

The efficacy and safety of antidepressants as alternative treatment of attention-deficit/hyperactivity disorder in pediatric populations

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Abstract

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a common, multifactorial neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and/or impulsivity. Beyond behavioral therapy approaches, methylphenidate and amphetamine stimulant agents are recommended as first-line pharmaceutical treatments for ADHD. Because of the adverse effect profile and misuse potential of stimulants, other psychiatric medications have been explored in the literature as a potential alternative treatment in pediatric patients with ADHD. This report aimed to consolidate the body of knowledge published surrounding the exploration of using the antidepressant class as primary treatment for ADHD in pediatric and adolescent populations.

Methods: PubMed secondary databases were used. Key terms included *pediatric ADHD*, *ADHD*, *ADHD treatments*, and *antidepressants in ADHD*. Randomized control trials and observational trials were included for analysis.

Results: Most (11/12) studies revealed that antidepressants were efficacious in reducing ADHD symptoms but not necessarily superior to first-line stimulant medications. Particular focus on selective serotonin reuptake inhibitors, SNRIs, tricyclic antidepressants, and bupropion was demonstrated in the literature.

Discussion: More research needs to be conducted to fully explore the effects and efficacy of antidepressants compared with first-line medications for ADHD. In addition, data supporting long-term effects and efficacy for antidepressants in ADHD are not yet established.

Keywords: ADHD, antidepressants, pediatrics, child, adolescent

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Introduction

Attention-deficit/hyperactivity disorder (ADHD), previously known as attention-deficit disorder (ADD), is a common neurodevelopmental disorder where patterns of inattention, hyperactivity, and/or impulsivity are displayed, interfering with social, occupational, or academic tasks.¹ ADHD is most often diagnosed in childhood, and treatments are aimed at improving symptoms, along with maximizing school performance and overall functioning. A 2022 national parent survey estimates that 11.4% of children aged 3 to 17 years in the United States have been

diagnosed with ADHD.² Male children are almost twice as likely to be diagnosed with ADHD.² A 2023 review encompassing 588 studies with 3 277 590 participants estimates that the global prevalence of ADHD in children and adolescents is 8%.³

Etiology of ADHD

ADHD is a multifactorial disorder with multiple genetic and environmental causes.⁴ One proposed etiology is reduced activity in the prefrontal cortex, cerebellum, and caudate, which are areas responsible for regulating behavior and attention.⁵ Dysfunction of the prefrontal cortex may impair regulation of attention, behavior, and emotion in patients with ADHD. Other notable theories are the hypoactive and hyperactive catecholamine hypotheses.⁵ Disruptions in dopamine and norepinephrine levels, in excess or deficiency, can impair prefrontal cortex function, causing ADHD symptoms.⁵ Dysfunction in noradrenergic systems creates abnormal levels of norepinephrine and dopamine, and may contribute to symptoms.⁶ This is supported by examining the mechanism of action of first-line stimulants for ADHD. Methylphenidate (MPH) and amphetamines block the reuptake of norepinephrine and dopamine, boosting catecholamine levels and improving symptoms.⁷ Emerging evidence indicates that dysregulation of the serotonin system may also contribute to ADHD, particularly through its role in modulating impulsivity, emotional regulation, and cognitive control. Genetic studies have identified polymorphisms in serotonin transporters and receptors. At the same time, neuroimaging findings suggest that serotonin interacts with dopamine systems at neural sites, such as presynaptic terminals and receptor subtypes, potentially creating neurotransmitter imbalances and influencing distinct ADHD phenotypes.⁸

Current Treatment Options

Parent training in behavioral management is recommended by the American Academy of Pediatrics (AAP) for first-line treatment in children aged 4 to 6 years with ADHD.⁹ In children 6 to 12 years, parent training in behavioral management and/or behavioral interventions is recommended along with pharmacological therapy.⁹ The AAP recommends stimulants as first-line pharmacotherapy for the treatment of ADHD in children 6 years and older.⁹ AAP guidelines also recommend that FDA-approved nonstimulants for ADHD (atomoxetine, and the long-acting alpha 2 adrenergic agonists, guanfacine and clonidine) be used as an adjunct to stimulants if needed in children 6 years or older or as monotherapy.⁹ The FDA-approved stimulants are MPH, amphetamines, dexamethylphenidate, and mixed amphetamine salts, available in both immediate- and extended-release formulations.¹⁰ However, misuse potential is a major concern. Stimulants are schedule II-controlled

medications, with risk for dependence, and have the tightest regulations of all prescription medications.¹¹ Children and adolescents with ADHD are reportedly more likely to misuse their medications compared with those using medications for other conditions, and adolescents who misuse stimulants are more likely to be diagnosed with substance use or conduct disorder.¹² However, a 2023 study found that there was no increased or decreased risk for later substance use disorder in children and adolescents treated with stimulants for ADHD.¹³ Stimulants should be prescribed with caution, especially if patients have a history of comorbid substance use disorder.¹⁴ Access to stimulants has also been unstable, with numerous supply shortages occurring since 2022.¹⁵ The coronavirus 2019 pandemic was associated with increases in prescriptions for stimulants and nonstimulants used to treat ADHD. A 2024 study found a 30% increase in schedule II-controlled medication prescriptions in patients aged 20 to 39 years, and an 81% increase in nonstimulant ADHD medication prescriptions in patients aged 20 to 39 years.¹⁶ In patients 20 years or younger, schedule II-controlled medication prescriptions decreased by 1% after the pandemic, and nonstimulant prescriptions in patients 20 years and younger increased by 7%.¹⁶ These increased rates of prescribing in adults may affect the availability of stimulants in pediatric patients. The risk of cardiovascular injury is another concern, including possible minimal increases in blood pressure and heart rate.⁹ Pediatric patients with preexisting heart conditions, history of symptoms like palpitations or syncope, or family history of heart conditions should be evaluated further with an electrocardiogram and/or cardiology referral.^{9,17}

Although stimulants are fast-acting and effective, their adverse effects and risks, coupled with persisting medication shortages, prompt the exploration of other medications that may equally mitigate symptoms. The American Academy of Child and Adolescent Psychiatry's (AACAP) guidelines recommend any agent approved by the FDA for first-line treatment of ADHD, not just stimulants.¹⁸ The AACAP also recommends atomoxetine as first-line pharmacotherapy for patients with intolerance to stimulants (ie, mood lability), comorbid anxiety, active substance misuse, or tics.¹⁸ The nonstimulants clonidine and guanfacine are more often used to treat ADHD in comorbid disorders or in conjunction with stimulants to mitigate stimulant-induced insomnia or tics.¹⁸ These medications are less widely used due to lower efficacy compared with stimulants. Although these agents are helpful with hyperactivity or impulsive symptoms, they are less effective for inattention.^{9,18}

Antidepressants are currently approved in pediatric patients for MDD, generalized anxiety disorder, and obsessive-compulsive disorder.¹⁹ For ADHD, the AACAP's guidelines mention off-label use of bupropion, nortriptyline, or imipramine if a patient fails a trial of FDA-approved medications.¹⁸ These are not as widely studied as FDA-approved options,

and their efficacy is comparable to behavioral therapy.¹⁸ Of note, antidepressant use in pediatric populations has been associated with increased suicidality, leading to the FDA-issued boxed warnings on common antidepressants, including fluoxetine, venlafaxine, and bupropion.²⁰ This warning does not mean these medications are contraindicated in pediatric populations, but rather reminds clinicians to balance potential risks with the hopeful benefits of these medications. It has also been suggested that the warning may reflect an increase in patient reporting of suicidal thoughts/behaviors, rather than an actual rise in occurrence.²⁰

Pharmacology of Antidepressants and Role in ADHD Treatment

Antidepressants have been theorized to work for the treatment of ADHD because of their actions on the neurotransmitters norepinephrine, serotonin, and dopamine. As discussed above, an imbalance of these may contribute to the etiology of ADHD.⁵

Selective serotonin reuptake inhibitors (SSRIs) increase concentrations of serotonin at nerve endings by inhibiting serotonin reuptake channels.²¹ SSRIs are generally considered safe (low risk of seizures and minimal toxicity in overdose) with better tolerability than other antidepressants.²¹ SNRIs inhibit serotonin and norepinephrine from reuptake at nerve endings, increasing their availability.²¹ This class avoids interaction with histaminic and cholinergic-adrenergic receptors, and is associated with fewer adverse effects, compared to tricyclic antidepressants (TCAs).²¹ One SNRI, venlafaxine, has dose-dependent properties as well. At doses less than 150 mg, it mainly inhibits serotonin reuptake, while at 150 mg or more, this agent inhibits reuptake of both serotonin and norepinephrine.²² At doses of 150 mg or more, venlafaxine also has some weak dopamine reuptake inhibition.²¹ SNRIs have similar efficacy and safety profiles to SSRIs, but can also cause hypertension.¹⁹ An increase of up to 15 mm Hg can occur with venlafaxine.²³ Inhibition of presynaptic norepinephrine reuptake indirectly increases synaptic dopamine levels, resulting in a cascade of increased sympathetic stimulation, higher cardiac output, and therefore raised blood pressure.²³ TCAs work by blocking reuptake of norepinephrine, serotonin, and dopamine, which influence the noradrenergic and dopaminergic systems to target cortical function.²⁴ TCAs also block histaminic, cholinergic, and alpha-1-adrenergic sites, creating troublesome side effects like dizziness, sedation, and orthostatic hypotension.²¹ Among TCAs, there is variation in selectivity at receptors. For instance, desipramine is more selective for the norepinephrine transporter. Clomipramine, however, is more selective for the serotonin transporter.²⁵ Last, the atypical antidepressant bupropion acts uniquely; it inhibits the reuptake of norepinephrine

and, to a lesser extent, dopamine. It has no interaction with histaminic, cholinergic, or alpha-1-adrenergic sites.²¹

This review will focus on studies evaluating the efficacy of medications that are FDA approved for depression in the antidepressant class, when used as monotherapy for ADHD, including SSRIs, SNRIs, TCAs, and bupropion.

Methods

An electronic literature review of articles from 1970 to 2024 was conducted using PubMed. The initial search reviewed *ADHD AND pediatrics AND antidepressants NOT adult*. Other key search terms included *pediatric ADHD, ADD, ADHD treatments, antidepressants in ADHD, ADHD in youth, AND ADHD in adolescents*. Only trials comparing antidepressants against first-line stimulants or placebo were included. Existing literature reviews were excluded; however, additional studies were identified from the reference lists of these reviews. Studies investigating any adult patients, or where the participants did not have an ADHD or ADD diagnosis, were excluded. Studies that described symptoms as “ADHD-like,” studies not in English, case studies, and studies where participants had any history of depression were also excluded. Studies where the primary measured outcomes were not behavioral ADHD symptoms were excluded. Viloxazine (approved for use after publication of treatment guidelines) and atomoxetine, commonly used nonstimulants for ADHD and classified as selective norepinephrine reuptake inhibitors, may be considered antidepressants. However, they are not FDA approved for depression.^{26,27} Because this review focuses specifically on FDA-approved antidepressants for pediatric ADHD, studies related to these 2 medications fall outside the defined scope.

Results

With the aforementioned search parameters, 217 articles were initially returned. Of these, 2 met the inclusion criteria. Subsequent searches with other key terms identified 10 additional articles that met the inclusion criteria. In the reviewed studies, the antidepressants of focus included fluoxetine ($n = 1$), venlafaxine ($n = 4$), desipramine monotherapy ($n = 3$), clomipramine plus desipramine ($n = 1$), and bupropion ($n = 3$).

Scales

The studies used various scales to evaluate the impact of medication on behavioral symptoms. Variations of the Conners Parent Rating Scale (CPRS) and the Conners Teacher Rating Scale (CTRS) were most commonly employed. Table 1 describes significant behavioral scales used across studies. Results from less frequently used scales will be discussed in

Table 1: Descriptions of the most significant behavioral scales used across studies

Scale	Description	Categories/Symptoms Evaluated
Original 39-item CTRS ⁴⁹	Divided into factors 1–5. Uses a 4-point Likert scale, ranging from a score of not at all (0) to very much (3). Scores are summed and converted to a T score. T-score interpretation: 1. 60–64: High average, borderline 2. 65–69: Elevated, significant concerns 3. ≥70: Very elevated, clinically significant ⁵⁰ Ten statements primarily focused on hyperactivity and excitability traits. Uses a 4-point Likert scale, where parents or teachers rate the extent to which they agree with statements related to hyperactivity. A raw score is summed, for a maximum score of 30. A score of 15 is generally considered the cutoff for ADHD. ⁵²	1. Defiance and aggression 2. Day-dreaming and inattention 3. Fear and anxiety 4. Hyperactivity ⁴⁹ 5. General health ⁴⁹
Abbreviated 10-item version of the Conners Scale, also referred to as the HI ⁵¹		1. Restlessness/overactivity 2. Excitable, impulsivity 3. Disturbs other children 4. Short attention span 5. Constantly fidgeting 6. Easily distracted 7. Easily frustrated 8. Cries often and easily 9. Mood changes quickly and often 10. Temper outbursts ⁵¹
48-item CPRS ⁵³	Divided into 6 factors, along with the 10-item HI. Uses a 4-point Likert scale, ranging from a score of never (0) to very much (3). T-score interpretation: 1. 60–64: High average, borderline 2. 65–69: Elevated, significant concerns 3. ≥70: Very elevated, clinically significant ^{50,54} This is derived from the Conners scales. A score of 30 indicates severe symptoms present. ⁵⁵	1. Conduct problem 1 2. Learning problems 3. Psychosomatic 4. Impulsivity and hyperactivity 5. Conduct problem 2 6. Anxiety + 10-item HI ⁵³
IOWA-Conners Parent and Teacher Questionnaire ⁵⁵		5-item inattention-overactivity subscale 1. Fidgets 2. Hums/makes other odd noises 3. Excitable, impulsive 4. Inattentive, easily distracted 5. Short attention span 5-item aggression subscale 1. Quarrelsome 2. Acts 'smart' 3. Temper outbursts, explosive behavior 4. Defiant 5. Uncooperative ⁵⁵
ARS-IV ^{56,57}	This can be completed by both parents and teachers; it is based on ADHD criteria from the fourth edition of the DSM. Scores are assigned for each behavior on a scale of 0–3, with 0 indicating that behavior is shown never to 3 indicating very often. Scores are summed and can be converted to T scores. Clinical elevations are usually indicated by T score > 65. ⁵⁶	1. Hyperactivity subscale a. On the go b. Runs about c. Difficulty waiting turn d. Interrupts e. Difficulty playing f. Blurts out answers g. Leaves seat h. Talks excessively i. Fidgets

Table 1: Descriptions of the most significant behavioral scales used across studies (continued)

Scale	Description	Categories/Symptoms Evaluated
CGI-S ⁵⁸	7-point scale that assigns ratings to a patient based on severity of illness after a trial compared with before. Clinicians complete this scale.	2. Inattentive subscale a. No follow through b. Forgetful c. Difficult organizing d. Avoids tasks e. Fails to give close attention f. Easily distracted g. Difficulty sustaining attention h. Loses things ⁵⁶ i. Does not listen ⁵⁶ 1 = Normal, not at all ill 2 = Borderline mentally ill 3 = Mildly ill 4 = Moderately ill 5 = Markedly ill 6 = Severely ill 7 = Among the most extremely ill patients ⁵⁸
CGI-I ⁵⁸	Assesses the extent of change from initiation of treatment. Clinicians assign ratings comparing the patient's condition before and after medication initiation in the study.	1 = Very much improved since the initiation of treatment 2 = Much improved 3 = Minimally improved 4 = No change from baseline (initiation of treatment) 5 = Minimally worse 6 = Much worse 7 = Very much worse since the initiation of treatment ⁵⁸

ADHD = attention-deficit/hyperactivity disorder; ARS = ADHD Rating Scale; CGI-I = Clinical Global Impressions Improvement Scale; CGI-S = Clinical Global Impressions Severity Scale; CPRS = Conners Parent Rating Scale; CTRS = Conners Teacher Rating Scale; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; HI = Hyperactivity Index; IOWA = Inattention-Overactivity With Aggression.

the context of each study, where relevant, to further illuminate findings. To establish a diagnosis of ADHD or ADD, all studies implemented criteria from the third or fourth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Table 2 summarizes all studies, and specifically notes which diagnostic tools and diagnoses were used by each study.

Selective Serotonin Reuptake Inhibitors

Fluoxetine's efficacy for ADHD was assessed in an open-label study of 19 patients (7–15 years), with 84% being male and 16% being female. Participants started on 20 mg of fluoxetine daily, with the dose adjusted on an individual case-by-base basis determined by side effects. Doses ranged from 20 to 60 mg daily, with the average daily fluoxetine dose being 27 mg or 0.6 mg/kg/day. There was no comparator. On the 10-item CPRS, there was a significant reduction in symptoms; the sample mean score was 23 at baseline and decreased to 10 at week 6 ($p < 0.001$).²⁸ The 10-item CTRS sample mean also indicated a statistically significant improvement from 18 at baseline to 14 at the conclusion of the study ($p = 0.014$). On the Clinical Global Impressions Severity (CGI-S) scale, there was a significant improvement in severity of symptoms rating, declining from 6 at baseline (severe) to 3.4 after the study (mild severity) ($p < 0.001$).²⁸ The study did not report on suicidal thoughts or behaviors.²⁸

Serotonin Norepinephrine Reuptake Inhibitors

The SNRI, venlafaxine, was the focus of 4 studies. In a 6-week open trial of 13 patients (6–15 years) venlafaxine was titrated from 18.75 mg/day to a maximum of 56.25 mg/day (mean, 40.38 ± 7.04 mg/day) or until side effects were experienced.²⁹ There was no comparator. Significant improvements were seen on 10-item CPRS scores, going from a baseline mean of 20 to an endpoint mean of 14.46 ($p < 0.002$).²⁹ More specifically, there was a statistically significant improvement in short attention span ($p < 0.01$), easy distractibility ($p < 0.05$), easy frustration ($p < 0.001$), and quick mood change ($p < 0.05$) items of the CPRS.²⁹ CGI-S scores were also improved from a baseline mean of 4.84 to an endpoint mean of 3.53 ($p < 0.05$).²⁹ Side effects noted were somnolence, stomach ache, and headache, which all resolved after week 2. Three subjects also experienced sedation at the maximum dose of 56.25 mg/day and had their dose decreased to 37.5 mg/day. Suicidality was not discussed.²⁹

Another open-label study was done over 5 weeks with 16 subjects (8–17 years). Venlafaxine was initiated at 12.5 mg and increased by 25 mg weekly to a maximum of 75 mg in children weighing more than 40 kg, and by 12.5 mg weekly to a maximum of 50 mg in children weighing less than

40 kg.³⁰ Mean dosing was 60 mg/day for completers, divided into 2 to 3 doses. There was no comparator. Three subjects discontinued because of hyperactivity, 1 from nausea, and 2 were lost to follow-up.³⁰ Of those remaining, improvement was indicated in the impulsivity or hyperactivity factor ($p = 0.008$) and Hyperactivity Index ($p = 0.003$) of the 48-item CPRS, but not on the Conduct Index ($p = 0.103$).³⁰ Cognition was assessed before and after the trial with the 1992 Continuous Performance Test (CPT). This involves presenting a series of letters to the child, instructing them to press a button on presentation of every letter except the letter X.^{30,31} Cognition was measured via reaction time, and errors of omission and commission; venlafaxine did not have any statistically significant effects on these.³⁰ Responders typically had fewer comorbidities (1–2) than nonresponders (2–3). Mild side effects reported were nausea, increased activity, drowsiness, and irritability. There were no changes in blood pressure or heart rate. Suicidality was not discussed in this study.³⁰

The third study of venlafaxine enrolled 21 children and 17 adolescents (5–17 years) in a 2-week open-label trial. Participants were given 0.5, 1, or 2 mg/kg/day of venlafaxine for 2 weeks, divided twice daily (BID) (max doses, 37.5, 75, and 150 mg/day).³² There was no comparator. On the Parent ADHD Rating Scale (ARS)-IV, significant improvement was shown across all subscales ($p < 0.001$). Teacher ARS-IV ratings showed significant improvement in inattentive symptoms only ($p = 0.02$). Patients with a Clinical Global Impressions Improvement (CGI-I) or CGI-S score of 1 or 2 were classified as “responders” to treatment.³² Of patients, 36% were responders based on CGI-I scoring, while 5% met responder criteria by CGI-S scoring.³² Headache and nausea were the most frequent side effects, with no reports of suicidal thoughts or behaviors. There was a statistically significant increase in diastolic blood pressures ($p = 0.04$), but no other significant differences in mean pressures or pulse.³²

The last study, a 6-week, parallel group, randomized clinical trial, enrolled 38 children (6–13 years) randomly assigned to receive MPH or venlafaxine. For venlafaxine, subjects received 50 mg/day (< 30 kg) or 75 mg/day (> 30 kg). During week 1, 25 mg venlafaxine was given once daily, 25 mg BID in week 2, and 25 mg 3 times daily (TID) for those weighing more than 30 kg in week 3. Dosing of MPH was similar, 20 mg/day for subjects weighing less than 30 kg and 30 mg/day for subjects weighing more than 30 kg.³³ MPH was given at 5 mg BID in week 1, 10 mg BID in week 2 (one capsule in the morning and 1 at midday), and titrated to 10 mg TID in week 3 for children weighing more than 30 kg (1 in the morning, 1 at midday, and 1 at 16:00). These were the maximum doses. The Parent and Teacher ARS-IV Scales were used to measure outcomes. The number of “responders,” or participants who

Table 2: Summary of all studies

First Author	Study Design and Washout Periods	Medications or Comparators	Diagnostic Procedures and Initial Screening Tools	Study Population Diagnoses	Primary Outcome Measures	Main Results and Conclusions
Barrickman, 1991 ²⁸	6-week, outpatient, open-label trial 2-week washout period	Fluoxetine hydrochloride only	DSM-III-R Criteria for ADHD Kiddie-SADS-E	ADHD (unspecified subtypes) Conduct Disorder Developmental Learning Disorder	10-item CPRS 10-item CTRS CGI-S Scale	Fluoxetine showed significant improvements in ADHD symptoms on the CTRS ($p = 0.014$) and CPRS ($p < 0.001$) and may be effective for treatment
Mukkaades, 2004 ²⁹	6-week, inpatient, open trial Must have been free of medications for 2 weeks	Venlafaxine only	DSM-IV Criteria for ADHD	ADHD (combined and inattentive subtypes) Tic Disorder ODD Dyslexia	10-item CPRS CGI-S CGI-I	Venlafaxine resulted in clinically and statistically significant improvements on the CPRS ($p < 0.002$) On the CGI-S there was a statistically significant improvement ($p < 0.05$) 61.5% were considered responders on the CGI-I
Olvera, 1996 ³⁰	5-week, outpatient, open trial 2-week washout period	Venlafaxine only	DSM-IV Criteria for ADHD DISC Parent form	ADHD (unspecified subtypes) GAD Separation Anxiety Disorder Conduct Disorder Social & Simple Phobia	48-item CPRS	Venlafaxine showed improvements on the impulsivity factor ($p = 0.008$) and HI ($p = 0.003$) of CPRS No significant support for improvement in cognitive symptoms with venlafaxine
Findling, 2007 ³²	2-week, outpatient, open-label, control trial Prior psychopharmacologic agents were stopped 1 week before initiating venlafaxine	Venlafaxine only	DSM-IV Criteria for ADHD DISC-IV Kiddie-SADS	ADHD (unspecified subtypes)	CGI-S CGI-I Scale ARS-IV (Parent & Teacher)	On the teacher completed ARS-IV, total scores showed significant improvement from baseline ($p = 0.03$) On the parent completed ARS-IV, significant improvement was shown in total scores, inattentive, and hyperactive-impulsive subscales (all $p < 0.001$)
Zarinara, 2010 ³³	6-week, outpatient, double-blind, parallel group, randomized clinical trial None of the participants were on any psychotropic medications before the start of the study	Venlafaxine vs MPH	DSM-IV Criteria for ADHD ARS-IV Kiddie-SADS Lifetime Diagnostic Interview	ADHD (combined subtype)	ARS-IV (Parent & Teacher)	No significant difference between venlafaxine and MPH Venlafaxine showed a more tolerable side effect profile) lower rates of insomnia and headaches This may make it preferred for those who cannot tolerate these side effects with MPH
Gualtieri, 1991 ³⁴	Inpatient, double-blind, dose-response, crossover, acute effects study None of the participants had responded to previous trials of other psychostimulant medication	Desipramine vs placebo	DSM-III criteria for ADD with hyperactivity	ADHD (unspecified subtypes)	10-item CPRS 10-item CTRS	Desipramine was an effective medication compared with MPH and placebo for behavioral management May enhance memory Slight but significant negative effects on motor performance

Table 2: Summary of all studies (continued)

First Author	Study Design and Washout Periods	Medications or Comparators	Diagnostic Procedures and Initial Screening Tools	Study Population Diagnoses	Primary Outcome Measures	Main Results and Conclusions
Donnelly, 1985 ³⁶	14-day, inpatient, noncrossover, double-blind, placebo-controlled study 2-week washout period	Desipramine vs placebo	DSM-III Criteria for ADD	ADHD (unspecified subtype) Conduct Disorder Oppositional Disorder Reading, Arithmetic, or Language Disorders	10-item CTRS	Desipramine resulted in a significant decrease in actometer-measured classroom motor activity ($p = 0.03$) No significant changes in cognition on commission errors, omission errors, or interstimulus intervals of the Continuous Performance Test Overall concluded that teacher rated inattentive and impulsive behaviors improved with desipramine
Garfinkel, 1983 ³⁸	20-week, inpatient and outpatient, crossover study 2-week washout period	Desipramine, clomipramine, MPH, placebo	DSM-III Criteria for ADD	ADD	39-item CTRS	Overall, MPH is more effective than clomipramine, desipramine, and placebo for controlling behavior symptoms
Biederman, 1989 ⁴⁰	6-week, outpatient, double-blind, parallel, placebo-controlled study 1-week washout period	Desipramine vs placebo	DSM-III Criteria for ADD DICA-P for ADD	ADD with hyperactivity ADD without hyperactivity Unspecified Learning Disorders Conduct Disorder ODD	10-item CPRS 10-item CTRS CGI-I CGI-S	Desipramine showed statistically significant improvements in ADHD symptoms on the CGI-S ($p < 0.0001$), CPRS ($p < 0.001$), and CTRS ($p < 0.01$) May be an effective treatment option
Conners, 1996 ⁴¹	6-week, multisite, outpatient and inpatient, randomized, double-blind, parallel group study Participants were free of any psychotropic medications for 14 days before the study	Bupropion vs placebo	DSM-III criteria for ADD	ADHD (unspecified subtypes)	10-item CPRS 10-item CTRS 93-item CPRS 39-item CTRS CGI-S CGI-I	Bupropion showed clinically significant improvement in behavior by teachers and parents, along with modest benefits on attention and memory It may be a useful add-on treatment for ADHD and for conduct disorder
Barickman, 1995 ⁴³	6-week, outpatient double-blind, crossover study 2-week washout period preceding the study; 2-week washout period in between 2 drug phases	Bupropion vs MPH	DSM-III Criteria for ADD Kiddie-SADS-E	ADHD (unspecified subtypes) Conduct Disorder ODD	CGI-S IOWA-Conners Parent and Teacher Questionnaire	There was no significant difference between the efficacy of MPH and bupropion for ADHD
Jafarinia, 2012 ⁴⁴	6-week, outpatient, randomized, double-blind study Participants had to be free of any psychotropic medications for at least 14 days before being eligible	Bupropion vs MPH	DSM-IV Criteria for ADHD ARS-IV Kiddie-SADS Schizophrenia-Present and Lifetime Diagnostic Interview	ADHD (unspecified subtypes)	ARS-IV (Parent & Teacher)	Bupropion and MPH showed to be similar in efficacy and safety Bupropion did not show any superior benefit in efficacy but had lower rates of headaches compared with MPH

ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; ARS = ADHD Rating Scale; CGI-I = Clinical Global Impressions Improvement Scale; CGI-S = Clinical Global Impressions Severity Scale; CPRS = Conners Parent Rating Scale; CTRS = Conners Teacher Rating Scale; DICA-P = Diagnostic Interview for Children and Adolescents Parents Scale; DISC = Diagnostic Interview Schedule for Children; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; GAD = generalized anxiety disorder; HI = Hyperactivity Index; IOWA = Inattention-Overactivity with Aggression; Kiddie-SADS-E = Kiddie Schedule for Affective Disorders and Schizophrenia Epidemiological Version; MPH = methylphenidate; ODD = Oppositional Defiant Disorder.

experienced at least a 40% decrease in symptoms, was not significant between groups (68.42% venlafaxine compared with 73.68% MPH).³³ Similarly, Teacher ARS-IV outcomes did not differ significantly between baseline and week 6 (63% venlafaxine, 68.42% MPH, $p = 0.30$).³³ The side effects observed in both groups included abdominal pain, restlessness, increases and decreases in appetite, insomnia, vomiting, nausea, somnolence, and headache. Increased appetite was also reported with venlafaxine. Venlafaxine was more tolerable, with significantly lower rates of insomnia ($p = 0.01$) and headaches ($p = 0.05$). The study did not report on suicidal thoughts or behaviors.³³

Tricyclic Antidepressants

An acute-effects placebo-controlled study of 12 patients (6–12 years) used regression analysis to compare placebo with desipramine at 0.5, 1, or 1.5 mg/kg, administered BID.³⁴ The medium dose of desipramine yielded the greatest improvements in clinical significance, global ratings, and 10-item CTRS scores compared with the low and high doses.³⁴ Several cognitive functions were also evaluated. The Finger Tapping Test, which assesses fine motor speed, improved linearly with each increased dose of desipramine ($p < 0.01$). The Trails A Test evaluated the ability to switch sets; performance was the worst with the medium desipramine dose compared with the high and low doses. Performance on this test was the best with the placebo group, although not significant ($p = 0.077$).³⁴ Concerning the Buschke Selective Reminding test, which assesses verbal learning and memory, consistency of recall and delayed sum recall factors were improved on the high dose of desipramine only.^{34,35} Suicidality was not discussed.³⁴

An earlier 2-week, placebo-controlled study of 29 males (6–12 years) initiated desipramine at 25 mg once daily and increased by 25 mg/day, to maximum 100 mg/day.³⁶ A significant improvement of symptoms was shown in the desipramine group on the 10-item CTRS on days 3 and 14, but no improvement was shown in the placebo group ($p = 0.003$).³⁶ Mean weekly activity counts measuring classroom motor activity revealed a significant decrease in classroom motor activity with desipramine. However, there were no significant changes in commission errors, omission errors, or interstimulus intervals of Rosvold's modified CPT.³⁶ This version of the CPT tests sustained attention and alertness. It displays letters to the patient and asks them to press a key only when the letter X is shown.^{36,37} This study also deemed desipramine to be well tolerated. The study did not report on suicidal thoughts or actions.³⁶

Another study of TCAs enrolled 12 males (5.9–11.6 years) with ADD in a crossover design. Over a 20-week period, each subject went through 4 total drug phases. For each drug phase, the subjects randomly received BID capsules of

either desipramine 25 mg, clomipramine 25 mg, MPH 5 mg, or placebo 100 mg for 3 weeks. A 7-day washout period occurred before switching to another medication.³⁸ Each participant took the remaining 3 medications under the same procedure, until having tried all four medications.³⁸ Parents or childcare workers completed the Werry-Weiss-Peters Activity Rating Scale daily. This assigns scores to behavior during sleeping, watching television, playing, and eating; higher scores correspond to more “disturbed” behaviors.^{38,39} Participants taking MPH showed the most improvement in total rating on the 39-item CTRS compared with the other medications ($p < 0.005$).³⁸ MPH showed significant improvement in aggression, impulsivity, and attention/concentration factors of the CTRS compared with the other 3 medications ($p < 0.001$). Childcare workers completed the CTRS as well, rating subject behaviors in settings away from the classroom. These findings showed that MPH was rated significantly better on the attention/concentration factor and total score compared with the other 3 medications ($p < 0.001$). On the Werry-Weiss-Peters Activity Rating Scale, clomipramine and desipramine significantly improved rating of behavior during eating, watching television, and playing compared to MPH or placebo ($p < 0.001$).³⁸ All drug groups caused increases in diastolic blood pressures of 4 mm Hg in the morning and 7 mm Hg in the afternoon, compared with placebo ($p < 0.001$). Suicidality was not discussed in this study.³⁸

The last study of desipramine, a 6-week placebo-controlled study, enrolled 42 children and 20 adolescents (6–17 years). Dosing for both desipramine and placebo was increased through the first 5 weeks as subjects could tolerate the increased dosing. At week 6, the mean dose of placebo was 4.8 mg/kg/day and 4.6 mg/kg/day of desipramine.⁴⁰ On the CGI-I scale, 21 out of 31 of those taking desipramine scored a 1 or 2 (“very much” or “much” improved) at the end of 6 weeks, compared with only 3 out of 31 placebo subjects. Significant improvement of scores on the 10-item CPRS was shown by the end of the trial with desipramine ($p = 0.0003$). Both groups reported experiencing dry mouth, decreased appetite, headaches, abdominal pain, tiredness, dizziness, and trouble sleeping. There was no mention of suicidal thoughts or behaviors in the study. This study concluded that desipramine showed statistically significant improvements in ADHD symptoms and may be an effective treatment option for pediatric patients with ADHD.⁴⁰

Bupropion

The first study of bupropion, a 6-week, randomized, double-blind trial, enrolled 109 children (6–12 years). During the first and last week, participants were administered a placebo, and in the middle 4-week phase, participants were randomized to either bupropion or placebo. Bupropion or placebo was titrated starting at 3 mg/kg/day on days 1 to 14, then

increased to 6 mg/kg/day on days 15 to 28. A maximum dose of 150 mg/day was given to participants weighing 20 to 30 kg, 200 mg/day for those weighing 31 to 40 kg, and 250 mg/day for those weighing more than 40 kg.⁴¹ On the 10-item CTRS, significant improvement in symptoms was shown by day 28 on the aggression subscale in observed ($p < 0.015$) and last observation carried forward scores ($p < 0.027$), as well as in the hyperactivity observed scores ($p < 0.01$). On the 10-item CPRS, there was no improvement.⁴¹ However, on the 93-item version of the CPRS, there was improvement shown for conduct problems and restless impulsive behavior ($p < 0.01$).^{41,42} CGI-I and CGI-S results did not indicate a significant improvement in symptoms when considering the data as a whole across the 4 sites.⁴¹ Dermatological and gastrointestinal side effects were the most common symptoms reported with bupropion, and 4 patients discontinued the study because of a rash with urticaria. This study did not report on suicidality.⁴¹

A crossover study of 15 subjects (7–17 years) compared bupropion with MPH. After 6 weeks on the first medication, another 2-week washout period occurred, and then patients received the other medication for an additional 6 weeks.⁴³ Doses for each medication were titrated to maximum effective dose; MPH doses ranged from 0.4 to 1.3 mg/kg/day, and bupropion doses ranged from 1.4 to 5.7 mg/kg/day.⁴³ Inattention-Overactivity with Aggression-Connors Parent and Teacher Questionnaire (ICQ) attention scores showed significant results favoring MPH ($p < 0.01$).⁴³ In the ICQ conduct subset scores, the 2 medications were not significantly different.⁴³ Of note, in the ICQ conduct subset, there was a difference based on the order of medications given; subjects given bupropion first did better than subjects given bupropion second.⁴³ In the overall rating on the ICQ, there was no significant difference in symptom reduction between bupropion and MPH.⁴³ Considering the CGI-S scale in this study, a reduction in symptoms significantly favored MPH ($p < 0.05$).⁴³ Suicidal thoughts or actions were not reported in either group.⁴³

Also, comparing bupropion against MPH, a 6-week, randomized, double-blind study of 44 patients (6–17 years) concluded that there was no statistically significant difference in the efficacy between the two.⁴⁴ Half were randomly assigned to take bupropion 100 to 150 mg/day, and the other half took 20 to 30 mg/day of MPH.⁴⁴ For participants weighing less than 30 kg, bupropion was started at 50 mg daily and titrated up to 100 mg/day, and for participants weighing more than 30 kg, it was started at 75 mg daily and titrated up to 150 mg/day. For MPH, participants started with 5 mg BID in week 1, then titrated to 10 mg BID in week 2, then to 10 mg TID (for participants >30 kg only) from week 3 and on. On the Parent ARS-IV, the hyperactivity ($p = 0.775$) and inattention ($p = 0.480$) subscales did not show a significant difference in scores between the 2

groups.⁴⁴ Similarly, the hyperactivity ($p = 0.437$) and inattention ($p = 0.530$) subscales of the Teacher ARS-IV did not show a significant score difference.⁴⁴ Common side effects in the MPH group were decreased appetite, insomnia, and headache. The bupropion group most commonly reported decreased appetite and insomnia. This study did not report on suicidal thoughts or behaviors.⁴⁴

Discussion

Currently, the AAP and AACAP recommend stimulants as first-line ADHD treatment in all pediatric age groups after behavioral therapy and in-school interventions (eg, individualized support plans, minimizing distractions, or extra instructional support).^{9,18} Common stimulant side effects include loss of appetite, sleep disturbance, and headaches; however, headaches are usually transient during early therapy.^{9,45} Cardiac side effects, consisting of mild increases in heart rate and blood pressure, or sudden cardiac death (in rare instances), are also noteworthy adverse effects.⁶ Stimulants have the favorable quality of rapid onset of action, allowing for more frequent dose adjustments. Immediate-release MPH takes 1.9 hours to reach peak plasma concentration, while the extended-release bimodal form has 2 peaks occurring 4 hours apart.^{46,47}

Although the results generally showed some efficacy of antidepressants in alleviating ADHD symptoms, it remains unclear what benefit they may offer compared to stimulants. Most (11/12) studies concluded that antidepressants were beneficial compared with placebo in some way for behavioral symptoms or comparable in effectiveness to MPH; only 1 study concluded that MPH was superior. In 8 of these studies, there was no comparison to a first-line stimulant, making it difficult to conclude if they are better or simply comparable. Antidepressants may be a useful alternative for children who cannot tolerate the side effects of psychostimulants or nonstimulant ADHD medications, or for patients with concomitant disorders that an antidepressant can also manage. Bupropion and venlafaxine were noted to have lower rates of headaches compared with MPH, a common complaint. However, venlafaxine is still associated with hypertension and may not be an acceptable alternative to stimulants if this is a clinical concern. Additionally, 1 study concluded that bupropion is a potentially useful add-on for children with ADHD and conduct disorder.⁴¹

A key limitation is the small sample size of existing studies, hindering generalizability. More research is needed that directly compares antidepressants with established first-line medications. Long-term effects of antidepressants in ADHD treatment, particularly in children diagnosed early in life, remain unclear as well. Antidepressants and nonstimulants can take weeks to show results, compared with the rapid onset of action of stimulants. Because of the discrepancy in

treatment duration, it can be difficult to compare the efficacy of the 2 classes. Additionally, 8 of 12 studies meeting inclusion criteria were from the 1990s or earlier, with the most recent study from 2012. Therefore, the DSM-5, published in 2013, or DSM-5-Text Revision (TR) from 2022, and the most current ADHD diagnostic criteria are not used in any of the included studies. Safety is another concern; while no study reported increased suicidality, many antidepressants carry a boxed warning for this risk in pediatric patients. In patients with ADHD, suicide risk has been shown to be higher than in those without ADHD, so a careful risk-benefit assessment is always crucial.⁴⁸

Existing literature reviews tend to focus on the evaluation of a broad range of medication classes when considering options other than first-line treatment for ADHD. This review uniquely adds to the current body of literature by concentrating exclusively on the antidepressant class, emphasizing efficacy and safety in pediatric ADHD treatment.

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