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Use of Serotonin Norepinephrine Reuptake Inhibitors in the Treatment of Attention-Deficit Hyperactivity Disorder in Pediatrics

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Abstract

Objective: To review the current literature on the efficacy and safety of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder (ADHD) in the pediatric population. **Data Sources:** A literature search from 1996 to August 2013 was conducted using MEDLINE, CINAHL, and EMBASE databases. Search terms included *attention-deficit hyperactivity disorder, serotonin norepinephrine reuptake inhibitor, pediatric attention-deficit hyperactivity disorder, venlafaxine, duloxetine, desvenlafaxine, milnacipran*, and *nefazodone*. **Study Selection and Data Extraction:** Relevant articles on duloxetine and venlafaxine for the treatment of pediatric ADHD were reviewed; 5 studies on venlafaxine and 1 study on duloxetine were evaluated. Studies included open-label and randomized, double-blind trials. Case studies in pediatric populations and all studies in adult populations were excluded. **Data Synthesis:** Patients 6 to 17 years old were evaluated in the venlafaxine and duloxetine studies. Trials on venlafaxine, ranging from 2 to 6 weeks, showed patient improvement as measured by the Conners Rating Scale and ADHD Rating Scale. Venlafaxine was initiated at 12.5 to 25 mg/d and titrated up to 1.4 to 3.8 mg/kg/d to a maximum of 150 mg/d. Duloxetine showed minimal efficacy in treating ADHD symptoms at doses of 60 mg/d at 6 weeks. The most common side effects for venlafaxine and duloxetine included drowsiness and decreased appetite, respectively. **Conclusions:** Data for venlafaxine and duloxetine are limited. However, venlafaxine may be considered as an alternative agent when patients cannot tolerate or fail stimulants, tricyclic antidepressants, or bupropion. Duloxetine has been studied in children; however, with only 1 study available, it is difficult to recommend.

Keywords

attention-deficit hyperactivity disorder, duloxetine, pediatric, serotonin norepinephrine reuptake inhibitor, venlafaxine

Request

What is the role of serotonin norepinephrine reuptake inhibitors (SNRIs) in the treatment of attention-deficit hyperactivity disorder (ADHD) in pediatrics?

Response

Background

ADHD is a common psychiatric and behavioral disorder affecting approximately 8% of children and adolescents.[1] ADHD is marked by characteristics of impulsivity, difficulty in focusing and paying attention, and hyperactivity.[2] Children may be diagnosed with the inattentive subtype, hyperactivity-impulsivity subtype, or a combination of both. The inattentive subtype includes symptoms such as difficulty with organization, being forgetful, and being easily distracted, whereas the hyperactivity-impulsivity subtype is characterized by the inability to stay still and having difficulty waiting one's turn.[2]

The proposed pathophysiology of ADHD includes abnormalities in catecholamine transmission in the prefrontal cortex.[3] The 2 primary neurotransmitters associated with ADHD symptoms and targeted by stimulants are dopamine

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and norepinephrine. Dopamine is responsible for regulating cognition and communication skills in the mesocortical pathway, whereas norepinephrine plays a role in attention, motivation, and energy.

Current treatment guidelines, such as those outlined by the American Academy of Pediatrics and the Texas Children's Medication Algorithm Project, suggest the use of a stimulant, such as methylphenidate or amphetamine products, as first-line therapy.[1,4] Although stimulants are favored based on efficacy rates (70%-90%) and onset of action (~1 day), they are associated with the risk of cardiovascular events, including sudden death, growth reduction, and appetite suppression.[5] Alternatives to ADHD treatment include antidepressants, which typically take 2 to 6 weeks to reach efficacy and have a 60% to 70% efficacy. Current antidepressants are considered third-line agents in guidelines to treat ADHD when patients fail or cannot tolerate stimulants.[5] Such antidepressants include bupropion, which targets dopamine and norepinephrine, and tricyclic antidepressants (TCAs), which function on serotonin and norepinephrine reuptake inhibition.[4]

A review of 26 studies using TCAs to treat ADHD in children demonstrated moderate and robust responses to TCAs in 8 and 16 trials, respectively.[6] However, TCAs are sometimes avoided in clinical practice because of cardiac toxicity, sudden death reports (eg, desipramine), and highly sedative/anticholinergic properties.[6,7] Lately, SNRIs such as duloxetine and venlafaxine have been used for depression over TCAs because they target the same neurotransmitters but are associated with a more favorable side effect profile because of their lower affinity toward cholinergic and histaminic receptors.[8] Currently, we are unaware of any guidelines that include the use of SNRIs in the treatment of ADHD. Although TCAs may be prescribed as an alternative in ADHD, pediatric patients may not be able to take them either due to adverse reactions or because parents/clinicians wish to avoid them based on concerns over documented reports of cardiovascular toxicity and death. Therefore, the purpose of this review was to evaluate the efficacy and safety of SNRIs in the treatment of ADHD in pediatric patients.

Literature Review

A literature search from 1996 to August 2013 was conducted using MEDLINE, CINAHL, and EMBASE databases. The following search terms were used: *attention-deficit hyperactivity disorder, serotonin norepinephrine reuptake inhibitor, pediatric attention-deficit hyperactivity disorder, venlafaxine, duloxetine, desvenlafaxine, milnacipran*, and *nefazodone*. A total of 12 relevant articles on venlafaxine and duloxetine to treat ADHD were evaluated. Data reporting the efficacy and adverse effects of venlafaxine and duloxetine were extracted. References from each article were also evaluated for relevance. Case reports on pediatric patients and all studies on adult patients with ADHD were excluded. Finally, 6 articles were identified: 5 trials on venlafaxine immediate release (IR) and 1 study on duloxetine (see Table 1).[9-14] Studies with other SNRIs have not been published.

Venlafaxine. An open-label study involving 16 children and adolescents, 8 to 17 years of age (mean age = 11.6 years), evaluated the use of venlafaxine IR in the treatment of ADHD over a 5-week period.[9] Initial doses were started at 12.5 mg/d, with daily dose increases of 25 mg adjusted weekly.[9] Study methodology stated that patients weighing 40 kg or more (n = 9) were titrated to 75 mg/d and those weighing less than 40 kg (n = 6) were titrated to 50 mg/d in 2 to 3 divided doses (weight for 1 patient not provided). However, 2 patients weighing less than 40 kg were actually titrated to 75 mg/d, and 1 patient (15 years old) whose weight was not provided was also titrated to 75 mg/d. In all, 4 patients discontinued the trial because of hyperactivity (n = 3) and severe nausea (n = 1).[9] Patients showed improvement from 2.0 to 1.4 in the hyperactivity subscale ($P = .003$) and 2.4 to 1.6 in the hyperactivity-impulsivity subscale ($P = .008$) of the Conners Parent Rating Scale (CPRS) with a mean daily dose of 60 mg or 1.4 mg/kg. Overall, venlafaxine was shown to have modest (approximately 33%) clinical improvement in 7 out of 16 patients (44%) at the end of 5 weeks in the aforementioned subscales.[9] All 7 patients who responded to treatment were on 25 mg 3 times daily, did not experience irritability as a side effect, and had fewer comorbid diagnoses compared with those in the nonresponder group. Of the remaining 9 patients, 2 were lost to follow-up, 4 were noncompleters, and 3 were considered nonresponders. The 3 patients who did not respond to treatment all had comorbid diagnoses of oppositional defiant disorder (ODD), a conduct disorder characterized by loss of temper, argumentative behavior, spitefulness, and refusal to comply with adults' rules.[2] Additionally, 2 out of 3 patients who were nonresponders received only 37.5 mg/d of venlafaxine, whereas the 2 patients with ODD who responded to treatment were on 75 mg/d. The remaining nonresponder was on 75 mg/d but also had a history of failed treatments, which included thioridazine, methylphenidate, and pemoline. Irritability was cited as an adverse effect in all 3 nonresponder patients. Previous data show that if venlafaxine is not titrated slowly, the incidence of agitation or irritability may be significantly increased, especially when targeting higher doses.[15] Therefore, pediatric patients with ADHD and comorbid anxiety disorders may have benefited from a lower initial dose of venlafaxine and slow titration to higher doses.

Another open-label trial evaluated venlafaxine IR in 13 children and adolescents, 6 to 15 years old (mean = 9.9 years), over a 6-week period.[10] All patients, regardless of

Table 1. Summary of Venlafaxine and Duloxetine Studies in the Treatment of Pediatric ADHD.

Study (Year)	Demographics (Sample Size); Age (years); Weight (kg)	Study Design	Drug	Dosing Schedule: TDD (mg/d)	Scale	Results (at Study Completion)	Adverse Effects
Olvera et al (1996)[9]	(n = 16); Ages 8-17, mean age = 11.6; mean weight = 44.4	5-Week, open-label	Venlafaxine	First week: 12.5; <40 kg: titrated to 50; ≥40 kg: titrated to 75 (mean: 60)	CPRS	CPRS: Hyperactivity subscale improvement from 2.0 to 1.4 (P = .003); hyperactivity-impulsivity subscale improvement from 2.4 to 1.6 (P = .008); 10 of 16 completed trial	Drowsiness (50%), nausea (38%), irritability (31%)[a]
Mukaddes and Abali (2004)[10]	(n = 13); Ages 6-15; mean age = 9.9; weight not specified	6-Week, open-label	Venlafaxine	Initial: 18.75; final: 37.5-56.25 (mean: 40.4)	CPRS; CGI-S	CRPS: total score improvement from 20 to 14.5 (P < .002); CGI-S: 62% responded to treatment (P < .05); 13 of 13 completed trial	Somnolence (15%), stomachache (15%), headaches (8%)[a]
Findling et al (2007)[11]	(n = 38); Ages 5-17; mean age = 10.7; weight not specified	2-Week, open-label	Venlafaxine	Dosing cohorts: 0.5 mg/kg (up to 37.5); 1.0 mg/kg (up to 75); 2.0 mg/kg (up to 150)	ARS-IV; CGI	ARS-IV (Parent): total improvement from 37.6 to 29.0, inattention subscale improvement from 20.7 to 15.7, hyperactivity-impulsivity subscale improvement from 16.9 to 13.2 (all P < .001); ARS-IV (Teacher): total improvement from 29.6 to 26.1, inattention subscale improvement from 16.7 to 14.9 (all P < .05); CGI-I: 26% children, 50% adolescents responded to treatment; CGI-S: 0% children, 12% adolescents responded to treatment; 34 of 38 completed trial	Headaches (32%), nausea (32%), stomachache (24%), somnolence (24%), restlessness (24%)[a]
Zarinara et al (2010)[12]	(n = 38); Ages 6-13; venlafaxine group: mean age = 9.4, mean weight = 32.6; methylphenidate group: mean age = 9.6, mean weight = 34.7	6-Week, parallel group, randomized double-blind comparison	Venlafaxine	First week: 25; second week: 50; third week: <30 kg, 50; >30 kg, 75	ARS-IV	ARS-IV (Parent): total improvement from ~31 to ~17 (P = .33); ARS-IV (Teacher): total improvement from ~31 to ~18 (P = .30); 18 of 19 completed trial	Abdominal pain (26%), somnolence (26%), restlessness (16%), headaches (16%),[b] insomnia (11%)[a,b]
			Methylphe-nidate	First week: 10; second week: 20; third week: <30 kg, 20; >30 kg, 30	ARS-IV	ARS-IV (Parent): total improvement from ~31 to ~15 (P = .33); ARS-IV (Teacher): total improvement from ~30 to ~16 (P = .30); 18 of 19 completed trial	Headaches (58%),[b] insomnia (53%),[b] restlessness (26%), nausea (26%), abdominal pain (16%), somnolence (16%)[a]

(continued)

Table 1. (continued)

Study (Year)	Demographics (Sample Size); Age (years); Weight (kg)	Study Design	Drug	Dosing Schedule: TDD (mg/d)	Scale	Results (at Study Completion)	Adverse Effects
Firoozkoohi et al (2008)[13]	(n = 40); Ages 6-12; venlafaxine group: mean age = 8.3, mean weight = 19.6; methylphenidate group: mean age = 8.5, mean weight = 19.7	6-Week, controlled, double-blind comparison	Venlafaxine, methyl-phenidate	First week, 18.75; second week, 37.5. Titrated to 75: first week, 5; titrated to 20	ARS-IV	ARS-IV (Parent): total improvement from 37.3 to 21.9 ($P < .05$); ARS-IV (Teacher): total improvement from 27.2 to 21.6 ($P < .05$); 18 of 20 completed trial; ARS-IV (Parent): total improvement from 28.9 to 13.1 ($P < .001$); ARS-IV (Teacher): total improvement from 29.1 to 15.3 ($P < .001$); 19 of 20 completed trial	Nausea (35%), somnolence (25%), dry mouth (25%), dizziness (15%),[a] anxiety (25%), appetite loss (25%), irritability (20%), stomach ache (15%)[a]
Mahmoudi-Gharaei et al (2011)[14]	(n = 17); Ages = 11-18; mean age = 12.2; weight not specified	6-Week, open-label	Duloxetine	First week: 30; second week: 60	CPRS-R	CPRS-R: ADHD index subscale improvement from 71.6 to 64.7 ($P = .005$), inattention subscale improvement from 69.3 to 63.6 ($P = .037$), hyperactivity subscale improvement from 75.4 to 67.3 ($P < .001$), oppositionality subscale improvement from 72.0 to 63.9 ($P = .001$); 13 of 17 completed trial	Appetite decrease (46%), dry mouth (30%), insomnia, somnolence, anxiety, nervousness (23%)[c]

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ARS, ADHD Rating Scale; TDD, total daily dose; CPRS, Conners Parent Rating Scale; CPRS-R, Conners Parent Rating Scale–Revised; CGI, Clinical Global Impression; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity.

[a]Percentage based on total number of enrolled patients.

[b]P value < .05.

[c]Percentage based on completers.

weight or age, were dosed initially at 18.75 mg/d and titrated upward to 56.25 mg/d (dosing schedule not provided) depending on tolerability. Venlafaxine, at a mean final dose of 40.4 mg/d, demonstrated modest (approximately 28%) clinical improvement and statistically significant changes in mean total score of CPRS from 20 to 14.5 and Clinical Global Impression–Severity item from 4.85 to 3.53.[10] All patients (n = 13) completed the study, and 62% were considered responders. Similar to the Olvera et al[9] study, patients with a comorbid diagnosis of ODD did not respond to venlafaxine at 37.5 mg/d.[10] Of 8 patients, 7 who responded to therapy received 37.5 mg/d, but the majority did not have any comorbidities (n = 6), whereas the remaining 2 patients had dyslexia. Interestingly, 3 of the 5 nonresponders had comorbidities of ODD (n = 2) and tic disorder (n = 1). These results suggest that patients with comorbid disorders do not appear to respond to low doses (37.5 mg/d), and titration to higher doses, if possible, are needed. Patients appeared to tolerate venlafaxine well, and only 2 patients experienced transient side effects of somnolence and stomachache, which disappeared after the second week of treatment.[10] The lower incidence and transient nature of the side effects may also be a result of the lower doses of 37.5 mg/d used and the fact that patients who could not tolerate 56.25 mg/d were lowered to their previous dose of 37.5 mg/d.

The Findling et al[11] study evaluated venlafaxine IR during a 2-week, open-label trial in children and adolescents 5 to 17 years old (mean = 10.7 years). The study used 3 cohorts with each one receiving a different dosing schedule: 0.5, 1.0, and 2.0 mg/kg/d divided into 2 equal doses. Patients in each cohort were divided into 2 groups of children and adolescents, containing 5 patients each. The first cohort was given 0.5 mg/kg/d (up to 37.5 mg/d) for 2 weeks. The first cohort was able to tolerate the dose at 0.5 mg/kg/d; therefore, the study continued with a new cohort dosed at 1.0 mg/kg/d (up to 75 mg/d) for an additional 2 weeks. Based on tolerability, the study continued for 2 more weeks with a new third cohort of patients receiving 2.0 mg/kg/d (up to 150 mg/d). In all, 4 patients discontinued the trial: loss to follow-up (n = 2), consent withdrawal (n = 1), and ADHD symptoms worsening after 8 days (n = 1). This study showed statistically significant changes in the ADHD Rating Scale (ARS-IV) Parent from 37.6 to 29.0, with improvement in 2 subscales: inattention (20.7 to 15.7) and hyperactivity-impulsivity (16.9 to 13.2) when all groups were combined for statistical analysis (see Table 1).[11] Results of the ARS-IV Parent demonstrate low to modest clinical relevance. In addition, the ARS-IV Teacher also showed statistical significance in total score (29.6 to 26.1) and inattention subscale score (16.7 to 14.9); however, these changes are not considered clinically significant. Limitations of the study included the short duration and the exclusion of patients with comorbid illnesses (eg, anxiety) or the hyperactive-impulsive subtype of ADHD.[11] These exclusion criteria may explain the absence of irritability as an adverse reaction—even at doses as high as 150 mg/d—as noted in other studies. This may also explain why this study demonstrated modest clinical improvement in the hyperactivity-impulsivity subscale for the ARS-IV Parent and clinically insignificant changes in the ARS-IV Teacher scales.

Two randomized, double-blind trials of venlafaxine IR versus methylphenidate have been published.[12,13] In the first trial, patients 6 to 13 years old (mean = 9.4 years for the venlafaxine group, mean = 9.6 years for the methylphenidate group) were assessed at baseline, day 21, and day 42. Both venlafaxine and methylphenidate were dosed based on weight and scheduled 2 to 3 times daily: once in the morning, the second dose at midday, and the third dose at 16:00 hours.[12] Patients weighing less than 30 kg were titrated to 50 mg of venlafaxine or 20 mg of methylphenidate. Those who weighed more than 30 kg were titrated to 75 mg of venlafaxine or 30 mg of methylphenidate. One patient from each group discontinued the trial because of lack of parent collaboration.[12] Venlafaxine was associated with milder side effects compared with methylphenidate, including fewer headaches (16% vs 58%, $P = .05$) and insomnia (11% vs 53%, $P = .01$; see Table 1).[12] Patients on venlafaxine showed improvement in total score on the ARS-IV Parent (~31 vs ~17) and Teacher (~31 vs ~18) scales. Patients on methylphenidate showed similar improvements in the ARS-IV Parent (~31 vs ~15) and Teacher (~30 vs ~16) scales.[12] Even though these changes may suggest moderate clinical significance, none of these differences reached statistical significance. Overall, the response rate, defined as a 40% improvement in ARS-IV Parent or Teacher scales, were approximately 65% for venlafaxine and 70% for methylphenidate. Moreover, venlafaxine did not yield a significant difference in symptom improvement compared with methylphenidate, even though lower doses (20-30 mg/d) were used than typically recommended. The optimal mean dose of methylphenidate appears to be 30 to 40 mg/d for most pediatric patients.[16]

In the second double-blind trial, patients 6 to 12 years old (mean of 8.3 years for the venlafaxine group and mean of 8.5 years for the methylphenidate group) were assessed at baseline, 2, 4, and 6 weeks.[13] Patients were initiated on 18.75 mg of venlafaxine, and all were titrated to 37.5 mg twice a day by the sixth week. The methylphenidate group was on 5 mg the first week, and all were titrated to 20 mg by the end of the second week. Statistically significant improvements from baseline to 6 weeks were seen with venlafaxine in 33% and 44% of patients in the ARS-IV Parent (37.3 vs 21.9) and Teacher (27.2 vs 21.6) scales, respectively. In contrast, 95% of patients responded to methylphenidate at 2 weeks ($P < .001$) with either the ARS-IV Parent (28.9 vs 13.1) or Teacher (29.1 vs 15.3) scales.[13] Symptom improvements in the venlafaxine group may be considered modestly to moderately clinically

significant; however, improvements in the stimulant group were moderately to highly clinically significant within a shorter time period, further supporting the use of stimulants as first-line therapy. The average weights of the venlafaxine and methylphenidate groups were 19.6 and 19.7 kg, respectively, which were lower than the average weights of children in the other trials.[9,12]

Duloxetine. A 6-week, open-label trial on duloxetine evaluated adolescents 11 to 18 years old (mean = 12.2 years), who were initiated on a dose of 30 mg/d during the first week and 60 mg/d in the second week until the end of the study.[14] Four patients discontinued the trial because of noncompliance (n = 1) and adverse drug reactions (n = 3). Results showed statistically significant reductions in ADHD symptoms at the end of 4 weeks in ADHD index (71.6 to 63.0), hyperactivity (75.4 to 59.7), and oppositionality (72.0 to 63.7).[14] Furthermore, patients demonstrated statistically significant improvements in all 4 subscores of the CPRS (ie, ADHD index: 71.6 to 64.7; inattention: 69.3 to 63.6; hyperactivity: 75.4 to 67.3; and oppositionality: 72.0 to 63.9) at the end of 6 weeks (see Table 1).[14] This study included patients with comorbid disorders (eg, ODD, generalized anxiety).[14] Patients experienced anxiety and nervousness as side effects, suggesting that these symptoms may be exacerbated when patients with ADHD have comorbid conditions and are started at higher doses of duloxetine. However, unlike venlafaxine, duloxetine did not appear to necessitate a dose reduction for intolerability of symptoms, and continued use of duloxetine resulted in an eventual reduction in side effects.[14] Also, patients showed some improvements in the oppositionality subcategory despite ODD presenting as a comorbidity in more than half of the patients. However, none of these improvements may be considered clinically significant.

Discussion

Despite limited studies, venlafaxine IR appears to be an alternative agent to treat ADHD in those who do not wish to use or cannot tolerate stimulants, TCAs, or bupropion. Currently, venlafaxine and duloxetine are not FDA approved for use in children and have a black box warning stating that use in children and adolescents may increase suicidal thinking and behavior. Therefore, caution may be warranted when using these agents in patients with comorbid psychiatric disorders (eg, depression). However, it is important to note that TCAs and bupropion carry the same black box warning on suicidality, and none of the studies evaluated in this review[9-14] noted any patient experiencing increased suicidal thoughts and ideations.

The most common adverse effects of venlafaxine were drowsiness/somnolence (15%-50%), headaches (8%-32%), nausea (32%-38%), and irritability/restlessness (16%-31%).[9-13] All 5 studies on venlafaxine included drowsiness/somnolence as an adverse effect (see Table 1). The most notable side effects for duloxetine were a decrease in appetite (46%) and dry mouth (30%).[14] Similar to venlafaxine, duloxetine was also associated with somnolence and nervousness (23%).[14]

The primary limitations of the clinical trials were the short-term duration and subject to bias. Trials ranged from 2 to 6 weeks, and 4 of the 6 studies were open-label studies. Therefore, it is difficult to assess the long-term efficacy of these treatments. When evaluating dosing regimens, the methodologies and results of the studies prevent one from being able to calculate a target dose in mg/kg/d. Olvera et al[9] report a 1.4-mg/kg mean daily dose for venlafaxine, and we calculated a 3.8-mg/kg mean daily venlafaxine dose for another study.[13] Furthermore, although one study had a maximum venlafaxine daily dose of 150 mg, it is unknown how many patients actually received this dose.[11] In addition, the adverse effects of the venlafaxine trials were calculated based on the total number of enrolled patients, whereas the duloxetine trial included percentages on the number of completers, making comparisons between medications more difficult. Future trials may consider the isoenzymes that metabolize duloxetine and venlafaxine. Duloxetine is primarily metabolized by CYP1A2 and CYP2D6, whereas venlafaxine is a substrate of CYP2D6. Studies show that children up until puberty metabolize CYP1A2 at higher rates than adults.[17] This may result in an increased duloxetine metabolism and subsequent conversion into nonactive metabolites. Therefore, higher doses of duloxetine may be considered for children who have not reached puberty.

Summary

Although stimulants remain the first-line agent to treat pediatric ADHD, SNRIs may be considered as an alternative treatment option. Venlafaxine appears to be well tolerated and may be an effective agent for ADHD in children and adolescents, 6 to 17 years old and in those who refuse to take or cannot tolerate stimulants, TCAs, or bupropion. As monotherapy over 4 to 6 weeks, venlafaxine appears to be 33% to 65% effective, showing decreases in ADHD symptoms by approximately 20% to 50% overall. Studies in combination with stimulants or other agents (eg, atomoxetine) are lacking. Venlafaxine doses may be initiated between 12.5 and 25 mg/d to a target of 1.4 to 3.8 mg/kg/d. Titration by 18.75 to 25 mg/wk to a target of 40 to 75 mg/d in divided doses appears to be consistent among the studies. Patients who have hyperactive-impulsive traits of ADHD may experience a higher likelihood of irritability symptoms and may need a slower titration. Additionally, those with comorbid illnesses (eg, ODD) should be titrated slower, and higher doses may be needed for optimal efficacy. Doses above 150 mg/d have not been adequately studied in this population. Duloxetine has been studied in patients 11 to 16

years old; however, current research is limited, and further studies are needed to assess its efficacy and tolerability.

Declaration of Conflicting Interests

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References

1. Subcommittee on Attention-Deficit/Hyperactivity Disorder. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128:1007-1022.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
3. Agster K, Clark B, Waterhouse B, et al. Experimental strategies for investigating psychostimulant drug actions and prefrontal cortical function in ADHD and related attention disorders. *Anat Rec (Hoboken)* 2011;294:1698-1712.
4. Pliszka S, Crismon M, Lopez M, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45:642-657.
5. Dopheide J, Pliszka S. Attention-deficit-hyperactivity disorder: an update. *Pharmacotherapy*. 2009;29:656-679.
6. Daly J, Wilens T. The use of tricyclic antidepressants in children and adolescents. *Pediatr Clin North Am*. 1998;45:1123-1135.
7. Amitai Y, Frischer H. Excess fatality from desipramine in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2006;45:54-60.
8. Bymaster F, Dreshfield-Ahmad L, Wong D, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001;25:871-880.
9. Olvera R, Pliszka S, Luh J, et al. An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 1996;6:241-250.
10. Mukaddes N, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci*. 2004;58:92-95.
11. Findling R, Greenhill L, Reed M, et al. Venlafaxine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17:433-445.
12. Zarinara A, Mohammadi M, Akhondzadeh S, et al. Venlafaxine versus methylphenidate in pediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. *Hum Psychopharmacol*. 2010;25:530-535.
13. Firoozkoohi M, Arabgol F, Rajezi S. Efficacy of venlafaxine and methylphenidate in the treatment of children with attention deficit hyperactivity disorder. *Zahedan J Res Med Sci*. 2008;10:69-77.
14. Mahmoudi-Gharaei J, Dodangi N, Tehrani-Doost M, et al. Duloxetine in the treatment of adolescents with attention deficit/hyperactivity disorder: an open-label study. *Hum Psychopharmacol*. 2011;26:155-160.
15. Thase M, Shelton R, Khan A. Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. *J Clin Psychopharmacol*. 2006;26:250-258.
16. Vitiello B, Severe J, Cantwell D, et al. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. *J Am Acad Child Adolesc Psychiatry*. 2001;40:188-196.
17. Lambert G, Schoeller D, Kotake A, et al. The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther*. 1986;9:375-388.