spectrum disorder (ASD), and sleep disorders was conducted. A review of pharmacologic modalities can be found in Table 1.

ADHD COMORBIDITIES

Anxiety

With comorbidity rates up to 50%, anxiety is one of the most common concurrent diagnoses of children with ADHD (Khoodoruth et al., 2022; Koyuncu et al., 2022; Leon-Barriera et al., 2022). Studies show children with both diagnoses experience more severe ADHD and anxiety symptoms (Golubchick & Weizman, 2020; Koyuncu et al., 2022; Leon-Barriera et al., 2022). Best treatment management includes an evaluation of which disorder has more impact on the child's daily function (Janiczak et al., 2020). Consideration of the child's anxiety relative to the presence of ADHD is recommended for ideal management .

Treatment has been controversial due to concerns ADHD treatment can exacerbate anxiety symptoms, especially with stimulants. However, an increasing number of studies support stimulant treatment. A study from Israel differentiated anxiety types, and although there was no change in panic and social anxiety symptoms, stimulant treatment for ADHD decreased both generalized and separation anxiety symptoms (Soul et al., 2021). Methylphenidate (MPH) is effective, well tolerated and considered first-line stimulant treatment for children with ADHD and mild to moderate anxiety (Leon-Barriera et al., 2022). When ADHD symptoms are the primary symptoms, MPH has shown to not only alleviate these symptoms and improve daily function but also improve mild anxiety symptoms. When evaluating adverse drug reactions in medications used for ADHD, MPH was shown to have the fewest side effects in children (Pozzi et al., 2019). Froehlich et al. (2020) found children with lower levels of sadness, anxiety, and irritability symptoms were more prone to adverse effects with MPH initiation, while those who reported higher levels of these symptoms prior to MPH use had an improvement of emotional symptoms. Caution is recommended in preschool children, especially with tic disorders, and adolescents with a history of drug misuse (Golubchick & Weizman, 2020).

Atomoxetine (ATX) is the first-line nonstimulant option in cases of more severe anxiety or an intolerance to stimulants (Leon-Barriera et al., 2022). A review article from Koodoruth et al. (2022) suggests children taking ATX had lower anxiety scores in comparison to those on MPH. Therapeutic action can take longer than stimulants, but with ATX there is a lack of abuse potential, lower side effects, and the ability to stop medication without a taper (Fedder et al., 2023; Janiczak et al., 2020). Providers should note the boxed warning of suicidal ideation in children and adolescents.

In the most severe cases of children with comorbid ADHD and anxiety, treatment options include the alpha-agonists guanfacine or clonidine, SSRIs, or SNRIs (Golubchick & Weizman, 2020). These drugs can be used as monotherapy or in combination with stimulants or nonstimulants (Golubchick & Weizman, 2020; Janiczak et al., 2020). Few studies exist and limited information is known on the effectiveness of these medications in children with comorbid anxiety and ADHD. One study suggests guanfacine had no effect on anxiety, and SSRIs had no effects on symptoms of ADHD (Janiczak et al., 2020). ATX in combination with fluoxetine has shown to decrease symptoms of anxiety, while Boaden et al. (2020) recommend fluvoxamine over fluoxetine for its effectiveness on anxiety. Careful consideration for treatment and close monitoring is recommended in more severe cases, especially considering the gap in research.

Depression

A review of published literature revealed there are limited studies regarding treatment of children with ADHD and depression. In a recent study on the effectiveness of antidepressants in children and adolescents, bupropion showed a

decrease in ADHD symptoms from clinician ratings, while desipramine was effective in decreasing symptoms based on teacher rating scales (Boaden et al., 2020). SSRIs are first-line treatment for depression, but little is known about the side effects of these medications on children and adolescents with ADHD. Fluoxetine is an effective treatment for major depressive disorder, but it is unknown how it affects symptoms of ADHD (Boaden et al., 2020). A study completed in Korea supported SSRI treatment of depression, specifically escitalopram, concluding it could lead to improvement in the inattention symptoms of ADHD (Choi et al., 2021).

ATX is another medication minimally studied for treatment in children with ADHD and depression. Although only FDA approved for ADHD treatment, adults have used this medication for off-label treatment of depression, which could lead to more studies for effectiveness in children and adolescents (Fedder et al., 2023). Another study from Egypt supported ATX as monotherapy treatment showing improvement in both ADHD symptoms and depression (Shaker et al., 2021). Based on the paucity of literature on treatment for children and adolescents with comorbid ADHD and depression, more research is recommended. This may include focuses studies on monotherapy or treatment for each diagnosis.

Oppositional Defiant Disorder

The most common comorbidity seen with ADHD is ODD, a disorder characterized by anger dysregulation and irritability (Azeredo et al., 2018; Brennan et al., 2022). Up to 40%−60% of children diagnosed with ADHD are also diagnosed with ODD (Brown et al., 2022). Numerous congruent biological and environmental factors may contribute to the overlap. Symptoms associated with hyperactivity and impulsivity in ADHD show a greater risk for oppositional behaviors (Brennan et al., 2022; Brown et al., 2022). While each carries risks of maladjustment, their coexistence results in more significant impairments in academic and social function, including family and peer relationships, diminished self-esteem, and increased risk of mental health outcomes (Brennan et al., 2022; Liu et al., 2019; Steiner & Remsing, 2007).

Treatment for children with comorbid ADHD and ODD is multifaceted and should be highly individualized. Unfortunately, conflicting evidence has complicated treatment recommendations, and guidelines are absent. The American Academy of Children and Adolescent Psychiatry's (AACAP) published recommendations in 2007 for managing ODD are reflected below. A positive, therapeutic relationship between the provider and patient is an important characteristic of the treatment plan (Steiner & Remsing, 2007). Evaluation tools and questionnaires can be helpful in the diagnosis process but should be taken from diverse informants, such as the patient, family members, and teachers (Steiner & Remsing, 2007). Psychotherapy and school-based programming for the patient and family are foundational for ODD treatment and should be utilized in conjunction with ADHD management (Liu et al., 2019). Therapy should include problem-solving and parent management training (Steiner & Remsing, 2007).

Pharmacological treatments are adjunctive to therapy and considered in the context of ADHD. Although few studies address pharmacotherapy in ODD, stimulant therapy is the first line of treatment of ADHD with or without comorbid ODD (Liu et al., 2019). The coexisting diagnosis of ODD has not been shown to diminish the effect of stimulants on children with ADHD. In one study, a combination of stimulants and behavior therapy showed the greatest benefit for children with ADHD and ODD. Limited evidence exists to support use of other psychotropics. Some studies on stimulants, ATX, alpha-agonists, atypical antipsychotics, lithium, bupropion, and SSRIs and combination treatments with stimulants and alpha agonists or atypical antipsychotics have shown improvement in patients with ADHD and comorbid ODD (Liu et al., 2019; Steiner & Remsing, 2007). In clinical trials, atypical antipsychotics showed a positive impact on disruptive behavior but was more costly and less effective than stimulants for treating ADHD (Liu et al., 2019). Of the atypical antipsychotics, risperidone has been studied the most. In cases of severe, chronic ODD, pharmacotherapy may be prolonged (Steiner & Remsing, 2007). If a child fails treatment with an atypical antipsychotic, AACAP recommends switching to a different atypical antipsychotic or to a mood stabilizer .

There are several concerning factors for pharmacotherapy in patients with ADHD and ODD. For instance, aggressive behavior and hostility are potential side effects of stimulants and also coincide with the symptoms of ODD (Liu et al., 2019). Furthermore, a potential conflict exists between the dopamine agonist effects with stimulants and dopamine antagonist effects of antipsychotics. Finally, safety and efficacy of combination therapy has not been well established, and possible side effects are substantial.

Autism Spectrum Disorder

ASD and ADHD often present as comorbid conditions with between 30% and 50% of individuals diagnosed with ASD demonstrating ADHD symptoms and nearly 66% of individuals with ADHD demonstrating ASD features (Davis and Kollins, 2012). Individuals with comorbid ASD and ADHD usually demonstrate higher levels of psychopathology, lower levels of functioning and more severe social impairment compared to those with ASD alone (Casseus et al., 2023).

Studies have shown stimulant and nonstimulant medications can be effective for managing ADHD symptoms in ASD (Hirota and King, 2023). Individuals with comorbid ADHD and ASD are more likely to experience side effects with simulant medication than those with ADHD alone and usually have lower response rates (Hirota and King, 2023; Research Units on Pediatric Psychopharmacology Autism Network [RUPP], 2005). The effect of treatment is usually limited to ADHD symptoms like hyperactivity and inattention rather than core ASD symptoms such as irritability or social withdrawal (Davis and Kollins, 2012).

Nonstimulant medications including ATX and guanfacine also have been shown to reduce ADHD symptoms in individuals with ASD and ADHD (Antshel & Russo, 2019). Most studies focusing on treatment of comorbid ADHD and ASD have used immediate-release MPH (Ghuman et al., 2009; Greenhill et al., 2006; RUPP, 2005), and a potentially fruitful area of future research could include investigating the effectiveness of long-acting stimulant formulations, different stimulant medications (dextroamphetamine, lisdexamfetamine) and different nonstimulant medications (clonidine, venlafaxine, bupropion).

The ability of cannabidiol to modulate neurotransmitters and act on social behavior has made it an emerging area of study for many conditions including ASD and ADHD, but overall safety, efficacy and an adequate therapeutic window must be determined before it could be safely used in practice, particularly for those with ASD (Pedrazzi et al., 2022).

Substance Use Disorder

Youth and adolescents with ADHD are at high risk for SUD during their lifetime (Taubin et al., 2022). The link between these two diagnoses could be explained by commonalities in genetic makeup, dysfunction of the cortical reward-system, or factors affecting general vulnerability (Özgen et al., 2021). Additionally, the link between SUD and ADHD has been observed to be bi-directional: those with a diagnosis of ADHD are at high risk for SUD, while the symptomatic consequences of ADHD may contribute to the development of SUD.

While some literature exists, there is little reported on ADHD and SUD in childhood and adolescents within the last 5−8 years. That which does exist, in addition to adult studies, suggest prioritization for ADHD screening and initiation of early treatment where applicable. A 2021 international consensus study concluded that nonpharmacologic treatments such as psychoeducation, cognitive behavioral therapy, and motivational interviewing should be considered in addition to pharmacologic treatment. When considering treatment options, nonstimulants options such as ATX, may be of some benefit, though Barbuti et al. (2023) suggest that this, as well as stimulant medications will likely contribute to improvement of ADHD symptoms, but not necessarily SUD. Additionally, providers should be aware that stimulant medications may require higher-than-typical dosing in adolescents with SUD (Özgen et al., 2021). Providers should be aware of the risk for stimulant misuse with frequent screening and close monitoring.

Tic Disorders

One of the most common comorbidities experienced by pediatric patients with ADHD is Tic Disorders (TD). Studies have shown 7% to 20% of pediatric patients with ADHD have a concomitant diagnosis of TD. Up to 60% of patients with TD will also receive an ADHD diagnosis (Jaffe and Coffey, 2022; Ogundele & Ayyash, 2018; Osland et al., 2018). Physiological inhibition deficits noted in the frontal lobe may contribute to the presence of the comorbidities (Jaffe and Coffey, 2022; Rothenberger & Heinrich, 2022). Additionally, myelination within these regions through childhood and adolescence may improve symptoms for both diagnoses (Jaffe and Coffey, 2022). The impact of coexisting ADHD and TD on patient outcomes can be significant. Studies have shown increased conflicts in peer relationships, learning, and diminished quality of life (Jaffe and Coffey, 2022; Rothenberger & Heinrich, 2022). A child with ADHD and suspected TD should complete a thorough diagnostic evaluation. Assessment tools, such as the Tic Symptom Self Report for patients and families and the Yale-Global Tic Severity Scale for clinicians, can help make the diagnosis (Jaffe and Coffey, 2022).

Since TD tends to evolve and waver, a child may experience extended periods of time without any symptoms (Jaffe and Coffey, 2022). Tics typically worsens through preadolescence but improve by early adulthood. Therefore, because ADHD is more persistent and frequently more disruptive, treating ADHD in these children is the priority (Jaffe and Coffey, 2022; Osland et al., 2018). Stimulants are the first line of therapy for children with ADHD with or without tics. Effectiveness between the stimulant categories is similar (Osland et al., 2018). Current FDA contraindications and warnings remain regarding potential exacerbation of TD with the use of these medications based upon case reports in the 1970s and 1980s (Jaffe and Coffey, 2022). However, several studies, including a Cohen meta-analysis, have shown no increase of TD with the use of stimulants (Jaffe and Coffey, 2022; Osland et al., 2018). Length of treatment, duration of action, and stimulant category also did not affect the presence or worsening of tics (Osland et al., 2018). In only one, three-week study, high dose dextroamphetamine reportedly worsened tics. Other studies did not show a relationship between dose and tic severity. Alpha-agonists such as clonidine and guanfacine represent another option for treatment and are the first-line of treatment for tics. Due to lower sedation effects and longer half-life, guanfacine is recommended over clonidine when used by itself (Jaffe and Coffey, 2022). One study found the combination of a stimulant and alpha2-agonist showed the best outcomes in treating comorbid ADHD and TD when compared to placebo or either therapy individually (Osland et al., 2018). For those with contraindications for stimulant therapy or when previously discussed medications are not effective, ATX represents another pharmacologic option (Jaffe and Coffey, 2022). Desipramine has been effective for the treatment of ADHD and TD, as well, but its use is limited due to its safety profile (Osland et al., 2018). A nonpharmacologic option for patients with ADHD and coexisting TD is comprehensive behavioral intervention for tics (CBIT), an evidence-based therapy for managing tics (Jaffe and Coffey, 2022). This may be especially poignant for those with worsened TD on stimulant therapy or with significantly impairing tics. CBIT can be combined with any pharmacologic treatment.

Epilepsy

ADHD is a well-recognized comorbidity of epilepsy in pediatric and adult patients alike, with higher epilepsy severity

linked to higher risk of ADHD (Ono et al., 2022). Domains most affected appear to be executive function and attention with poor planning, initiation, impulse control, and problem solving of complex issues. Clinicians caring for those with epilepsy should prioritize evaluation for ADHD symptomatology to lessen the burden on quality of life.

Ono et al. (2022) recommend that all children with epilepsy and suspected ADHD undergo neuropsychological testing. Treatment thereafter should include psychosocial treatment for patients of all ages, in combination with stimulant medication for those over the age of 6 years of age. For those under 6, stimulants should be considered if psychosocial treatment fails. In both age groups, next options would include nonstimulant medication choices (i.e., ATX, guanfacine).

Leeman-Markowski et al. (2021) reported MPH as an effective treatment option in adult patients with epilepsy and ADHD. This did not produce a statistically significant seizure rate increase and helped to improve ADHD symptoms. Interestingly, and in contrast, Ono et al. (2022) describes a 10%–15% increase in seizure rate in those with epilepsy taking MPH, in addition to improved ADHD symptoms. This contrast demonstrates the need for close clinician monitoring for unacceptable side effects. Additional research is also recommended to strengthen guidance on treatment for children and adolescents with comorbid epilepsy and ADHD.

Learning Disabilities

An estimated 5% to 15% of children have a LD, which is a persistent impairment in reading, written expression and/or math (Frolov and Schaepper, 2021). LD occur in upto 25% of cases of children with ADHD (DuPaul and Stoner, 2014). Individuals with comorbid ADHD and LD are undertreated compared to peers with ADHD alone, possibly due to providers attributing school performance problems to the LD alone and lacking sufficient studies to change negative perceptions they may have about treating this population (Williamson et al., 2014). Another challenge affecting treatment is conflicting results of the available studies. A 2006 study by Grizenko et al. (2006) found that the response of children ages 6 to 12 years old with co-occurring ADHD and LD to MPH dosed twice a day was lower than that of children with ADHD alone, those with a mathematics impairment having a particularly low response rate (Grizenko et al., 2006). Williamson et al. (2014) assessed the use of Osmotic Oral Release System MPH in children aged 9 to 12 years old with ADHD with and without LD. The authors found that children in both groups showed improved performance with medication (Williamson et al., 2014). Higher doses were usually needed for those with comorbid ADHD and LD (Williamson et al., 2014). Differences in the results could be due to many factors, most obviously the use of immediate release versus long-acting MPH, but this demonstrates the need for further research into the treatment of those with ADHD and LD.

Sleep Disorders

Sleep disorders impact up to 70% of individuals with ADHD compared to 20%–30% of unaffected peers (Larsson et al., 2023). Multiple factors likely contribute to this high overlap including shared neurobiological pathways affecting regulation and arousal; side effects of stimulant medication, particularly longer-acting formulations; ADHD-associated disruptive behavior; and frequent comorbid psychiatric disorders that also impact sleep quality (Tsai et al., 2016). While environmental and behavioral interventions remain core sleep improvement strategies, sleep problems often persist despite these changes (Stein et al., 2022). A multimodal approach to treatment may be most effective (Stein et al., 2022)

One of the most common medications used for sleep in those with ADHD is melatonin, which is a hormone secreted by the pineal gland that aids in regulation of the sleep-wake cycle (Moon et al., 2022). Exogenous melatonin can advance the onset of endogenous melatonin and shorten sleep onset latency. The use of melatonin in children is supported by published guidelines (Salanitro et al., 2022). Melatonin increases total sleep time and decreases sleep onset latency but does not decrease nighttime waking (Bruni et al., 2015). Current expert-based dosing recommends a maximum of 3 mg/nocte for children and 5 mg/nocte for adolescents, although some studies show that higher doses may be beneficial and further research on maximum doses is needed (Salanitro et al., 2022). There is no current evidence demonstrating that long-acting formulations are superior to immediate-acting formulations (Bruni et al., 2015).

Clonidine is an alpha2-agonist that is FDA-approved for the treatment of ADHD in children, but there has been increasing interest in "off-label use" as a sleep medication (Jang et al., 2022). The use of clonidine to treat sleep disturbances in ADHD has shown adequate safety and efficacy (Tsai et al., 2016), although most evidence has come from observational case studies or retrospective chart review (Stein et al., 2022).

Given how prevalent sleep problems are in this population, there are surprisingly few studies investigating alternative medications, and areas of potential future research in those with comorbid ADHD and sleep problems include medications commonly used "off-label" for sleep in children and adolescents (hydroxyzine, diphenhydramine, trazodone, or mirtazapine), as well as those that can be used in adults, (eszopiclone, zolpidem, or ramelteon).

CONCLUSION

ADHD is the most common mental health disorder among children and adolescents, and patients are at a higher risk of medication side effects, impaired functioning, and lifelong adverse outcomes when ADHD presents with comorbidities. This investigation summarizes recommended ADHD treatment in the context of common co-occurring conditions based on current available studies but also highlights the need for further research and standardized treatment guidelines. Given this lack of evidence and guidance, patients

may be at risk for insufficient treatment. Providers who treat pediatric patients with ADHD should be aware of the best available treatment options as well as the limitations of available research when developing individualized treatment plans and counseling patients and their families about their options. Given the prevalence of ADHD, more robust investigation into ADHD and comorbidity treatments could benefit clinicians, patients, and their caregivers.

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CONFLICTS OF INTEREST

No relevant conflicts of interest to disclose.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

No AI or AI-assisted technologies were used for the writing process.

SUBMISSION DECLARATION

The article has not been previously published and is not under consideration for publication elsewhere.

ETHICAL STATEMENT

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AUTHOR CONTRIBUTIONS

Molly A. Lalonde, MS collaborated in conceptualizing and designing the article, completed background research, drafted the initial manuscript, and critically reviewed and revised the manuscript.

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SUPPLEMENTARY MATERIALS

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CE QUESTIONS

1. The best initial treatment for a child exhibiting primarily ADHD symptoms with mild anxiety is
   A. Atomoxetine
   B. Methylphenidate
   C. Clonidine
   D. Fluoxetine

2. According to the research in the article, the best medication option for a child with ADHD and severe anxiety who failed treatment with atomoxetine and methylphenidate is
   A. Guanfacine
   B. Clonidine and methylphenidate
   C. Fluoxetine
   D. Guanfacine and atomoxetine

3. Stimulant therapy for children with ADHD and ODD should only be prescribed
   A. In conjunction with an alpha-agonist therapy
   B. By itself
   C. As adjunct treatment with psychotherapy
   D. After failed treatment with an atypical antipsychotic

4. Which of the following medications has been shown to reduce ADHD symptoms in a child with ASD?
   A. Bupropion
   B. Dextroamphetamine
   C. Venlafaxine
   D. Atomoxetine

5. An adolescent reveals during a well check that they have been drinking alcohol 4 days per week, and grades are falling. After discussing risk behavior, and considering alcohol cessation resources, the provider should prioritize screening for ADHD. T/F

6. A majority of the research supports avoiding stimulants in children with ADHD and tic disorders due to the worsening of tics with this class of medication. T/F

7. In children with ADHD and tic disorders who have failed stimulant therapy, the next BEST course of treatment is
   A. Atomoxetine
   B. Desipramine
   C. Guanfacine
   D. Risperidone

8. Evaluation of all children with epilepsy should include
   A. Neuropsychological testing
   B. Transcranial magnetic stimulation
   C. Functional magnetic resonance imaging
   D. Autism Diagnostic Interview-Revised

9. Children with co-morbid ADHD and learning disabilities are less likely to be treated with medication than peers with ADHD alone. T/F

10. Which medication would be the best initial treatment for a child with ADHD and difficulty falling asleep?
    A. Guanfacine
    B. Melatonin
    C. Hydroxyzine
    D. Trazadone

Answers available online at ce.napnap.org.