Meta-analysis on the efficacy of the norepinephrine reuptake inhibitors reboxetine and atomoxetine for the treatment of schizophrenia and attention deficit hyperactivity disorder

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2023;32(5):511–522

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Funding sources
None declared

Conflict of interest
None declared

Received on February 28, 2022
Reviewed on August 2, 2022
Accepted on September 17, 2022

Published online on November 30, 2022

Abstract

Background. Norepinephrine transporter inhibitors that can alter the level of neurotransmitter in the brain are used to treat neurological disorders. However, a number of studies have reported their limited significance as a result of their slow onset of action and moderate efficacy.

Objectives. To determine the effects of norepinephrine reuptake inhibitors (NRIs), reboxetine and atomoxetine on schizophrenia and attention deficit hyperactivity disorder (ADHD).

Materials and methods. Relevant articles published between 2000 and 2022 were searched in the MEDLINE, CINAHL (via Ebsco), Web of Science and Scopus databases. Among the various NRIs, studies concerning the 2 potent drugs – reboxetine and atomoxetine – were selected for analysis. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated, along with the exploration of heterogeneity and publication bias, using RevMan software.

Results. A total of 14 eligible studies with a combined sample size of 970 patients were included. Using a random effects model, an OR of 0.55 (0.32–0.94), a Tau^2 value of 0.23, a χ^2 value of 12.31, 8 degrees of freedom (df), an I^2 of 35%, a Z value of 2.19, and a p-value of 0.03 were recorded for reboxetine. Atomoxetine had an OR of 0.35 (0.13–0.97), a Tau^2 value of 0.58, a χ^2 value of 7.31, 4 df, an I^2 of 45%, a Z value of 1.53, and a p-value of 0.04. All results were statistically significant with a low risk of publication bias, as was evident from the p-values >0.05 derived from the Egger's test and the Begg's test. These drugs provided comparable changes to control drugs in Hamilton Depression Rating Scale (HAM-D) scores, Positive and Negative Syndrome Scale (PANSS) scores and ADHD ratings. This confirms the efficacy of reboxetine for the treatment of schizophrenia and atomoxetine for the treatment of ADHD.

Conclusions. The present meta-analysis suggests that NRIs are efficacious and therefore they are potential candidate drugs for the treatment of schizophrenia and ADHD.

Key words: schizophrenia, neurological disorders, atomoxetine, attention deficit hyperactivity disorder, reboxetine

Cite as
Hu X, Pan L, Li W. Meta-analysis on the efficacy of the norepinephrine reuptake inhibitors reboxetine and atomoxetine for the treatment of schizophrenia and attention deficit hyperactivity disorder. *Adv Clin Exp Med*. 2023;32(5):511–522. doi:10.17219/acem/155802

DOI
10.17219/acem/155802

Introduction

Neurological disorders, including schizophrenia, attention deficit hyperactivity disorder (ADHD), depression, anxiety, and bipolar disorders, are very common medical ailments reported worldwide. These disorders are mainly associated with symptoms such as delusions, disorganized thinking, depression, abnormal social and motor behaviors, and hallucinations.[1] Treatment of these neurological disorders is achieved through cognitive therapy, rehabilitation, psychoeducation, family therapy, behavioral therapy, and the use of a variety of antipsychotic and anti-tremor medicines.[2] Among the various medications, drugs that can specifically alter the level of neurotransmitters in brain cells, such as dopamine reuptake inhibitors, gamma-aminobutyric acid reuptake inhibitors, and a variety of norepinephrine reuptake inhibitors (NRIs) are of much use.[3] Norepinephrine reuptake inhibitors have the capacity to alter the activity of the norepinephrine transporter, which is a solute carrier protein that controls the movement of sodium and chloride ions. This mechanism of NRIs is dependent upon the reuptake of the neurotransmitters norepinephrine and dopamine, and therefore such drugs are potential candidates for the treatment of neurological disorders.[4–6]

A variety of NRI drugs, including atomoxetine, reboxetine, viloxazine, and edivoxetine, are currently available for the treatment of neurological disorders (Fig. 1). Indeed, a number of randomized controlled trials have suggested the potential benefits of reboxetine for the treatment of schizophrenia patients.[7–16] Similarly, the potential benefits of atomoxetine for the treatment of ADHD have been reported in randomized controlled trials.[17–21] Salazar de Pablo et al. reported in their meta-analysis that these disorders are more prevalent in younger females.[22] Meanwhile, Tanaka et al. reported in their review article that such neurological disorders arise due to neurodevelopmental defects or the alteration of normal brain development during early embryonic life.[23] Such defects can be investigated using functional magnetic resonance imaging, as reported by Nyatega et al.[24] Furthermore, these developmental defects led to higher levels of dissociative schizophrenia symptoms, as shown by Panov.[25] Rog et al.[26] reported in their study that altered fatty acid metabolism was responsible for schizophrenia, while Gaebler et al.[27] demonstrated that vitamin D deficiency was responsible, and Correia et al.[28] suggested that alterations in serum lipid levels as a major cause of schizophrenia. Therefore, NRIs that can alter the level of neurotransmitters are potential candidate drugs for these neurological disorders.[29,30] Additionally, De Crescenzo et al. contended that pharmacotherapy using noradrenergic agents was effective in the management of ADHD.[31]

Objectives

In this study, a meta-analysis was conducted to assess the efficacy of 2 NRI medications, reboxetine and atomoxetine, in the treatment of schizophrenia and ADHD, respectively.

Materials and methods

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) normative recommendations were followed and the study protocol was registered at Shandong University, Jinan, China (registration No. SU#/IRB/2021/554).

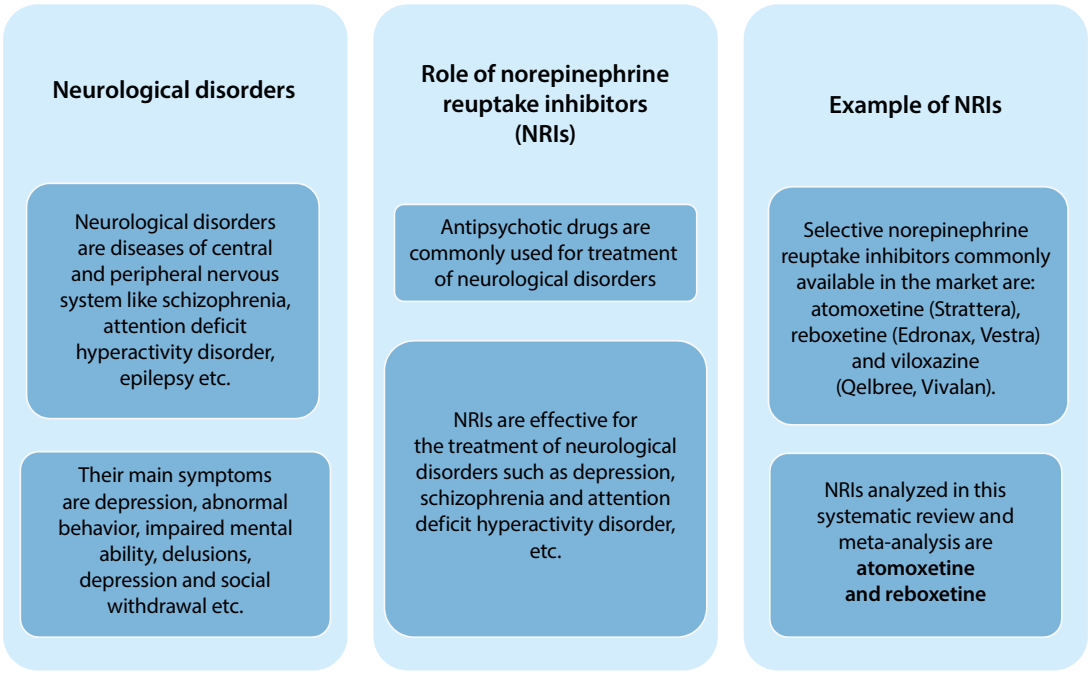

Fig. 1. Study details

Search strategy

This meta-analysis was based on an extensive literature search of MEDLINE (via PubMed), CINAHL (via Ebsco), Scopus, and Web of Science databases. Studies published between the years 2000 and 2022 were searched using the following keywords: "neurological disorder", "neurotransmitters", "schizophrenia", "systematic review", 'meta-analysis", and "norepinephrine transporter inhibitors". All of the included articles[8–21] were assessed using the PRISMA guidelines, and studies were selected randomly irrespective of the language, publication status or the type of study (prospective, retrospective, clinical trial). A demographic summary of the patients was designed, with consideration to the variables included in the searched studies.

To assess the efficacy and safety of NRIs, as well as their genetic variants, reboxetine and atomoxetine were selected for analysis. Event data from the selected studies were extracted. In the selected studies, patients of different age groups were treated with either reboxetine, atomoxetine or control drugs, and their Hamilton Depression Rating Scale (HAM-D) score, Positive and Negative Syndrome Scale (PANSS) score and metabolic parameters were observed. Statistical parameters, including diagnostic odds ratio (OR) with 95% confidence interval (95% CI) and heterogeneity of data of both drugs, were calculated with RevMan software v. 4.1 (https://training.cochrane.org/online-learning/core-software/revman). Data for both drugs were summarized using forest plots.

Two authors (XH and LP) scanned the relevant sources for related studies separately. Full-text articles of the studies were collected and abstracts were only used if they contained sufficient information for the review and meta-analysis. Obsolete references were excluded and useful studies were included as per the inclusion criteria. Event data with useful variables were collected by 2 researchers (XH and LP) independently.

Inclusion and exclusion criteria

Studies published between 2000 and 2022 that reported on the safety and efficacy of NRIs and their genetic variants for the treatment of schizophrenic patients were included. Mostly the full-text studies were included but some abstracts were also taken into account if had sufficient data, while studies with insufficient data, reporting the use of medicines other than NRIs, and those published before 2000, were excluded (Fig. 2).

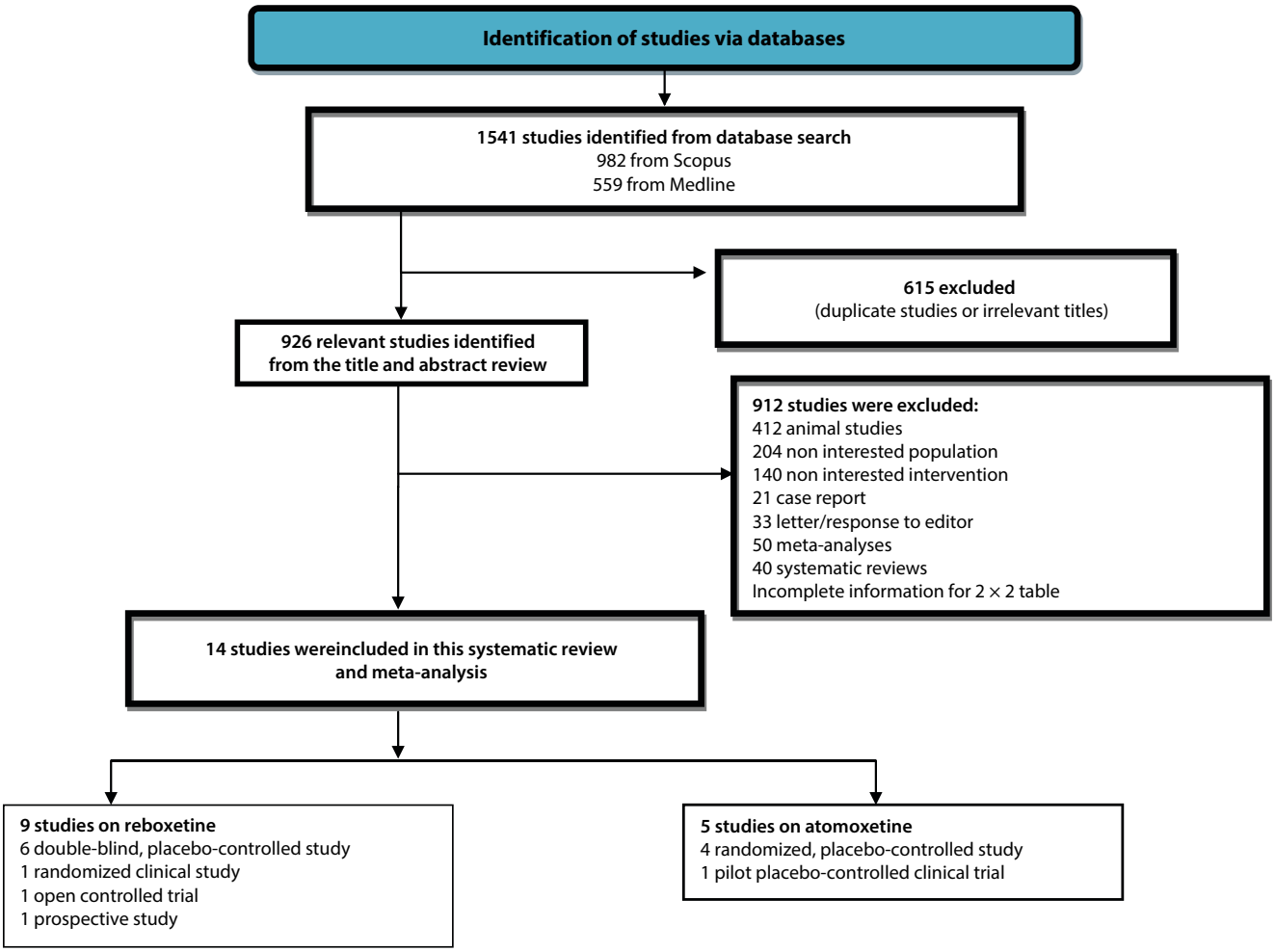

Fig. 2. Flow diagram for the selection of the studies based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Evaluation of the analytical standard

Two reviewers (XH and LP) separately evaluated the methodological validity of the included studies and calculated the heterogeneity of the data. Author WL was responsible for resolving any disagreements between the authors XH and LP. The risk of bias of all the included studies was assessed and summarized using RevMan software.

Sources of heterogeneity

Investigated sources of heterogeneity included the use of full-text publication compared to abstracts, randomized controlled trials compared to retrospective studies, age group, number of patients, duration of treatment, scale of analysis, and comparison of St. John's wort with different selective serotonin reuptake inhibitor controls.

Statistical analyses

Diagnostic ORs for both reboxetine and atomoxetine were calculated using the DerSimonian and Laird technique. For this, a 2 × 2 table was constructed and a meta-analysis was performed. Pooled diagnostic ORs were then calculated with their 95% CIs, and their respective forest plots were designed. To investigate heterogeneity, Tau^2 value, χ^2 test, Z value, and I^2 index in random bivariate mode were calculated. To assess the risk of publication bias, the Deek's funnel plot for both types of studies, using either reboxetine or atomoxetine, was designed using MedCalc software v. 20.118 (MedCalc Software Ltd., Ostend, Belgium). The risk of publication bias was assessed using Egger's test and Begg's test.

Results

Literature search results

A total of 1541 studies were found in different databases. Among these studies, 615 were excluded after reading their titles and abstracts, and 926 records were further examined. Moreover, 912 studies were excluded as 412 were animal studies, 204 were of a population of non-interest, 140 studies were of non-interest interventions, 21 were case reports, 33 were letters/responses to the editor, 50 were meta-analyses, 40 were systematic reviews, and 12 were excluded due to incomplete information. Key reasons for omission were inadequate evidence and inappropriate comparison criteria required to create 2 × 2 tables for review. Only 14 studies were selected for final screening and meta-analysis (Fig. 2). Of the 14 studies included, 9 were related to the benefits of reboxetine and 5 were related to atomoxetine treatment.

Demographic details of the studies included in this meta-analysis are shown in Table 1. It describes authors of the study, year of publication, publishing journal, type of study, duration of study, total sample size, type and dosage of NRI used, control drug and its dosage, age and gender of patients, test scores analyzed, number of patients with positive outcomes, HAM-D scores, PANSS scores, metabolic parameters of patients, and p-values indicating statistical significance of the data. The risk of bias (Table 2) was assessed, summarized (Fig. 3) and shown as a bar graph (Fig. 4). Studies included in the analysis presented a low risk of bias, as is evident from the tables and graphs.

Fourteen clinical studies with a total of 970 schizophrenia patients were included, according to the inclusion criteria.

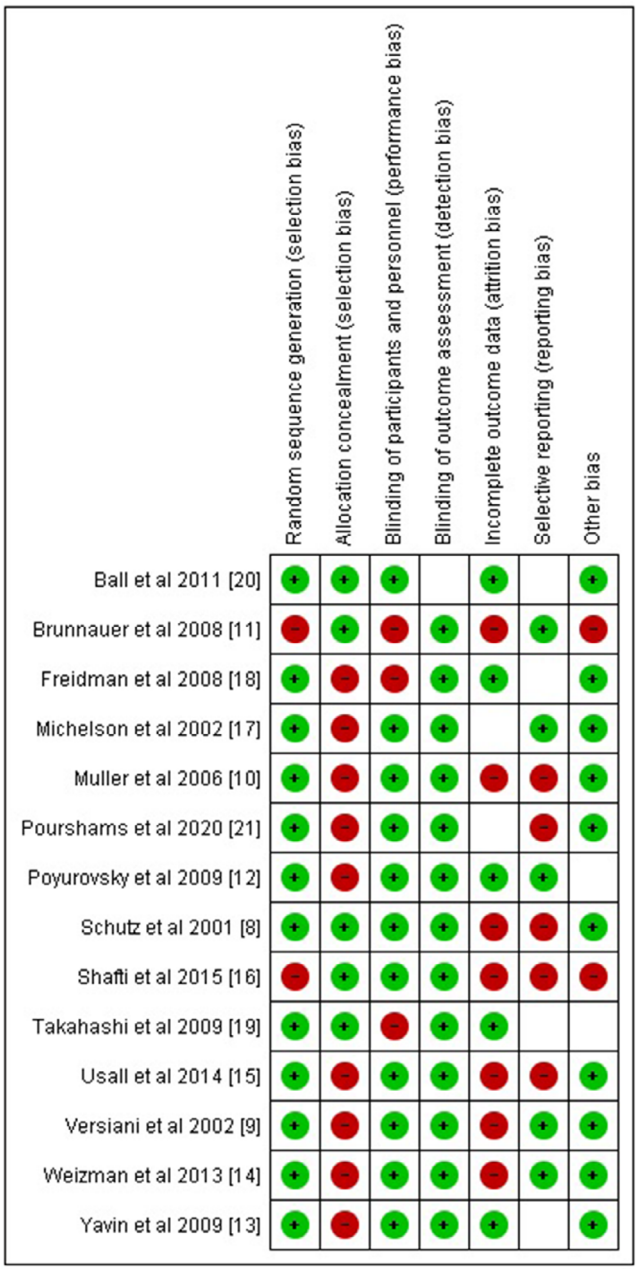

Fig. 3. Risk of bias summary

Table 1. Demographic summary of included studies

Study ID and year	Journal title	Type of study	Norepinephrine transporter inhibitor studied	Total number of patients	Duration of study	Age of patient [years]	Evaluation of results	Gender	Drug dose	Evaluated HAM-D and PANSS scores	Positive outcome	p-value
Schutz and Berk[8] 2001	*International Clinical Psychopharmacology*	double-blind study	reboxetine	30	6 weeks	25–40	change in the baseline PANSS score	1 M/14 F	reboxetine (4–10 mg/day)	15.8 ±7.29	12/15	0.7556
								1 M/14 F	placebo (10 mg day)	14.1 ±5.68	11/15	
Versiani et al.[9] 2002	*Journal of Clinical Psychiatry*	double-blind study	reboxetine	75	8 weeks	18–65	change in the baseline PANSS score	12 M/25 F	reboxetine (10 mg day)	5.2	31/38	<0.05
								13 M/25 F	placebo (10 mg day)	3.2	19/37	
Müller et al.[10] 2006	*Molecular Psychiatry*	prospective study	reboxetine	40	6 weeks	23–65	reduction in the HAM-D score	8 M/12 F	4–10 mg reboxetine plus placebo	12.1 ±8.3	8/20	<0.0001
								12 M/8 F	10 mg reboxetine plus 400 mg celecoxib	7.9 ±7.1	10/20	
Brunnauer et al.[11] 2008	*Journal of Clinical Psychiatry*	randomized clinical study	reboxetine	40	2 years	40–60	reduction in the HAM-D score	11 M/9 F	reboxetine 4.5 mg/day	24.2 ±6.7	16/20	<0.01
								11 M/9 F	mirtazapine 30 mg/day	22.6 ±6.5	15/20	
Poyurovsky et al.[12] 2009	*Israel Journal of Psychiatry and Related Science*	double-blind, placebo-controlled study	reboxetine	33	3 years	20–50	HAM-D score	10 M/6 F	reboxetine 4 mg/day	10.31 ±3.34	11/17	0.92
								11 M/6 F	olanzapine 10 mg/day	10.18 ±4.65	11/16	
Cohen-Yavin et al.[13] 2009	*Clinical Neuropharmacology*	open controlled trial	reboxetine	27	8 weeks	6–16	total DAS score	16 M	reboxetine 2–8 mg/day	15.6 ±11.7	11/16	<0.005
								11 M	methylphenidate 10–20 mg/day	13.4 ±13.1	11/11	
Amrami-Weizman et al.[14] 2013	*Psychopharmacology*	double-blind, placebo-controlled study	reboxetine	54	6 weeks	20–40	change in serum insulin level (microIU/mL)	17 M/12 F	olanzapine/reboxetine 4 mg bid	2.76 ±33.37	27/25	<0.05
								13 M/12 F	olanzapine/placebo (10 mg day)	0.83 ±13.79	19/29	

Table 1. Demographic summary of included studies – cont.

Study ID and year	Journal title	Type of study	Norepinephrine transporter inhibitor studied	Total number of patients	Duration of study	Age of patient [years]	Evaluation of results	Gender	Drug dose	Evaluated HAM-D and PANSS scores	Positive outcome	p-value
Usall et al.[15] 2014	*Journal of Clinical Psychiatry*	double-blind study	reboxetine	90	6 months	35–55	change in the baseline PANSS score	18 M/5 F	citalopram 4.5 mg/day	73.13 ±10.31	17/23	0.6511
								27 M/7 F	reboxetine 6 mg/day	72.06 ±15.15	24/33	
								22 M/11 F	placebo 6 mg/day	75.06 ±18.62	23/34	
Shoja Shafti et al.[16] 2015	*Therapeutic Advances in Psychopharmacology*	double-blind study	reboxetine	50	12 weeks	2–43	reduction in the HAM-D score	25 M	25 patients received reboxetine 4 mg/day	5.36 ±1.83	19/25	<0.01
								25 M	25 patients received placebo 4 mg/day	1.69 ±6.02	6/25	
Michelson et al.[17] 2002	*American Journal of Psychiatry*	randomized, placebo-controlled study	atomoxetine	170	6 weeks	6–16	reduction in the ADHD rating scale	60 M/25 F	atomoxetine, 40 mg/day	12.8 ±12.4	68/85	<0.001
								60 M/25 F	placebo 40 mg/day	5.0 ±10.4	66/85	
Friedman et al.[18] 2008	*Journal of Clinical Psychopharmacology*	pilot placebo-controlled clinical trial	atomoxetine	20	8 weeks	above 18	change in the baseline PANSS score	10 (6 M/4 F)	atomoxetine, 40 mg/day	4.7 ±5.1	8/10	0.15
								10 (5 M/5 F)	placebo 40 mg/day	4.4 ±8.9	6/10	
Takahashi et al.[19] 2009	*Journal of Child and Adolescent Psychopharmacology*	randomized, double-blind, placebo-controlled study	atomoxetine	245	8 weeks	6–18	ADHD rating scale	52 M/10 F	atomoxetine 0.5 mg per day	38 ±61.3	61/62	0.01
								52 M/10 F	placebo (10 mg day)	37 ±59.7	60/62	
Ball et al.[20] 2011	*Clinical Schizophrenia & Related Psychoses*	double-blind controlled trial	atomoxetine	36	2 weeks	35–60 years	SAS total scores	13 M/6 F	atomoxetine 40 mg/day	1.2 ±1.7	13/17	0.02
								12 M/5 F	placebo 40 mg/day	1.1 ±1.1	5/18	
Pourshams et al.[21] 2020	*Clinical Schizophrenia & Related Psychoses*	randomized controlled clinical study	atomoxetine	60	2 years	21–39 years	change in baseline PANSS score	16 M/14 F	atomoxetine, 40 mg/day	62.33 ±9.37	30/30	0.002
								17 M/13 F	placebo 40 mg/day	52.16 ±8.33	25/30	

PANSS – Positive and Negative Syndrome Scale; HAM-D – Hamilton Depression Rating Scale; DAS – Depression, Anxiety and Stress score; ADHD – attention deficit hyperactivity disorder; SAS – Social Adjustment Score.

Table 2. Risk assessment for included studies

Study ID and year	Schutz and Berk[8] 2001	Versiani et al.[9] 2002	Müller et al.[10] 2006	Brunnauer et al.[11] 2008	Poyurovsky et al.[12] 2009	Cohen-Yavin et al.[13] 2009	Amrami-Weizman et al.[14] 2013	Usall et al.[15] 2014	Shoja Shafti et al.[16] 2015	Michelson et al.[17] 2002	Friedman et al.[18] 2008	Takahashi et al.[19] 2009	Ball et al.[20] 2011	Pourshams et al.[21] 2020
Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the study avoid inappropriate exclusions?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did all patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all patients included in the analysis?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was the sample frame appropriate to address the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were study participants sampled in an appropriate way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were valid methods used for the identification of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there appropriate statistical analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

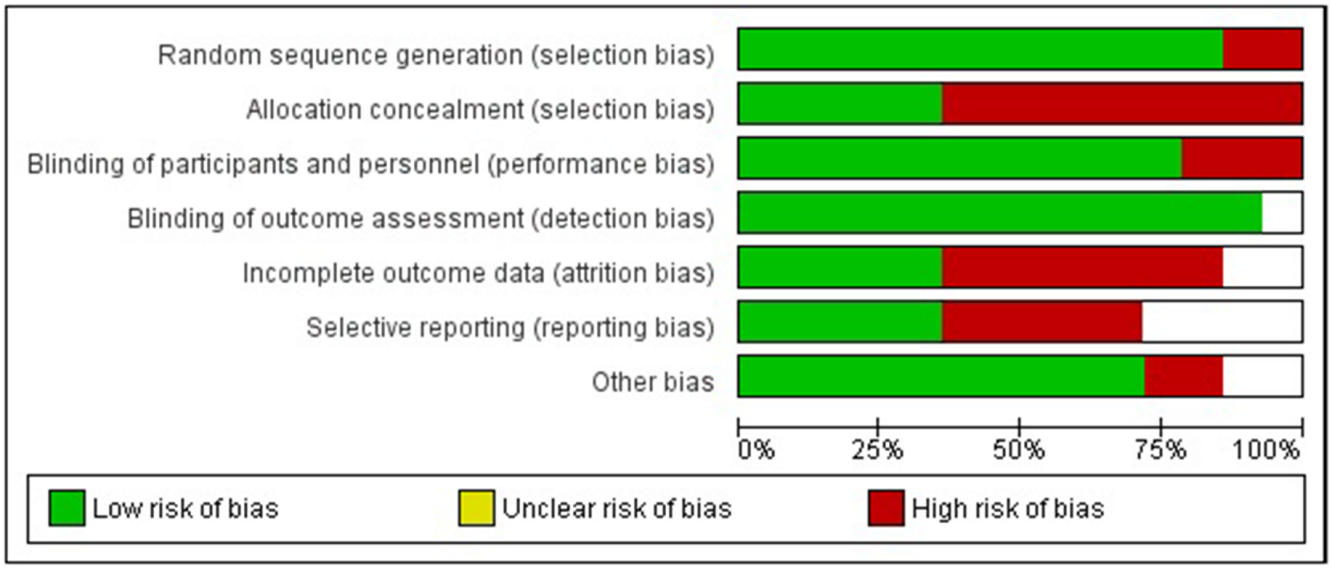

Fig. 4. Risk of bias graph

The included studies encompassed adult patients of different age groups who were chosen randomly and treated with either placebo or NRIs. In both cases, reductions in HAM-D score and PANSS score, as well as changes in metabolic parameters were observed.

Meta-analysis results

Meta-analysis of the included studies using a random effects model indicated that they had a low risk of publication bias since both the Egger's test and the Begg's test

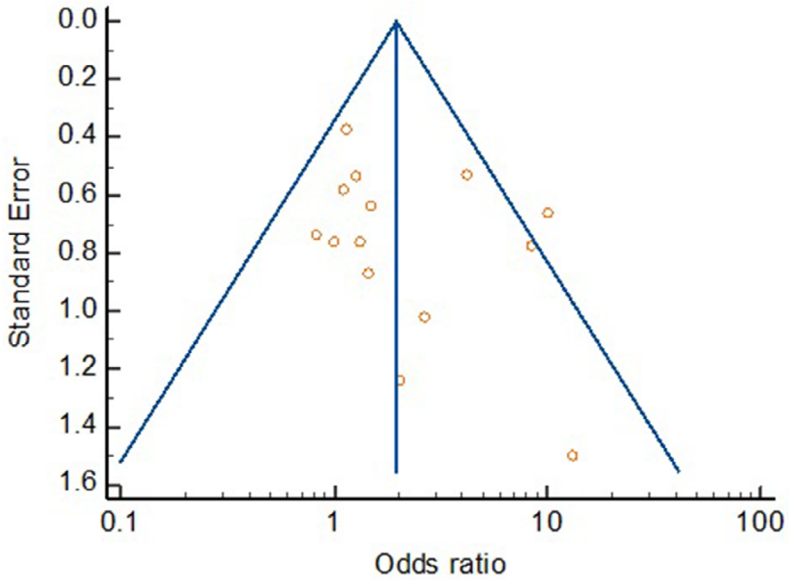

Fig. 5. Funnel plot for publication bias

95% CI – 95% confidence interval.

Publication bias	
Egger's test	
Intercept	1.2002
95% CI	-0.9821 to 3.3826
Significance level	P = 0.2539
Begg's test	
Kendall's Tau	0.3187
Significance level	P = 0.1124

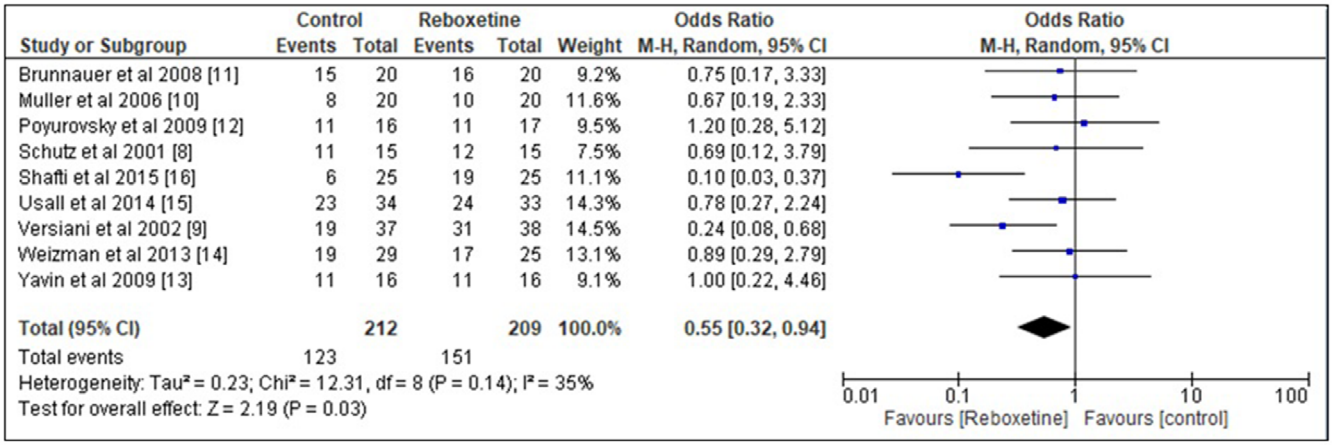

Fig. 6. Funnel plot for reboxetine

95% CI – 95% confidence interval; df – degrees of freedom; M–H – Mantel–Haenszel method.

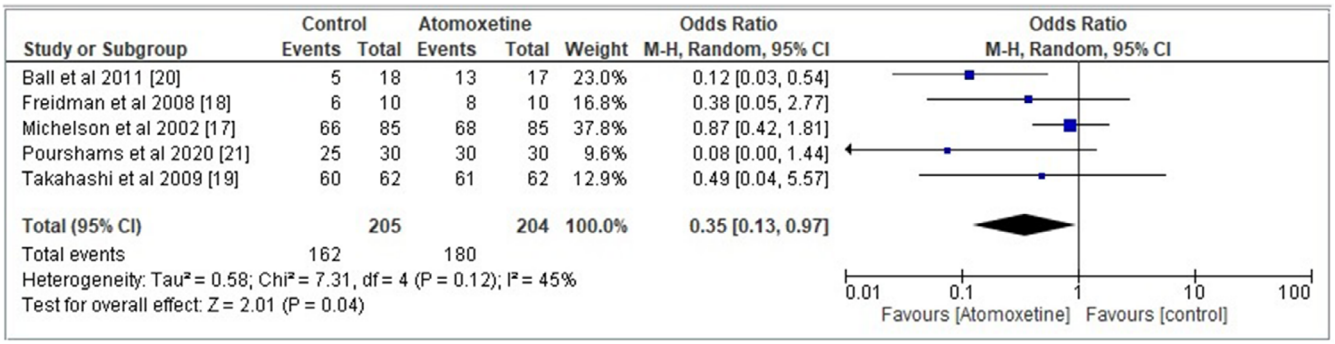

Fig. 7. Forest plot for the odds ratio of atomoxetine

95% CI – 95% confidence interval; df – degrees of freedom; M–H – Mantel–Haenszel method.

p-values were > 0.05. Specifically, the Egger's test gave a p-value of 0.25 and the Begg's test gave a p-value of 0.11 (Fig. 5). The analysis of reboxetine resulted in an OR value of 0.55 (0.32–0.94), a Tau^2 value of 0.23, a χ^2 value of 12.31, 8 degrees of freedom (df), I^2 value of 35%, a Z value of 2.19, and a p-value of 0.03 (Fig. 6). Similarly, atomoxetine produced an OR of 0.35 (0.13–0.97), with Tau^2 value of 0.58, χ^2 value of 7.31, 4 df, an I^2 value of 45%, a Z value of 2.01, and a p-value of 0.04 (Fig. 7). All results were statistically significant and heterogeneous.

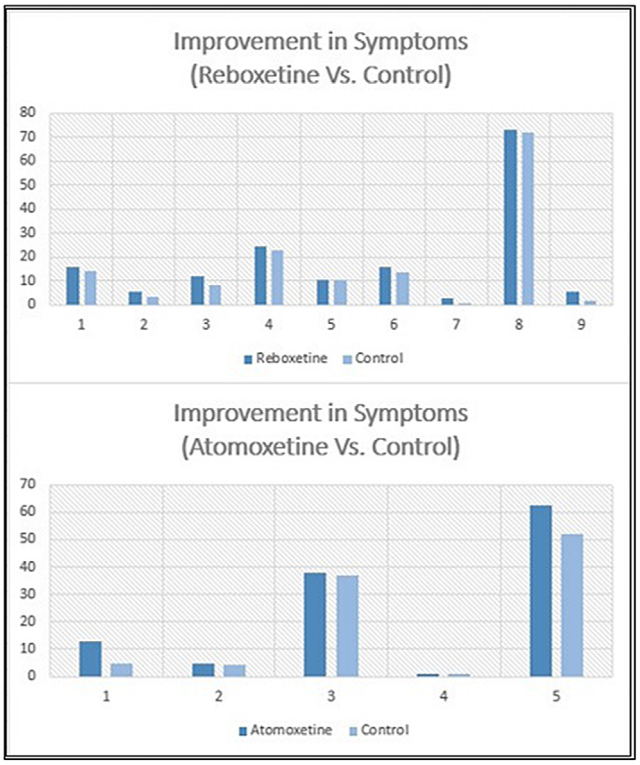

Fig. 8. Improvement in symptoms with norepinephrine reuptake inhibitors (NRIs) compared to controls

Greater efficacy and safety of the NRIs reboxetine and atomoxetine were demonstrated for the treatment of schizophrenia and ADHD patients. Indeed, both drugs led to a larger change in the evaluated test scores, including HAM-D and PANSS, in comparison to the control drugs (Table 3 and Fig. 8).

A statistical summary of the meta-analysis results is shown in Table 4. The pooled OR < 1 for both drugs suggests that they have comparable efficacy, and both have potential use in the treatment of schizophrenia and ADHD.

Combining all results of the meta-analysis, it is clear that reboxetine and atomoxetine are safe and as effective as comparable drugs. Indeed, these NRIs were effective in reducing HAM-D and PANSS scores, along with other clinical symptoms in schizophrenia patients. In fact, they have shown greater efficacy in comparison to control drugs and had fewer adverse side effects. Therefore, these drugs are a better alternative for the treatment of schizophrenia and ADHD.

Discussion

Neurological disorders such as schizophrenia and ADHD are serious health disorders that result in individuals becoming socially isolated, depressed, confused, unhappy, less organized, and sad. If left untreated, they can lead to more serious neurological issues such as borderline personality disorder, which can provoke suicide attempts.[32–36] Studies suggest that fear conditioning, changes in the immune system and metabolic changes are also responsible for the development of these neurological disorders.[37–40] Therefore, these disorders need to be detected in a timely manner using various neuroimaging modalities[41–44] and should be treated using available strategies such as behavioral therapy, family therapy or with anti-psychotic medications.[45,46] Indeed, NRIs are widely applied in the treatment of mental disorders.

Table 3. Comparison of norepinephrine transporter inhibitor drugs with control drugs

Study ID and year	Evaluation of results	Norepinephrine transporter inhibitors	Control
Reboxetine			
Schutz and Berk[8] 2001	change in the baseline PANSS score	15.8 ±7.29	14.1 ±5.68
Versiani et al.[9] 2002	change in the baseline PANSS score	5.2	3.2
Müller et al.[10] 2006	reduction in the HAM-D score	12.1 ±8.3	7.9 ±7.1
Brunnauer et al.[11] 2008	reduction in the HAM-D score	24.2 ±6.7	22.6 ±6.5
Poyurovsky et al.[12] 2009	HAM-D score	10.31 ±3.34	10.18 ±4.65
Cohen-Yavin et al.[13] 2009	total DAS score	15.6 ±11.7	13.4 ±13.1
Amrami-Weizman et al.[14] 2013	change in serum insulin level (microIU/mL)	2.76 ±33.37	0.83 ±13.79
Usall et al.[15] 2014	change in the baseline PANSS score	73.13 ±10.31	72.06 ±15.15
Shoja Shafti et al.[16] 2015	reduction in the HAM-D score	5.36 ±1.83	1.69 ±6.02
Atomoxetine			
Michelson et al.[17] 2002	reduction in the ADHD rating scale	12.8 ±12.4	5.0 ±10.4
Friedman et al.[18] 2008	change in the baseline PANSS score	4.7 ±5.1	4.4 ±8.9
Takahashi et al.[19] 2009	ADHD rating scale	38 ±61.3	37 ±59.7
Ball et al.[20] 2011	SAS total scores	1.2 ±1.7	1.1 ±1.1
Pourshams et al.[21] 2020	change in the baseline PANSS score	62.33 ±9.37	52.16 ±8.33

PANSS – Positive and Negative Syndrome Scale; HAM-D – Hamilton Depression Rating Scale; DAS – Depression, Anxiety and Stress score; ADHD – attention deficit hyperactivity disorder; SAS – Social Adjustment Score.

Table 4. Statistical summary of included studies

Reboxetine: study ID and year	Odds ratio# (95% CI)	Atomoxetine: study ID and year	Odds ratio# (95% CI)
Brunnauer et al.[11] 2008	0.75 (0.17–3.33)	Ball et al.[20] 2011	0.12 (0.03–0.54)
Müller et al.[10] 2006	0.67 (0.19–2.33)	Friedman et al.[18] 2008	0.38 (0.05–2.77)
Poyurovsky et al.[12] 2009	1.20 (0.28–5.12)	Michelson et al.[17] 2002	0.87 (0.42–1.81)
Schutz and Berk[8] 2001	0.69 (0.12–3.79)	Pourshams et al.[21] 2020	0.80 (0.00–1.44)
Shoja Shafti et al.[16] 2015	0.10 (0.03–0.37)	Takahashi et al.[19] 2009	0.49 (0.04–5.57)
Usall et al.[15] 2014	0.78 (0.27–2.24)		
Versiani et al.[9] 2002	0.24 (0.08–0.68)		
Amrami-Weizman et al.[14] 2013	0.89 (0.29–2.79)		
Cohen-Yavin et al.[13] 2009	1.00 (0.22–4.46)		
Total (95% CI)	0.55 (0.32–0.94)	Total (95% CI)	0.35 (0.13–0.97)

Odds ratio is calculated using the Mantel–Haenszel (M–H) method with random effects; 95% CI – 95% confidence interval.

As Maletic et al. reported in their systematic review, alpha-adrenergic receptors play an important role in the aberrant regulation of arousal and cognition in schizophrenia.[47] Similarly, Mäki-Marttunen et al. noted the importance of the locus coeruleus-norepinephrine system in cognition and the pathophysiology of schizophrenia.[48] A study conducted by Navarra et al. reported on the potential benefits of atomoxetine for reducing clinical symptoms in an animal model of schizophrenia.[49] Furthermore, Locher et al. presented potential benefits of NRIs for the treatment of these psychiatric disorders in children.[50] Additionally, Outhred et al.,[51] Ruhé et al.,[52] Rubia et al.,[53] and Papakostas et al.[54] showed that NRIs are efficacious in the treatment of neurological disorders.

Similar to the available literature, current systematic review and meta-analysis also has low risk of bias of and demonstrated that reboxetine and atomoxetine have significant ORs and favorable statistical parameters for the treatment of schizophrenia and ADHD. Indeed, comparable pooled OR values were 0.55 (0.32–0.94) for reboxetine and 0.35 (0.13–0.97) for atomoxetine. Both of these values are significant as they are less than 1. The results were heterogeneous and significant ($p < 0.05$) and there was a low risk of publication bias. These results are predictive of the potential benefits of atomoxetine and reboxetine for the treatment of neurological disorders and favor their use as beneficial drug candidates.

Limitations

Limitations of the present study include the variability of NRIs and control drugs used for the treatment of schizophrenia and ADHD patients. Also, the calculation of different scores including HAM-D scores, PANSS scores and metabolic parameters, using varying analytical tests performed by different persons, increased the risk of false-negative results. Furthermore, the data could be impacted to some extent by the fact that several analyzed studies did not report on the comparable efficacy of NRIs with conventional drugs. Data from other relevant studies on the efficacy of NRIs for the treatment of schizophrenia and ADHD could have also included more results to guide the use of NRIs more precisely. Additionally, detailed data on patient's case history, physical examination, social well-being, and pathological tests would make the results of the studies more useful in planning the treatment.

Conclusions

For the treatment of neurological disorders such as schizophrenia and ADHD, various medications that can block the activity of selective neurotransmitters are currently in use. The current study was designed to conduct a meta-analysis on the efficacy of the NRIs reboxetine and atomoxetine for the treatment of schizophrenia and ADHD, respectively. On the basis of the statistically significant findings and alleviation clinical symptoms in patients with the use of these drugs, we recommend the use of these NRIs for the treatment of these medical disorders.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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