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REVIEW

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Efficacy, safety, and tolerability of serotonin-norepinephrine reuptake inhibitors in controlling ADHD symptoms: a systematic review and meta-analysis

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Abstract

Introduction The aim of this study is to assess the effectiveness of serotonin-norepinephrine reuptake inhibitors (SNRIs) in managing ADHD symptoms compared to placebo, stimulants, or compared as pre- and post-treatment.

Methods Clinical trials assessing the potency of SNRIs in treating ADHD patients were imported from PubMed, Web of Science, and Scopus (until February 2023). Data were extracted by two independent researchers. Random- and fixed- effect meta-analysis was performed to pool the data. Publication bias and study heterogeneity were assessed. The Cochrane Collaboration tool was utilized to determine the risk of bias. The certainty of outcomes was evaluated by the Grade criteria.

Results Of the initial 830 studies, 13 were finally imported after two screening stages which two separate researchers carried out. The pooled standardized mean difference (95% CI) of reducing the score of different ADHD questionnaires (showing reduction in total inattentive and hyperactivity/impulsivity symptoms) by SNRIs, venlafaxine, and duloxetine were − 2.20 [− 3.00, − 1.40], − 1.86 [− 2.69, − 1.02], − 2.65 [− 3.35, − 1.96], respectively. While the most reported side effects were nausea, abdominal pain, and sedation, all studies reported that side effects were not serious and were well tolerated. Outcomes for the effectiveness of venlafaxine and duloxetine got high and moderate certainty, respectively.

Conclusions Duloxetine and venlafaxine can be administered to treat symptoms of ADHD while being well tolerated. It seems that duloxetine is more potent in reducing ADHD symptoms. It can also be concluded that venlafaxine is more effective in females, and is more effective on inattentive symptoms of ADHD rather than hyperactive symptoms.

Keywords ADHD, Duloxetine, Meta-analysis, SNRI, Systematic review, Venlafaxine

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Introduction

Attention deficit hyperactivity disorder (ADHD) profoundly impacts the affected people's daily lives [1]. This disorder is characterized by hyperactivity, inattention, impulsivity (the tendency to act without thinking), and significant problems with emotions and communication. ADHD also correlates with comorbidities [2] like mood disorders, sleep disturbances, and learning disabilities. According to the reports, ADHD is prevalent in 7–8% of school students and 4–5% of adults [3]. The prevalence rates vary across different countries and cultures, but it is generally more common in males than females [4]. Some other risk factors rather than being male are reported to be antisocial personality disorder, a dysfunctional family, downward socioeconomic standing, developmental deficit, and anxiety [5, 6].

Regarding treatment approaches, there are either pharmacological or non-pharmacological interventions [7]. Examples of non-pharmacological treatments include behavioral therapies such as parent/teacher education and cognitive behavioral therapy (CBT) [8], cognitive trainings, game-based trainings, mindfulness, neurofeedback, and physical exercise [9]. Although non-pharmacological interventions are popular among patients who prefer not or cannot use medications, pharmacological approaches still remain the first-line therapy [10]. Stimulants such as lisdexamfetamine, methylphenidate, and dexmethylphenidate are the most commonly used medications [11]. However, there are several concerns regarding their abuse potential and their serious side effects [12]. These side effects include loss of appetite, irritability, insomnia, nervousness, serious cardiovascular side effects, and dysphoria [13].

Along with stimulants, non-stimulant medications, including atomoxetine, clonidine, and guanfacine, have been proven efficient in treating ADHD [7]. Additionally, it has been proved that other psychiatric medications, such as antidepressants, can be effective in treating ADHD symptoms as well [14–16]. Among all, one of the promising groups of medications that seems to be a good alternative in treating ADHD symptoms is serotonin-norepinephrine reuptake inhibitors (SNRIs). They are useful in many diseases since they act by increasing both synaptic serotonin and norepinephrine concentrations. Two important medications in this group are venlafaxine and duloxetine. These two medications have a broad spectrum of indications, such as generalized anxiety disorder (GAD), major depressive disorder (MDD), and obsessive–compulsive disorder (OCD) [17–22]. However, there are some side effects of these medications as well. These side effects include decreased appetite, nausea, constipation, hyperhidrosis, dry mouth, fatigue, somnolence, hypertension, blurred vision, and increased risk of suicide-relevant behavior in children and adults [23–26].

Given the fact that some patients may be unable to tolerate side effects, be resistant to first-line ADHD treatments, or be contraindicated to use stimulants, it is of great importance to find new agents for the treatment of ADHD. Therefore, it is prone evaluating the efficacy of SNRIs and compare it with their safety profile to see if they are promising options for treating ADHD symptoms. Therefore, the present systematic review and meta-analysis aims to answer this question: In people with ADHD, are SNRIs effective in decreasing disease symptoms compared to placebo?

Methods

A complete research protocol was created before the study and registered in PROSPERO with the CRD42023412366 ID. This protocol was then followed throughout the entire procedure. For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reference was utilized [27]. Additionally, the abstract was written using the "PRISMA for Abstract" reference [28].

Search strategy

Supplementary Table 1 presents the full search syntax that was applied to each database. The search stage was conducted by two researchers without any restriction on publication year. However, there was a restriction on language—only English studies were included. Unpublished work (i.e., dissertations, conferences) and gray literature were also investigated as far as possible. Although these articles were not included directly, they were used to help assess publication bias (if any).

The following search phrases were used in the systematic search in Scopus, Web of Science, and PubMed: "drug name" (venlafaxine or duloxetine) AND "attention deficit hyperactivity disorder" OR "attention-deficit hyperactivity disorder" OR "ADHD" OR "hyperactivity" OR "ADD" OR "attention deficit disorder" OR "attention-deficit disorder." Studies with search phrases in their titles or abstracts were found and imported into Mendeley. After removing duplicates and finishing the screening phases, the final selection of studies was made by the study team.

Eligibility criteria and study selection

The exposure of interest for this investigation was ADHD. The reduction in ADHD symptoms was compared between two arms. The intervention was defined as taking venlafaxine or duloxetine. Two independent researchers carried out removing duplicate studies and assessing the rest of the publications according to the stated goals of the study throughout the first screening stage. The following studies were excluded through the first screening stage:

> Studies that were not clinical trials, studies on other diseases (i.e., autism and bipolar disease), other reviews and meta-analyses, studies on toxicity, protocols, studies on side effects, studies on pregnancy and lactation, commentaries, case reports, letters, studies on plasma concentration of drugs, pharmacology studies (including animal studies), pharmacoeconomic studies, safety studies, non-English studies, and other irrelevant studies. Conference papers and case-series studies were not excluded through the first screening stage. They remained to undergo a full-text screening to see if their data was useful for synthesis.

Clinical trials were included in the second screening stage if:

- The participants' desired information (age, comorbidities, gender, current medications) was given.
- Venlafaxine or duloxetine were compared with a placebo, other medications, or data were given as pre- and post-treatment outcomes.
- Results were reported as the improvement in symptoms (as continuous, binary, or correlation values).

Studies were excluded if:

- The dosage and method of administering the drug were not clearly reported.
- Other important interventions were considered besides SNRIs that may affect the outcomes.
- The study was on withdrawal management (i.e., Cocaine and smoking cessation).
- The study was on managing the side effects of stimulants.

When the second screening stage was finished, each researcher presented their papers, and the group chose the final studies to be included.

Data extraction

Two independent reviewers entered data from the final included studies into Microsoft Excel. The following details were included in the abstracted information:

- Publication details and characteristics: author(s), title, date, study location, number of participants, participants' age, comorbidities, the approach used for identifying ADHD, and inclusion and exclusion criteria of clinical trials.
- Critical data: dose and administration routine of medication, number of participants in control and treatment arm, comparator arm, comparator arm's administration routine, trial duration, outcome measure (different ADHD questionnaires), adverse effects (if reported), number of participants lost and the associated reason, tolerability (percentage of participant who left the trial because of side effects), and final results for treatment and control group (reduction in ADHD scores as mean ± SD, median ± SE, number of patients with improved symptoms, and Pearson correlation coefficient).

Finally, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria [29] were used to assess the certainty of outcomes.

Meta-analysis

A meta-analysis was used to pool the effect sizes of SNRIs in reducing scores of ADHD questionnaires. Mean ± SDs were pooled when two or more papers reported their data as the comparison of SNRIs with placebo, comparison of SNRIs with other medications, or as the pre- and post-treatment means. Since the outcome measures differed among reference studies, the standardized mean difference (SMD) approach was utilized to pool the effect sizes. The fixed-effect model was used. However, if heterogeneity was high, a random-effect model was considered. The residual maximum likelihood (REML) approach was the estimation method. When one reference study reported more than one outcome measure for the same group of patients (i.e., both CAARS and CGI-S were reported for the same population), the outcomes with a bigger sample size and smaller SD/mean ratio were used for the meta-analysis.

The Q statistic and I-squared (%) were used to assess the heterogeneity within and between subgroups. In cases of observed heterogeneity, meta-regression and subgroup analysis were conducted by gender, age (qualitative and quantitative), and trial duration to find the source of heterogeneity. Subgroup analysis by the mean dose of medication was not possible since several studies used flexible dosing and did not report a final mean medication dose. Publication bias was assessed by Egger's test. A sensitivity analysis was also conducted. Statistical significance was defined as a two-sided P value < 0.05. STATA version 17 was used to conduct all statistical analyses.

Risk of bias assessment

The Cochrane Collaboration's tool was used to assess the risk of bias in the final included studies [30]. Two independent reviewers carried out this procedure.

The Cochrane Collaboration's risk assessment method assesses each study's potential for bias in six different areas: "selection bias," "performance bias," "detection bias," "attrition bias," "reporting bias," and "other bias." The "selection bias" verifies that the allocation sequence generation procedure is sufficiently described in the study to assess whether or not it offers comparable groupings. By providing sufficient details regarding how the allocation sequence was concealed, it also confirms if the study has indicated whether allocations might have been expected at the time of enrolment. The "Performance bias" checks to see if the study mentions the steps used to keep researchers from knowing participants' intervention status. The "Detection bias" section ensures that all steps are taken to keep the intervention of each participant unknown at the time of evaluating outcomes. The "Attrition bias" indicates if the study, taking attrition and analytical exclusions into account, reflects how complete each outcome is. The "Reporting bias" part, which is the last one, looks at the study's description of the technique for analyzing selective outcome reporting.

Results

Study selection

A flowchart of the screening stages can be found in Fig. 1. Utilizing the search protocol stated earlier, 830 articles were initially imported, including 458 from Web of Science, 211 from Scopus, and 161 from PubMed. Of these 830 articles, 573 were for venlafaxine and 257 were for duloxetine. It can be concluded that venlafaxine has received more attention than duloxetine for treating ADHD. After 263 duplicates (184 for venlafaxine and 79 for duloxetine) were removed, a total of 567 items (389 for venlafaxine and 178 for duloxetine) made it to the first screening phase. Title and abstract screening during the first step ultimately led to the exclusion of 544 articles due to the standards outlined in the methods section. The 23 papers that remained were subjected to full-text screening, and 10 research were removed. Among the five studies excluded from the venlafaxine group and five from the duloxetine group, some were only abstracts, some were clinical trial registrations, and some were case reports [31, 32]. After meeting all inclusion criteria, data from 13 studies [33–45] were finally used (10 for venlafaxine and three for duloxetine).

Basic characteristics of the selected studies

Venlafaxine

The basic characteristics of the final 13 included studies can be found in Table 1. As can be seen, out of 10 articles for venlafaxine, six were conducted in the United States (US) [36, 37, 41, 42, 44, 45], three were carried out in Iran [38, 39, 43], and one took place in Turkey [40]. Regarding the study date, only two studies were carried out after 2010 [38, 43], and all others were relatively old. This may be due to the fact that researchers mostly focus on the use of SNRIs in other mental illnesses rather than ADHD, and these medications are not well-known for treating ADHD symptoms. Sample sizes varied from one study to another, ranging from 10 to 44 people. Among all studies, three included children and adolescents, while two and five studied children and adults, respectively. The mean age ranged from 9.49 to 43 across studies.

Regarding the health status of subjects, while participants of some studies did not have any other comorbidities at all, some participants of other studies had oppositional defiant disorder (ODD), bipolar disease (BD), major depressive disorder (MDD), tic disorder, GAD, reading disorder, and separation anxiety disorder (SAD). The full details regarding the health status of each study's participants are shown in Table 1. Studies used various inclusion and exclusion criteria for choosing their participants. For the inclusion criteria, most of the references used the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria [46] for identifying ADHD. The DSM-IV is the official manual of the American Psychiatric Association. Its goal is to offer a framework for organizing diseases into categories and setting diagnostic standards for each disorder listed. Another scoring scale used was Conners' Parent Rating Scale (CPRS) [47]. To get parental reports of behavioral issues in children, researchers and clinicians frequently use the CPRS. Other used scales were the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) [48], Conners' Adult ADHD Rating Scale (CAARS) [49], Clinical Global Impression ADHD Severity Scale (CGI-S) [50], and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) [51].

Getting back to the inclusion criteria of included studies, participants in the first trial [36] had to have CPRS scores that were at least 1.5 SDs higher than the mean for their age and sex. Another study that was carried out on 40 children included patients who had problems with side effects or did not respond to methylphenidate [38]. One of the studies [43] included first-degree relatives of children who had ADHD to be its participants. Finally, one study [45] utilized the Wender Utah Rating Scale (WURS) [52] and Attention deficit hyperactivity questionnaire (ADHQ) [53] scales for finding ADHD subjects as well. WURS is a self-report tool adults use to assess the persistence of childhood symptoms and behaviors associated with ADHD in adulthood.

Finally, the exclusion criteria of included studies were recorded. Although investigators utilized various exclusion criteria among studies, they all tried to exclude

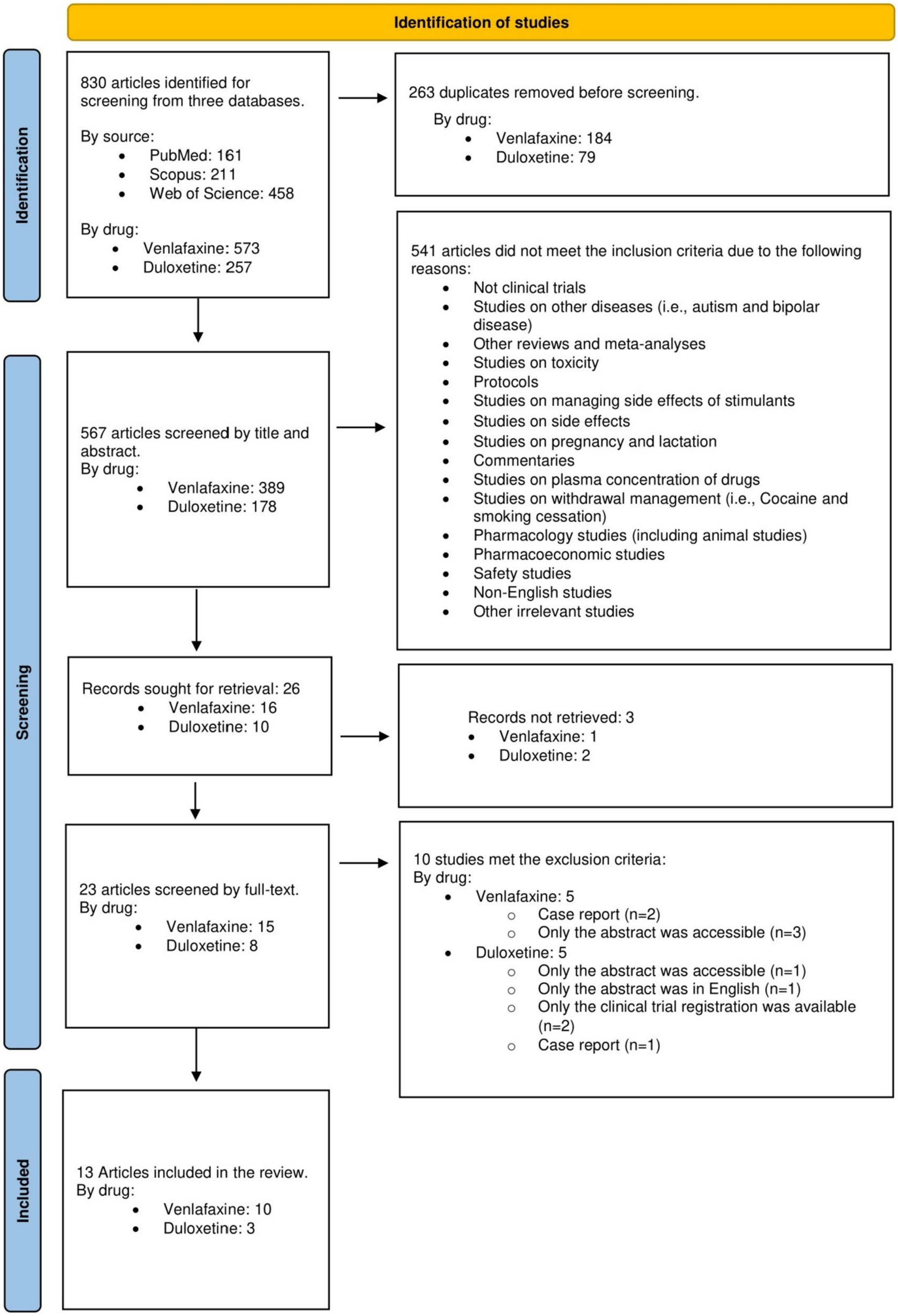

Fig. 1 A summary of the study selection process

Table 1 The main characteristics of the included studies

Autor, year	Study location	Sample size (percentage of males)	Studied population, Mean age (range)	Comorbidity[a]	Inclusion criteria	Exclusion criteria
Venlafaxine						
Olvera et al. 1996 [36]	USA	16 (90%)	Children and adolescents, 11.6 (8–17)	Some subjects had: • ODD[b] • MDD • GAD • SAD • BD	• Meeting the DSM-IV criteria for ADHD • Having a score of the CPRS that was at least 1.5 SDs above the mean for the patient's age and sex	–
Findling et al. 2007 [37]	USA	38 (87%)	Children and adolescents, 10.7 (5–17)	• 31% ODD	• Meeting DSM-IV criteria for ADHD of at least moderate severity	• Evidence of a current or past significant medical or neurological illnesses • BD, mental retardation, MDD, OCD, PTSD, GAD • First-degree relatives of bipolar patients • Substances abusers • Patients with a past or current history of clinically significant suicidal ideation or self-injurious behavior • Females who were sexually active but not using effective birth control methods
Hashemian and Nazemian 2015 [38]	Iran	40	Children, (7–11)	–	• Meeting DSM-V criteria • Patients who suffered from side effects or had a lack of response to methylphenidate	-
Zarinara et al. 2010 [39]	Iran	38 (71%)	Children, 9.49 (6–13)	–	• Meeting the DSM-IV-TR diagnostic criteria for ADHD • Total or subscale scores on ADHD-RS-IV of at least 1.5 standard deviations above norms for patient's age and gender	• History or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric disorders (DSM-IV axis I) • Any current psychiatric comorbidity that required pharmacotherapy • Any evidence of suicide risk and mental retardation (IQ < 70) • A clinically significant chronic medical condition, including organic brain disorder, seizures, or current abuse or dependence on drugs the last six months • Hypertension or hypotension

Table 1 (continued)

Autor, year	Study location	Sample size (percentage of males)	Studied population, Mean age (range)	Comorbidity[a]	Inclusion criteria	Exclusion criteria
Amiri et al. 2012 [43]	Iran	44 (58%)	Adults, 30.5 (18–45)	–	• Being parents or siblings of children diagnosed with ADHD • Meeting DSM-IV diagnostic criteria for adult ADHD	• Current psychiatric disorders other than adult ADHD • Suffered from a significant chronic medical disease such as seizures or cardiovascular disease • Had a history of drug or alcohol abuse or dependency within the past six months • Was breastfeeding or pregnant
Mukaddes and Abali 2004 [40]	Turkey	13 (69%)	Children and adolescents, 9.9 (6–15)	• 15% ODD • 7% tic disorder • 15% reading disorder	• Meeting DSM-IV diagnostic criteria for adult ADHD	• Seizure disorder • Evidence of systemic disease • Comorbidity of depression
Hornig-Rohan and Amsterdam 2002 [41]	USA	17 (70%)	Adults, 43 (21–67)	• 100% chronic MDD of > 2 years • 52% BD • 41% history of treatment-resistant depression	• Meeting DSM-IV diagnostic criteria for adult ADD	• BD Type I or Type II, OCD, panic disorder, GAD, alcohol and/or substance abuse within the past 12 months
Adler et al. 1995 [45]	USA	12 (50%)	Adults, 34.9 (19–59)	• 25% panic disorder • 8% MDD	• Meeting WURS and ADHQ diagnostic criteria for adult ADHD • Meeting DSM-IV diagnostic criteria for adult ADHD	–
Findling et al. 1996 [42]	USA	10 (50%)	Adults, 38.5 (18–54)	• Some subjects had GAD or MDD	• Meeting DSM-IV diagnostic criteria for adult ADHD	• Presence of organic mental disorder • mental retardation • Psychosis, BD, GAD, MDD • Substance abusers
Hedges et al. 1995 [44]	USA	18 (66%)	Adults, 35	–	• Meeting WURDS diagnostic criteria for adult ADHD	• MDD • Personality disorders
Duloxetine						
Bilodeau et al. 2014 [33]	Canada	30	Adult, 33.2 (18–50)	–	• Having a minimal baseline score of 20 on the CAARS • Having a score of at least four on the CGI-S • Having completed high school or having an IQ of 80 or greater	• Psychotic disorders, BD, MDD, GAD, • Substance or alcohol use disorder was present six months before the study • Pregnancy • Any medical condition or medication incompatible with duloxetine treatment

Table 1 (continued)

Autor, year	Study location	Sample size (percentage of males)	Studied population, Mean age (range)	Comorbidity[a]	Inclusion criteria	Exclusion criteria
Mahmoudi-Gharaei et al. 2011 [34]	Iran	17	Adolescents, 12.23 (11–18)	• 53% ODD • 15% Depression • 46% GAD • 23% OCD	• Meeting DSM-IV diagnostic criteria for adult ADHD • Meeting K-SADS-PL diagnostic criteria for adult ADHD	• Pervasive developmental disorder, BD, conduct disorder, Mental retardation, and psychotic disorder • Clinically significant medical illness requiring pharmacotherapy • History of hypersensitivity to duloxetine • Current substance abuse or dependence within three months • Pregnancy and breastfeeding
Dodangi et al. 2015 [35]	Iran	13	Children, 8.4 (6–11)	• 60% ODD • 20% GAD • 20% OCD • 10% Learning Disability	• Meeting DSM-IV diagnostic criteria for adult ADHD • Meeting K-SADS-PL diagnostic criteria for adult ADHD	• Pervasive developmental disorder, BD, conduct disorder, Mental retardation, and psychotic disorder • Clinically significant medical illness requiring pharmacotherapy • History of hypersensitivity to duloxetine

[a] Percentage of occurrence among the sample size

[b] *ODD* oppositional defiant disorder, *MDD* major depressive disorder, *GAD* generalized anxiety disorder, *SAD* separation anxiety disorder, *BD* bipolar disorder, *OCD* obsessive–compulsive disorder, *PTSD* post-traumatic stress disorder, *CPRS* Conners' Parent Rating Scale, *DSM IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *ADHD-RS-IV* Attention-Deficit/Hyperactivity Disorder Rating Scale-IV, *WURS* Wender Utah Rating Scale, *ADHQ* attention deficit hyperactivity questionnaire, *CAARS* Conners' Adult ADHD Rating Scale, *CGI-S* Clinical Global Impression–ADHD–Severity Scale, *K-SADS-PL* The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version

subjects likely to show serious side effects or have serious comorbidities. While some studies excluded patients with MDD, OCD, post-traumatic stress disorder (PTSD), seizures, and BD, some studies did not exclude any of the patients at all. Sexually active women who did not use effective birth control methods were excluded in some studies. Moreover, most studies excluded substance abuse patients and participants with mental retardation. None of the studies used other interventions rather than venlafaxine. Except for two studies [38, 45], participants of all other studies had to be off any medication at least 1 week before the study. One of the remaining two studies [38] progressively reduced the dose of methylphenidate that patients used and gradually eliminated it. The other study [45] had some participants who used medications such as clonazepam due to their comorbidities. However, all patients taking other medicines were stabilized on their medication one week prior to the study.

Duloxetine

Two of the three studies were conducted in Iran [34, 35] and one in Canada [33]. Compared to venlafaxine, studies for duloxetine were relatively new since they all were conducted after 2010. Sample sizes varied from 13 to 30, and the included studies studied populations with different age ranges. One of them studied children, one of them studied adolescents, and the other one studied adult patients. Regarding the health status of participants, like the venlafaxine studies, some participants had ODD, GAD, OCD, and MDD. These three studies used other scales on top of DSM-IV for the inclusion criteria. One of them [33] used CAARS and CGI-S. The study included participants with a minimal baseline score of 20 on the CAARS scale and scoring at least four on the CGI-S. The other two studies used the DSM-IV criteria and K-SADS-PL for diagnosing ADHD.

Regarding the exclusion criteria, substance and alcohol abusers were excluded, as well as pregnant women. The full list of exclusion criteria used in these three studies can be found in Table 1. In all three studies, there were no other interventions rather than duloxetine. All the patients had to eliminate their use of any other psychotropic drug before the study began.

Qualitative analysis

Table 2 presents the research results investigating the effect of venlafaxine or duloxetine use on managing ADHD symptoms.

Venlafaxine

All the trials reported that venlafaxine significantly reduced the symptoms of ADHD (measured by different questionnaires), with some of them getting reduced more than 1 SD. While one study reported that venlafaxine had the same effectiveness as bupropion [38] and another one reported that venlafaxine had the same efficacy as methylphenidate [39], one study reported that there was no difference between the venlafaxine and placebo [43] (however, they both reduced symptoms significantly). Moreover, one study that particularly studied patients who had major depressive disorder on top of ADHD [41] reported that the improvements obtained by venlafaxine were nearly double the improvements with methylphenidate. The commonly reported side effects were abdominal pain, nausea, and sedation.

Duloxetine

Although studies on duloxetine were few in number, they all reported the same outcome: duloxetine significantly reduced the symptoms of ADHD. The single study that compared duloxetine with placebo also reported that duloxetine and placebo had significant differences [33]. Regarding side effects, while one study reported a 46% reduction in appetite [34], the other reported no weight changes at all [35]. Dry mouth and dizziness were other reported side effects.

Quantitative synthesis

Meta-analysis was conducted for the outcomes reported as pre- and post-treatment mean score changes. The meta-analysis of venlafaxine consisted of three separate sections: the meta-analysis of the hyperactivity subscale, inattentive subscale, and total scores. A random effect model was used for pooling data for the "SNRIs" and the "Overall" section of venlafaxine meta-analyses, and the fixed effect model was used for pooling the data for "Hyperactivity-Impulsivity" and "Inattentive" meta-analyses of venlafaxine, and the duloxetine meta-analysis.

Table 3 shows summary results of using SNRIs (the whole group), venlafaxine alone, and duloxetine alone in controlling symptoms of ADHD. As can be seen, the pooled SMD (95% CI) of reducing the score of different ADHD questionnaires by SNRIs, venlafaxine (overall), and duloxetine were -2.20 $[-3.00, -1.40]$, -1.86 $[-2.69, -1.02]$, -2.65 $[-3.35, -1.96]$, respectively. In the following, the analysis of each section along with the results of subgroup analysis and meta-regression is reported separately (The results of risk of bias assessment in Fig. 2).

Meta-analysis of the efficacy of SNRIs in ADHD

The pooled SMDs for the efficacy of SNRIs in ADHD are shown in Fig. 3 as a forest plot. As can be seen, the overall ADHD symptoms significantly decrease by consuming SNRIs (effect size: -2.20 SMDs; 95% CI: $[-3.00, -1.40]$; p value < 0.001; I-squared: 86.93%; p

Table 2 Summary result of clinical trials assessing the efficacy of SNRIs in ADHD

Autor, year	Medication administration routine[a]	Comparator arm	Trial duration	Result[b]	Side effect	Tolerability[c]
Venlafaxine						
Olvera et al. 1996 [36]	• For < 40 kg: 50 mg daily • For > 40 kg: 75 mg daily	Pre- and post-treatment	5 weeks	• Significant improvements in the CPRS were observed • There were no statistically significant effects on the CPT • Seven out of the original 16 subjects (44%) responded positively to venlafaxine, based on the CPRS. These responders displayed a decrease of at least 1 SD from their baseline	• 50% drowsiness • 37% nausea • 31% irritability • 31% worsening of hyperactivity • There was no evidence of akathisia among these patients and no appreciable effect on blood pressure or heart rate	10%
Findling et al. 2007 [37]	• First two weeks: 37.5 mg daily • Second two weeks: 75 mg daily • Third two weeks: 150 mg daily	Pre- and post-treatment	6 weeks	• Parent ARS-IV total scores indicated a significant improvement in this measure over baseline for the total score, inattentive, and hyperactive-impulsive subscales (all $p < 0.001$) • The total score was significantly improved over the baseline on the teacher version of the ARS-IV ($p < 0.03$) • But the improvement in hyperactivity-impulsivity symptoms did not reach statistical significance ($p < 0.06$)	• 31% headache and nausea • There were no statistically significant changes in mean BP or pulse rate	0.2%
Hashemian and Nazemian 2015 [38]	• 0.5 mg/kg in the first week and 0.1 mg/kg were added every week to reach 1.4 mg/kg in the 10th week	Pre- and post-treatment • Bupropion: • First week: 1.4 mg/kg • 0.51 mg/kg was added weekly to reach 6 mg/kg in the 10th week	10 weeks	Each group had significant effects by the intervention ($p < 0.05$), but the difference between the two groups (F = 0.199, sig = 0.659) was not significant in this regard ($p > 0.05$)	-	–
Zarinara et al., 2010 [39]	• 50 mg/day for < 30 kg • 75 mg/day for > 30 kg	Pre- and post-treatment Methylphenidate: • 20 mg/day for < 30 kg • 30 mg/day for > 30 kg	6 weeks	A significant effect of both protocols on the Parent ARS scores ($p < 0.001$) was observed. The differences between the two protocols were not significant at the endpoint ($p = 0.17$)	• 26% abdominal pain • 16% restlessness • 21% nausea and vomiting • 26% somnolence	–

Table 2 (continued)

Autor, year	Medication administration routine[a]	Comparator arm	Trial duration	Result[b]	Side effect	Tolerability[c]
Amiri et al. 2012 [43]	• Week one and two: 75 mg OD • Week three and four: 75 mg BD • Week five and six: 75 mg TDS	Placebo Pre- and post-treatment	6 weeks	Analysis revealed a significant decrease in ADHD symptoms, as measured by total score, by both subscales and the ADHD index, in both the venlafaxine group ($p < 0.001$) and the placebo group ($p < 0.001$). However, the difference between the two groups for the decrease in the inattentive symptom subscale ($p = 0.539$), the hyperactive/impulsive symptoms subscale ($p = 0.172$), the ADHD symptoms total score ($p = 0.268$), and the ADHD index ($p = 0.188$) did not reach statistical significance	• No serious adverse effects were reported during the trial • There was no significant change in weight • The same was true for changes in systolic and diastolic blood pressure • 50% Dry mouth • Some participants had decreased appetite, insomnia, nausea, vertigo, constipation, anxiety, stomachache, and irritability	5%
Mukaddes and Abali 2004 [40]	• Venlafaxine was initiated at a dose of 18.75 mg/day OD • The dose was flexibly titrated up to 56.25 mg/day (until unwanted effects occurred)	Pre- and post-treatment	6 weeks	• There was a statistically significant improvement in the mean total score of the Conner 10-item parent index from baseline to endpoint • Also, the CGI severity item showed a statistically significant change from baseline to endpoint ($p < 0.05$)	• 15% somnolence • 15% stomach ache • 7% headache • 7% behavioral activation • 23% sedation only at higher doses (56.25 mg/day)	0%
Hornig-Rohan & Amsterdam, 2002 [41]	• Venlafaxine 100–500 mg daily (mean 329 ± 150 mg)	Stimulant (dextroamphetamine or methylphenidate)	8 to 12 weeks	• Four of five (80%) venlafaxine-treated patients responded partially or completely to MDD and ADD symptoms • In contrast, only two of six patients (33%) treated with stimulant monotherapy showed a partial response to both MDD and ADD symptoms	• Mild nausea • Mild insomnia	–
Adler et al., 1995 [45]	• The starting dose was 25–37.5 mg daily • Raised weekly to 225 mg per day	Pre- and post-treatment	8 weeks	• WURS rating scale decreased by an average of 48% at the end of the treatment	• Sedation • Agitation • Nausea	34%

Table 2 (continued)

Autor, year	Medication administration routine[a]	Comparator arm	Trial duration	Result[b]	Side effect	Tolerability[c]
Findling et al. 1996 [42]	• 37.5 mg BD at first. If each subject had any ADHD symptoms after 4 weeks, then the dose was raised to 75 mg BD	Pre- and post-treatment	8 weeks	• There was an overall significant effect for inattention, hyperactivity-impulsivity, and total ADHD scores • CGI scores showed a consistent decline over the study period	• 40% nausea • 30% constipation • 30% somnolence • 30% anxiety	11%
Hedges et al. 1995 [44]	• Started with 18.75 mg per day. The dose was increased until either a response or a side effect happened	Pre- and post-treatment	4 weeks (longer but data are reported for 4 weeks)	• Based on the CGI score, 61% of patients had some response, with 50% moderately or very much improved and 11% mildly improved	• 39% had significant side effects • 50% nausea • 33% fatigue • 17% lowered libido • 17% gas and abdominal pain	39%
Duloxetine						
Bilodeau et al. 2014 [33]	• Duloxetine 60 mg OD	Placebo	6 weeks	• The duloxetine group showed significantly lower symptom severity than the placebo group (24.86% reduction in DSM-IV ADHD Symptoms Total)	• 40% xerostomia, increased anxiety, nausea, and dizziness • All participants reported that their symptoms resolved, except 1 participant who reported reduced appetite at the study conclusion	40%
Mahmoudi-Gharaei et al. 2011 [34]	• First week: 30 mg/day OD • From week 2 to the end of the study: 60 mg/day	Pre- and post-treatment	6 weeks	• A significant decrease in all four subscales of CPRS-R (oppositionality, inattention, hyperactivity, and ADHD index) was observed at the end of the study	• 46% decreased appetite • 30% dry mouth • 23% insomnia, headache, nausea, somnolence, anxiety, and nervousness • The side effects were mild or moderate in severity and did not necessitate dose reduction or any other intervention	17%

Table 2 (continued)

Autor, year	Medication administration routine[a]	Comparator arm	Trial duration	Result[b]	Side effect	Tolerability[c]
Dodangi et al. 2015 [35]	• First week: 15 mg/day OD • The next 5 weeks: 30 mg/day OD	Pre- and post-treatment	6 weeks	• Data analysis showed that the decrease in the overall Conners score and its subscales (except for the inattentiveness subscale) • The attention-deficit hyperactivity subscale showed a significant decrease compared with baseline values from the fourth week afterward • The overall reduction in the Conners scale compared with the baseline values in the second, fourth, and sixth weeks was 22%, 33%, and 33%, respectively	• No weight changes • Changes in blood pressure, pulse, electrocardiography, and laboratory parameters, including cell blood count, fasting blood sugar, thyroid function tests, blood urea nitrogen, creatinine, liver function tests, and electrolytes, were insignificant • 7% were excluded because of severe GI problems • 14% anorexia • 7% mild nausea	7%

[a] *OD*, once daily, *BD* twice a day, *TDS* three times a day

[b] *CPRS* Conners Parent Rating Scale, *CPT* Conners Continuous Performance Test, *ARS-IV* ADHD Rating Scale IV, *WURDS* Wender Utah Rating Scale

[c] Percentage of participants who left the study due to side effects

Table 3 Meta-analysis results of the efficacy of SNRIs in ADHD

Measure	Number of studies	Pooled SMD (95% CI)	Heterogeneity assessment		
			I Squared%	Model	*P* value
SNRIs	10	− 2.20 [− 3.00, − 1.40]	86.93	Random	< 0.001
Venlafaxine (overall)	7	− 1.86 [− 2.69, − 1.02]	86.20	Random	< 0.001
Venlafaxine (Hyperactivity-Impulsivity)	4	− 1.00 [− 1.35, − 0.65]	86.45	Fixed	< 0.001
Venlafaxine (Inattention)	3	− 1.52 [− 1.92, − 1.12]	90.32	Fixed	< 0.001
Duloxetine	3	− 2.65 [− 3.35, − 1.96]	79.34	Fixed	< 0.001

value < 0.001). Subgroup analysis and meta-regression were carried out to find the source of heterogeneity. Meta-regression was conducted by choosing the percentage of males, mean age, medication, and trial duration as moderators. It was revealed that none of these moderators could explain study heterogeneity (Supplementary Table 2). Moreover, a subgroup analysis was conducted. Results did not show any significant differences in age range, percentage of males, and mean age (Supplementary Table 3). However, different groups of trial duration showed significant differences; the 6-week treatment duration had the most efficacy among others, followed by the > 6-week trials and < 6-week trials. Publication bias was observed (Coefficient: − 5.93; *p* value < 0.001) among studies evaluating the efficacy of SNRIs in ADHD. The sensitivity analysis did not show any changes in the results.

Meta-analysis of the efficacy of venlafaxine in ADHD

The pooled SMDs for the efficacy of venlafaxine in ADHD (overall) are shown in Fig. 4 as a forest plot. As can be seen, the overall ADHD symptoms significantly decrease by consuming venlafaxine (Effect size: − 1.86 SMDs; 95% CI: [− 2.69, − 1.02]; *p* value < 0.001, I-squared: 86.02%, *p* value < 0.001). Subgroup analysis and meta-regression were carried out to find the source of heterogeneity. Meta-regression was conducted by choosing the percentage of males, mean age, and trial duration as moderators. It was revealed that the percentage of males is one of the sources of study heterogeneity (R-squared: 49.54%, Supplementary Table 2). Moreover, a subgroup analysis was conducted. Results did not show any significant group differences for age range and mean age. However, different groups of trial duration and different percentages of males showed significant differences; the 6-week treatment duration has the most efficacy among others, followed by the > 6-week trials and < 6-week trials. In the case of gender, 40–60% of males had the most effectiveness, followed by 60–80% and 80–100%, respectively. It seems that venlafaxine is more effective in females. Publication bias was observed (Coefficient: − 5.70; *p* value < 0.5). The sensitivity analysis did not show any changes in the results.

The pooled SMDs for the efficacy of venlafaxine in ADHD (hyperactivity-impulsivity subscale) are shown in Fig. 5. As can be seen, the hyperactivity-impulsivity symptoms of ADHD significantly decrease by consuming venlafaxine (Effect size: − 1.00 SMDs; 95% CI: [− 1.35, − 0.65]; *p* value < 0.001; I-squared: 86.45%, *p* value < 0.001). Subgroup analysis and meta-regression were not carried out since the included studies were few in number. Publication bias was observed within this subgroup (Coefficient: − 4.98, *p* value < 0.001). The sensitivity analysis did not show any changes in the results.

The pooled SMDs for the efficacy of venlafaxine in ADHD (Inattentive subscale) are shown in Fig. 6. As can be seen, the inattentive symptoms of ADHD significantly decrease by consuming venlafaxine (Effect size: − 1.52 SMDs; 95% CI: [− 1.92, − 1.12]; *p* value < 0.001; I-squared: 90.32%, *p* value < 0.001). Subgroup analysis and meta-regression were not carried out since the included studies were few in number. Publication bias was observed within this subgroup (Coefficient: − 5.94, *p* value < 0.001). The sensitivity analysis did not show any changes in the results.

Meta-analysis of the efficacy of duloxetine in ADHD

The pooled SMDs for the efficacy of duloxetine in ADHD are shown in Fig. 7. As can be seen, the symptoms of ADHD significantly decrease by consuming duloxetine (Effect size: − 2.65 SMDs; 95% CI: [− 3.35, − 1.96]; *p* value < 0.001; I-squared: 79.34%, *p* value < 0.05). Subgroup analysis and meta-regression were not carried out since the included studies were few in number. Publication bias was observed within this subgroup (Coefficient: − 6.40, *p* value < 0.01). The sensitivity analysis did not show any changes in the results.

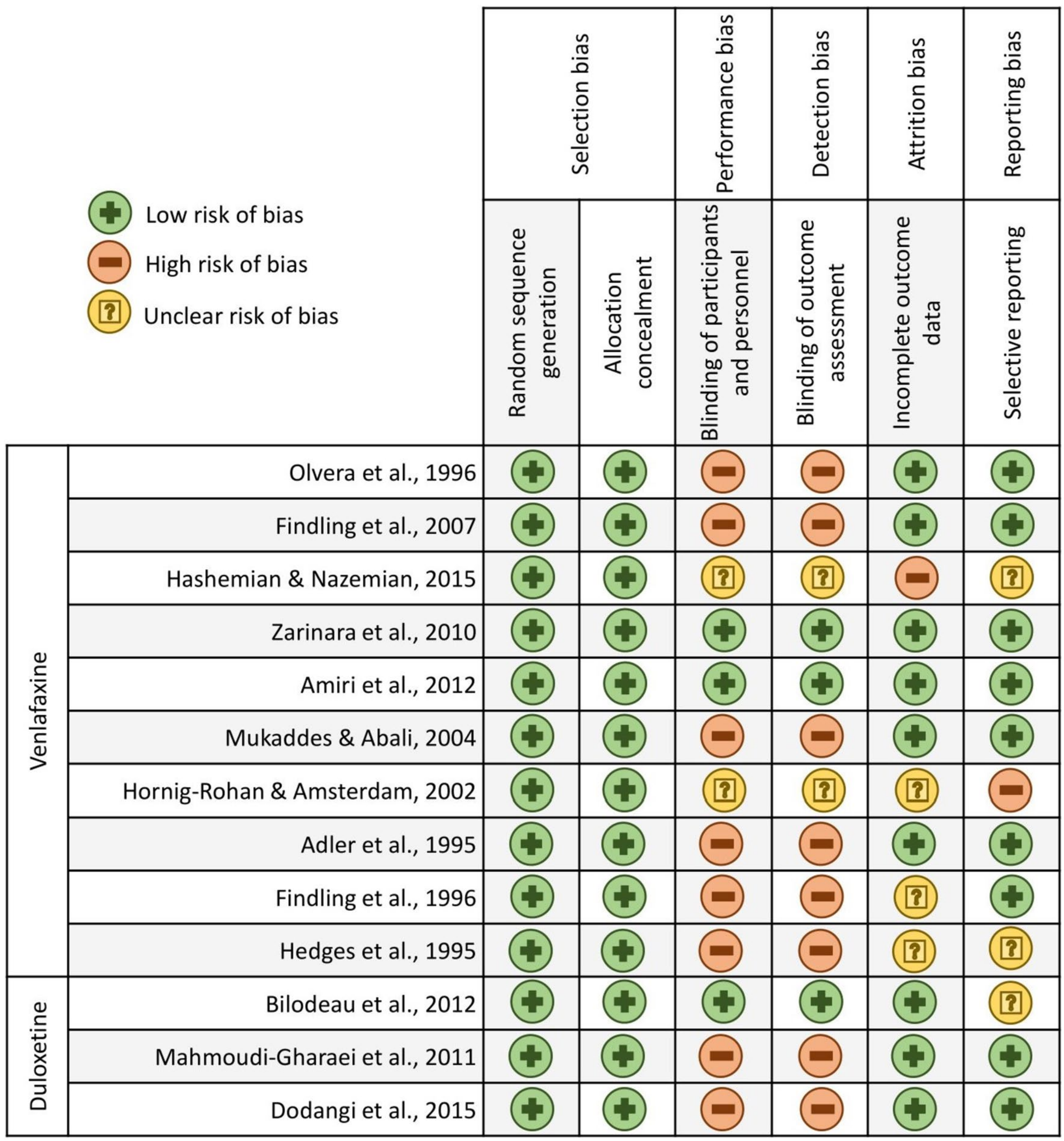

Fig. 2 The results of risk of bias assessment for included studies

Outcomes certainty

Table 4, the outcome of the certainty assessment, helps conclude about the certainty of results for using SNRIs in ADHD. As can be seen, results are reported separately for each drug and the whole group. For using venlafaxine in all ADHD patients without any age range, the certainty of outcomes is high after reviewing the results for 246 patients. When we classify the participants by age, the certainty of outcomes still remains high for the “Children and adolescents” and the “Adults” groups. The sample size for these two conclusions was 145 and 101, respectively.

Regarding the side effects, the same certainty was acquired. It seems that venlafaxine is well tolerable in all age groups. Moreover, some mixed conclusions were reported only in single studies, and their certainty was very low. For example, while one study reported that the efficacy of venlafaxine was as high as methylphenidate, another study reported that the effectiveness of

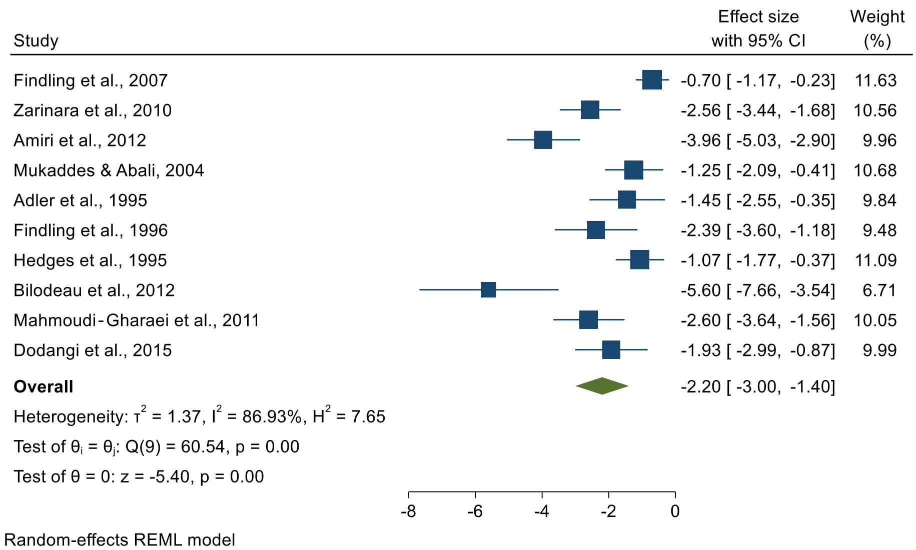

Fig. 3 The pooled effect size of SNRIs is reducing ADHD symptoms

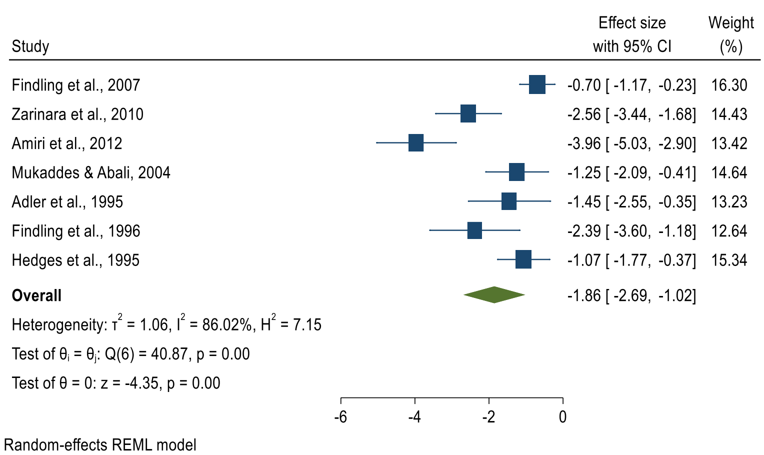

Fig. 4 Meta-analysis results of the efficacy of venlafaxine in treating ADHD (overall) along with the results of heterogeneity assessment

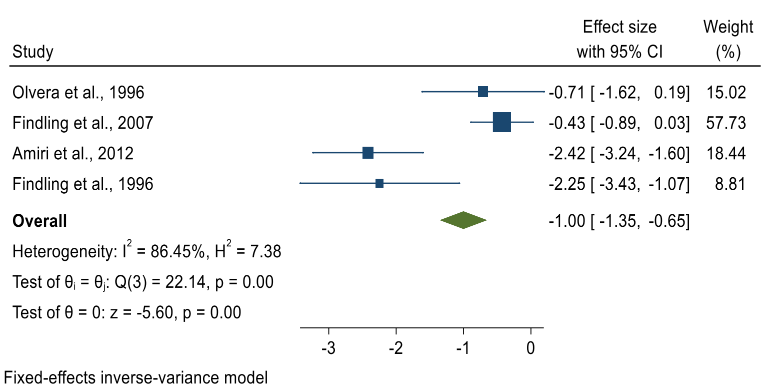

Fig. 5 Meta-analysis results of the efficacy of venlafaxine in treating ADHD (hyperactivity-impulsivity subscale) along with the results of heterogeneity assessment

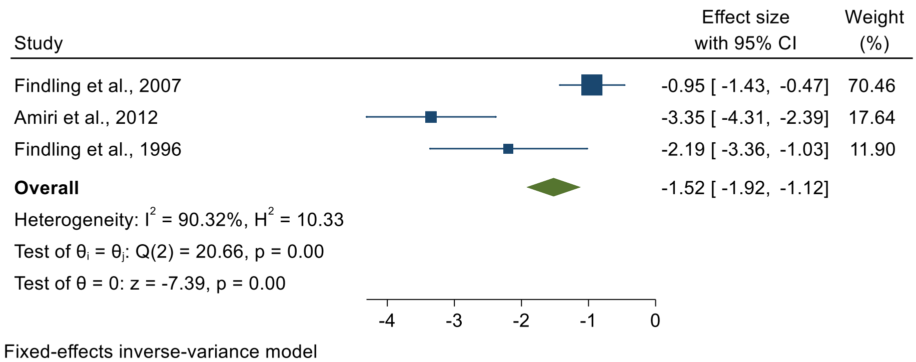

Fig. 6 Meta-analysis results of the efficacy of venlafaxine in treating inattentive symptoms of ADHD along with the results of heterogeneity assessment

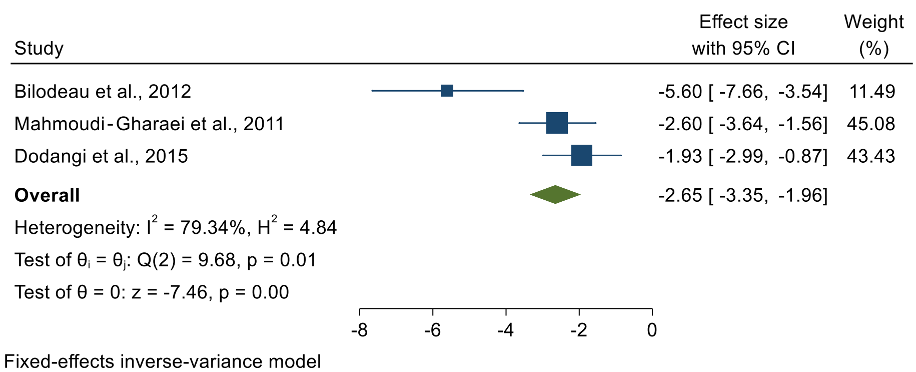

Fig. 7 Meta-analysis result of the efficacy of duloxetine in treating ADHD along with the results of heterogeneity assessment

venlafaxine was not higher than placebo. These results need more clinical trials to be verified.

Regarding duloxetine, one main drawback that led to lower certainties was the low number of references. Although all the references reported improved symptoms, this outcome gets moderate reliability since this conclusion is based only on three studies. The scores were very low regarding side effects, and it seems that duloxetine is not as well tolerated as venlafaxine. Overall, the certainty of reducing ADHD symptoms by SNRIs is high after studying 306 patients, and the certainty of side effect tolerability is moderate.

Risk of bias assessment

Figure 2 displays the outcomes of the risk of bias assessment. As can be seen, all 13 studies had a low risk of bias in the "Random sequence generation" and the "Allocation concealment" sections. Regarding the "Performance bias," three, two, and eight studies got a low, unclear, and high risk of bias, respectively. The high rate of increased risks in this section was due to the fact that many of the included studies were open trials. The results of detection bias were the same as performance bias. Nine studies had a low risk of bias in the "Attrition bias" section. Three had unclear risks, and one had a high risk of bias. Finally, regarding the "reporting bias" section, nine, three, and one studies had a low, unclear, and high risk of bias, respectively.

Discussion

Efficacy of SNRIs in ADHD

Although serotonin-norepinephrine reuptake inhibitors are mostly used in depression and anxiety, this study showed that they can also reduce attention deficit hyperactivity disorder symptoms in children, adolescents, and adults. Aligned with our research, a systematic review [54] also reported the effectiveness of venlafaxine in controlling ADHD in children and adolescents. In line with our findings, that study also reported that the most common side effects of venlafaxine were somnolence and stomach pain. There were no other systematic reviews about the efficacy of venlafaxine in ADHD. Moreover, there was also no former systematic review regarding the efficacy of duloxetine in ADHD.

Another piece of evidence related to this study is a review by Verbeeck et al. [16] in which they systematically

Table 4 GRADE evidence profile: using SNRIs is treating ADHD symptoms

Certainty assessment								Population size	Certainty
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
Venlafaxine									
Venlafaxine significantly improves ADHD symptoms in ADHD patients (no age range)	10	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	246	High
Venlafaxine significantly improves ADHD symptoms in children and adolescents	5	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	145	High
Venlafaxine significantly improves ADHD symptoms in adults	5	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	101	High
The side effects of venlafaxine in ADHD patients were not serious and were tolerable (no age range)	10	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	246	High
The side effects of venlafaxine in children and adolescent ADHD patients were not serious and were tolerable	5	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	145	High
The side effects of venlafaxine in adult ADHD patients were not serious and were tolerable	5	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	101	High
Bupropion and venlafaxine are equal in efficacy for treating ADHD symptoms in children	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	40	Very low

Table 4 (continued)

Certainty assessment								Population size	Certainty
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
Methylphenidate and venlafaxine are equal in efficacy for treating ADHD symptoms in children	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	38	Very low
Placebo and venlafaxine are equal in efficacy for treating ADHD symptoms in adults	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	44	Very low
Venlafaxine is better than methylphenidate in treating ADHD patients suffering from chronic MDD	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	17	Very low
Venlafaxine improves inattentive symptoms but not hyperactivity/impulsivity symptoms in children and adolescents	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	38	Very low
Duloxetine									
Duloxetine significantly improves ADHD symptoms (no age range)	3	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	60	Moderate
Duloxetine significantly improves ADHD symptoms in children and adolescents	2	RCT	Serious	Serious	Serious	Not serious	Not serious	30	Low
Duloxetine significantly improves ADHD symptoms in adults	1	RCT	Serious	Serious	Serious	Not serious	Not serious	30	Very low

Table 4 (continued)

Certainty assessment								Population size	Certainty
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
The side effects of duloxetine in ADHD patients were not serious and were tolerable (no age range)	3	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	60	Low
The side effects of duloxetine in children and adolescent ADHD patients were not serious and were tolerable	2	RCT	Serious	Serious	Serious	Not serious	Not serious	30	Very low
The side effects of duloxetine in adult ADHD patients were not serious and were tolerable	1	RCT	Serious	Serious	Serious	Not serious	Not serious	30	Very low
Duloxetine improves hyperactivity/impulsivity symptoms but not inattentive symptoms	1	RCT	Not serious	Serious	Serious	Not serious	Not serious	13	Very low
SNRIs									
SNRIs significantly improve ADHD symptoms (no age range)	13	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	306	High
SNRIs significantly improve ADHD symptoms in children and adolescents	7	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	175	High
SNRIs significantly improve ADHD symptoms in adults	6	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	131	High
The side effects of SNRIs in ADHD patients were not serious and were tolerable (no age range)	13	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	306	Moderate

Table 4 (continued)

Certainty assessment								**Population size**	**Certainty**
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
The side effects of SNRIs in children and adolescent ADHD patients were not serious and were tolerable	7	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	175	Moderate
The side effects of SNRIs in adult ADHD patients were not serious and were tolerable	6	RCT	Not serious	Not serious	Not serious	Not serious	Not serious	131	Moderate

RCT randomized clinical trial

reviewed the efficacy of antidepressants in managing ADHD. However, they only found that one medication, bupropion, is among the effective antidepressants for ADHD. Results for desipramine, paroxetine, and lithium were not sufficient for drawing a conclusion. It is worth mentioning that the efficacy of reboxetine, a selective norepinephrine reuptake inhibitor, was reported, confirming the participation of the noradrenergic system in ADHD. This conclusion is also aligned with the pharmacology of atomoxetine, an FDA-approved medication for ADHD, which is a selective noradrenaline reuptake inhibitor. Interestingly, when that study reviewed the efficacy of selective serotonin reuptake inhibitors (SSRIs), it suggested that the addition of a noradrenergic treatment combined with SSRIs can significantly enhance the efficacy of SSRIs in ADHD. Our study's results firmly confirm this suggestion.

In the case of other SNRIs, data are very limited. While desvenlafaxine was not noticed for ADHD, there were some restricted studies on milnacipran. The first study [55] was a case-report of a 24-year-old woman suffering from ADHD. Results showed that her inattention and hyperactivity were significantly improved by consuming milnacipran. The second study [56] showed that milnacipran can be an effective add-on therapy for patients suffering from ADHD and GAD who are taking methylphenidate. The last study [57] was conducted on patients with Adult Asperger's disorder who had some symptoms of ADHD too. The mean ADHD scores (both inattention and hyperactivity/impulsivity) significantly improved in all of the 15 participants. However, it is important to note that these studies are limited in scope and more research is needed to fully understand the potential benefits and risks of using milnacipran for ADHD. It is also worth noting that there is currently no data on the use of levomilnacipran for ADHD.

The dosage and administration routine of SNRIs that were reported to be effective in ADHD patients were as follows:

Venlafaxine in children:

- Starting from 0.5 mg/kg daily, gradually rising to 1.4 mg/kg daily.
- 50 mg/day for < 30 kg and 75 mg/day for > 30 kg.

Venlafaxine in children and adolescents:

- For < 40 kg: 50 mg daily, for > 40 kg: 75 mg daily.
- First two weeks: 37.5 mg daily, second two weeks: 75 mg daily, third two weeks: 150 mg daily.
- Starting from 18.75 mg/day OD and gradually rising, reaching 56.25 mg/day OD.

Venlafaxine in adults:

- Week one and two: 75 mg OD, weeks three and four: 75 mg BD, weeks five and six: 75 mg TDS.
- Starting from 25–37.5 mg daily OD and gradually raising, reaching 225 mg daily.
- Starting from 37.5 mg BD and gradually raising, reaching 75 mg BD.

Duloxetine in children:

- First week: 15 mg/day OD, the next weeks: 30 mg/day OD

Duloxetine in adolescents:

- First week: 30 mg/day OD, from week 2: 60 mg/day

Duloxetine in adults:

- 60 mg OD

Safety and tolerability profile of SNRIs in ADHD patients

Regarding safety and tolerability, eight out of ten studies included for venlafaxine reported that nausea and abdominal pain were of the major side effects of this drug in ADHD patients. This side effect is aligned with the general safety profile reported for venlafaxine [58]. Sedation takes place as the next frequently reported side effect (seven out of ten studies). Moreover, since ADHD patients experience hyperactivity and impulsivity, some side effects like behavioral activation, agitation, and worsening of hyperactivity, which were reported in five out of ten studies, are prone to notice. These side effects seem not to be reported as the common side effects for venlafaxine [58] but seem relatively frequent in ADHD patients. It is suggested for future research to study this particular side effect among ADHD patients. Finally, regarding the concerns for cardiovascular side effects of venlafaxine, three studies [36, 37, 43] made clear reports that no changes in blood pressure and heart rate were seen. This is while no other studies reported any cardiovascular side effects. Overall, it can be claimed that venlafaxine is tolerable in ADHD patients since studies reported no serious side effects. Among the reported side effects, several studies reported that side effects disappeared after dose reduction or after a while.

In the case of duloxetine, xerostomia seemed to be the prominent side effect, while nausea, decreased appetite, and headache were also reported. All these side effects align with the general safety profile of duloxetine, and nothing new was reported. Similar to venlafaxine, studies reported that side effects were mild to moderate and disappeared after dose reduction or after a while.

ADHD pathophysiology and possible mechanism of action of SNRIs in treating ADHD

Medications used to treat ADHD show that there may be a dopamine and norepinephrine deficit in ADHD patients. However, the underlying dysregulation seems to be extensively complicated. Although the precise etiology of ADHD is unknown, a mix of genetic and environmental factors is thought to be responsible for affecting the development and functioning of the brain [59]. Research has shown differences in the structure and function of certain brain areas in individuals with ADHD compared to those without [60–62]. These differences may affect attention, impulse control, motivation, and other cognitive processes. Knowing the disease's pathophysiology helps reveal the mechanisms by which SNRIs may be effective.

This is widely accepted that there is a strong genetic component to ADHD [62, 63]. Studies have shown that individuals with ADHD are more likely to have family members with the disorder [63]. Several genes have been implicated in ADHD, including those involved in dopamine regulation and synaptic function [63–66]. While molecular mechanisms underlying genetic contributions to ADHD are still being studied, dopamine and norepinephrine dysregulation are believed to be the primary neurotransmitter abnormalities associated with ADHD [62]. These neurotransmitters play a crucial role in regulating attention, motivation, and reward processing [67]. Research has shown that medications such as stimulants and non-stimulants can effectively increase dopamine and norepinephrine levels in the brain, improving symptoms of ADHD. It is worth mentioning that studies have shown that serotonin also plays an important role in regulating mood, behavior, and attention. Studies have found [68, 69] that individuals with ADHD may have lower serotonin levels in their brains, which can contribute to symptoms such as impulsivity, hyperactivity, and difficulty focusing. However, it is important to note that a serotonin deficiency does not solely cause ADHD and that other factors also play a role.

On the other hand, abnormalities in the prefrontal cortex, caudate nuclei, and cerebellum [61, 62], which are involved in regulating attention and behavior, have been linked to ADHD. These abnormalities include reduced volume and activity in the prefrontal cortex, which is responsible for executive functioning, attention, impulse control, and decision-making, as well as decreased activity in the basal ganglia, which plays a role in motor control and reward processing [59, 60]. Dopamine and norepinephrine work together to maintain the network activity between these areas by acting on multiple receptors.

Regarding the norepinephrine receptors, it is thought that the α2 receptors play a part in the pathophysiology of ADHD, which is completely consistent with the mechanism of action of the ADHD medication guanfacine, a direct postsynaptic α2A stimulant. It is worth noting that the prefrontal cortex has the highest concentration of α2A receptors [59]. There are other proofs suggesting that the prefrontal cortex has a role in ADHD, like a study by [70], which reported people with ADHD have a substantially slower rate of prefrontal brain development. Moreover, impairment in inhibitory behavior, reward reversal, and working memory deficits are some symptoms of prefrontal cortex lesions, which present similarly to ADHD. Poor focus, being easily distracted, and impulsiveness are further characteristics of both ADHD and lesions of the prefrontal cortex [71, 72]. Regarding other brain centers that are shown to be altered in ADHD, the cerebellum [73, 74], corpus striatum [75, 76], inferior parietal cortex [77, 78], and dorsal anterior cingulate cortex can be mentioned [79, 80].

Reports show that dopaminergic brain deficiency has been linked to ADHD, particularly in the mesocortical, mesolimbic, and nigrostriatal pathways [81, 82]. Dysregulation in these pathways leads to impaired cognition. Cognitive deficiencies are linked to dysfunction in the mesocortical dopamine system, whereas hypoactivity in the mesolimbic dopaminergic pathway is thought to contribute to the motivational difficulties seen in ADHD patients. Another important component of the “reward” circuitry, which is compromised in ADHD, is the mesolimbic pathway. The substantia nigra and striatum are connected by the dopaminergic nigrostriatal pathway, which is recognized to be essential for dopamine signaling involved in cognitive function and the regulation of voluntary movements [83, 84].

Now, this question may arise: How do stimulants help reducing hyperactivity? At first look, it seems that stimulants should worsen hyperactivity, but the physiological pathways are more complicated. The answer lies in the molecular mechanisms involved in ADHD. In normal people, the dopamine 2/dopamine 3 (D2/D3) presynaptic receptors, which produce inhibitory signals to inhibit dopamine release, get stimulated modestly during the tonic pool of synapses. Guided attention, focus, and organizational skills are favored by a moderate stimulation of dopamine and norepinephrine postsynaptic receptors. It is theorized that in ADHD, the tonic pool (for both dopamine and norepinephrine) decreases, allowing for a massive phasic release of neurotransmitters and, as a result, disordered behavior that results in inattention, hyperactivity, and other problems. In simpler words, a neurotransmitter deficiency in the presynaptic terminal leads to a hyper-stimulation of the postsynaptic receptors. Stimulants increase the tonic pool by preventing neurotransmitter absorption into the presynaptic terminal, which inhibits the massive phasic release brought on by the action potential [59].

Too much about genetic and physiological reasons, environmental reasons can also play a role in the presence of ADHD. Prenatal and perinatal risk factors, such as maternal smoking [85, 86] or alcohol consumption during pregnancy [87, 88], have been linked to an increased risk of developing ADHD. It is important for individuals with ADHD to be aware of these potential risk factors and take steps to minimize their exposure. The impact of stress and trauma on ADHD symptoms should also be taken into consideration. Research has shown that individuals who have experienced trauma or chronic stress may have an increased risk of developing ADHD or experiencing more severe symptoms. Therefore, incorporating stress-reducing techniques such as mindfulness, exercise, and therapy can be beneficial in managing ADHD symptoms. Additionally, addressing environmental factors such as diet, sleep habits, and screen time can significantly impact symptom management.

To summarize, knowing the norepinephrine deficiency in stimulating inhibitory presynaptic α2 receptors, SNRIs positively affect these patients by inhibiting the reuptake of norepinephrine, which leads to moderate stimulation of the postsynaptic receptors and inhibits a larger-than-normal phasic release. Moreover, adding the proven role of serotonin deficiency in ADHD patients to the inhibitory effect of SNRIs on re-uptaking serotonin, these medications also benefit ADHD patients by increasing the concentration of synaptic serotonin.

Finally, while medication can be an effective treatment option for some individuals with ADHD, it is not always necessary or appropriate for every individual with ADHD. Alternative treatments such as CBT, mindfulness practices, and lifestyle changes can also effectively manage symptoms. The optimum course of treatment for each person with ADHD should be decided through discussion with a medical expert. Additionally, ongoing support from family members, friends, and mental health professionals can help individuals with ADHD navigate the challenges they may face throughout their lives. With proper treatment and support, individuals with ADHD can lead fulfilling lives and achieve their goals.

Strengths, limitations, and suggestions for future works

This study is the first meta-analysis ever to evaluate the efficacy of SNRIs in ADHD patients. The strength of this study is its comprehensiveness in reporting outcomes. Moreover, the safety and tolerability profile of SNRIs in ADHD patients was precisely reviewed as well. All the possible conclusions and outcomes were extracted and reported precisely (GRADE table), even if the certainties were very low. This clears the way for future researchers to show in which areas we need more studies to increase the reliability of outcomes in the treatment of ADHD symptoms. Another strength of this study is suggesting potential replacements for stimulants without a risk of abuse or serious side effects.

The main limitations of this study are the short period of included trials and the small sample size, which should be rectified in later trials. It is difficult to determine these medications' prolonged efficacy, safety, and possible long-term adverse effects. Moreover, studies of duloxetine were very limited in number. Another limitation was that the data were not sufficient for a meta-analysis of controlled trials and only the open trials were included in the meta-analysis. Future studies are needed to assess the comparative effectiveness of SNRIs with other medications for ADHD. Moreover, more trials are needed in the case of duloxetine.

Conclusion

Duloxetine and venlafaxine can be administered to manage symptoms of ADHD in children, adolescents, and adults while being well tolerated. It seems that duloxetine is more potent in reducing ADHD symptoms. It can also be concluded that venlafaxine is more effective in females.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
CBT	Cognitive behavioral therapy
SNRIs	Serotonin-norepinephrine reuptake inhibitors
GAD	Generalized anxiety disorder
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder
BD	Bipolar disease
MDD	Major depressive disorder
SAD	Separation anxiety disorder
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders 4th edition
CPRS	Conners' Parent Rating Scale
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV
CAARS	Conners' Adult ADHD Rating Scale
CGI-S	Clinical Global Impression ADHD Severity Scale
K-SADS-PL	The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version
WURS	Wender Utah Rating Scale
ADHQ	Attention deficit hyperactivity questionnaire
PTSD	Post-traumatic stress disorder
OD	One daily
BD	Two times a day
TDS	Three times a day

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43045-024-00400-1.

Additional file 1: Supplementary table 1. The syntax used for searching each database and the number of results on February 2023. **Supplementary table 2.** The results of meta-regression analysis. **Supplementary table 3.** The results of the subgroup analysis.

Additional file 2.

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Authors' contributions
RAD and SHK conducted the search and the screening stages. RAD and AH extracted data and designed tables. RAD drafted the paper. ED was the supervisor.

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Availability of data and materials
All the used data are available within the article or its supplementary materials.

Declarations

Ethics approval and consent to participate
This research was approved by the ethics committee of Alborz University of Medical Sciences (103–6176). Consent to participate is not applicable.

Consent for publication
Not applicable,

Competing interests
The authors declare no competing interests.

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