**TITLE:** **Nonstimulant Medications for Attention-Deficit/Hyperactivity Disorder (ADHD) in Adults: Systematic Review and Meta-analysis**

Nevena V. Radonjić MD, PhD1\*, Alessio Bellato, PhD2\*, Nayla M. Khoury MD1, Samuele Cortese MD, PhD3,4,5,6,7\*\*, Stephen V. Faraone PhD8\*\*

1Department of Psychiatry and Behavioral Sciences, Upstate Medical University, Syracuse, NY, USA,

2School of Psychology, University of Nottingham Malaysia, Jalan Broga, Semeniyih, Malaysia

3Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

4Solent NHS Trust, Southampton, UK

5Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK.

6Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA

7Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

8Departments of Psychiatry and Behavioral Science and Neuroscience and Physiology, Upstate Medical University, Syracuse, NY, USA

\*equal contribution as first author

\*\*equal contribution as senior author

**Short Running Header:** Non-stimulant Treatment of ADHD

**Corresponding author**

Stephen V. Faraone, PhD

Departments of Psychiatry and Behavioral Science and Neuroscience and Physiology SUNY Upstate Medical University

Institute for Human Performance, Room 3707

505 Irving Ave. Syracuse, NY 13210, USA

sfaraone@childpsychresearch.org

Phone: (315) 464-3113

**STATEMENTS AND DECLARATIONS**

**Funding**

**Dr. Radonjić** is supported by the European Union’s Horizon 2020 research and innovation Commission under grant agreement No 945151 and Patrick Lee Foundation. **Dr. Faraone** is supported by the European Union’s Horizon 2020 research and innovation programme under grant agreement No 965381; NIMH grants U01AR076092-01A1, 1R21MH1264940, R01MH116037; 1R01NS128535 – 01; Oregon Health and Science University, Otsuka Pharmaceuticals, Noven Pharmaceuticals Incorporated, and Supernus Pharmaceutical Company.

**Drs. Bellato, Cortese, and Khoury** have declared that they have no funding to disclose

**Conflict of interest**

**Dr. Cortese** declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. In the past year, **Dr. Faraone** received income, potential income, travel expenses continuing education support and/or research support from, Aardvark, Akili, Genomind, Ironshore, KemPharm/Corium, Noven, Ondosis, Otsuka, Rhodes, Supernus, Takeda, Tris and Vallon. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from: Alcobra, Arbor, Aveksham, CogCubed, Eli Lilly, Enzymotec, Impact, Janssen, Lundbeck/Takeda, McNeil, NeuroLifeSciences, Neurovance, Novartis, Pfizer, Shire, and Sunovion. He also receives royalties from books published by Guilford Press: *Straight Talk about Your Child’s Mental Health*; Oxford University Press: *Schizophrenia: The Facts*; and Elsevier: *ADHD: Non-Pharmacologic Interventions*. He is also Program Director of www.adhdinadults.com.

**Drs. Radonjić, Bellato, and Khoury** declare that they have no financial disclosures.

Ethics approval: not applicable.

Consent to participate: not applicable.

Availability of data and material: not applicable.

Code availability

All authors contributed to writing of the manuscript. Drs. Faraone, Bellato and Cortese conceived and designed the analysis. Drs. Bellato and Cortese collected the data and performed analysis.

**Financial Disclosures**

**Funding Acknowledgements**

# ABSTRACT

**Background:** For some adults with Attention-Deficit/Hyperactivity Disorder (ADHD), nonstimulants need to be considered either as a monotherapy or as an adjunct to stimulants.

**Objectives:** To assess the efficacy, acceptability, and tolerability of nonstimulants in adults with ADHD.

**Methods:** Data sources, searches, and study selection were based on a previously published network meta-analysis of randomized clinical trials (RCTs) [1], which we updated in March 2022. Specifically, we searched PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials, EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov for double-blind RCTs with a placebo arm, lasting at least one week, including adults with a diagnosis of ADHD based on DSM-III, DSM-III-R, DSM-IV(TR), DSM-5 or ICD-9- or 10, and reporting data on efficacy, tolerability (drop-out due to side effects) and acceptability (drop-out due to any cause) of guanfacine, clonidine, or atomoxetine. Additionally, we searched for RCTs of viloxazine ER, approved for ADHD in 2021. Random-effects meta-analyses were conducted, and the risk of bias for individual RCTs was assessed using the Cochrane Risk of Bias tool.

**Results:** We included 18 studies in the meta-analyses (4308 participants) plus one additional study in the narrative synthesis (374 participants). The meta-analysis showed that atomoxetine (Hedge’s g = -0.48, 95% CI = [-0.64; -0.33]), guanfacine (two RCTs) (Hedge’s g = -0.66, 95% CI = [-0.94; -0.38]) and viloxazine ER (one RCT) were significantly more efficacious than placebo. Atomoxetine was less well tolerated than placebo, while tolerability of guanfacine and viloxazine ER could not be meta-analysed, since only one study, for each medication, reported on it.

**Discussion:** All investigated non-stimulants were more efficacious in the treatment of ADHD in adults, than placebo, while the placebo had better acceptability and tolerability.

**Short Running Header:** Non-stimulant Treatment of ADHD

**Protocol:** https://osf.io/5vnmt/?view\_only=2bf87ed12ba94645babedceeee4c0120

**Key Points**:.

* Atomoxetine, guanfacine and viloxazine ER are effective in the treatment of ADHD in adults
* Observed side effects do not create an impediment to the use of studied nonstimulants in adults with ADHD

# INTRODUCTION

The first observations of the clinical phenomenon today recognized as Attention Deficit/Hyperactivity Disorder (ADHD) have been available since the beginning of the 18th century [2], and the clinical benefits of stimulant use had been noticed already in 1937 [3]. Although stimulants are typically considered as first-line treatments for ADHD [4], for some patients nonstimulant options need to be explored either as a monotherapy or as an adjunct to stimulants due to either lack of efficacy or tolerability of stimulants and no clear guidelines are currently available to guide the selection of nonstimulant medication for these patients. The first FDA-approved nonstimulant medication for ADHD was atomoxetine in 2002, followed by extended-release (ER) versions of guanfacine and clonidine in 2009 and 2010 respectively, and viloxazine ER in 2021. While atomoxetine and viloxazine ER have FDA approval for use in pediatric and adult populations, guanfacine ER and clonidine ER are approved for pediatric use only [5].

Nonstimulant medications are a heterogeneous group of compounds with various mechanisms of actions that result in the modulation of adrenergic and/or dopaminergic neurotransmission. Atomoxetine is a selective reuptake inhibitor of the norepinephrine transporter (NET) that increases extracellular levels of both dopamine (DA) and norepinephrine (NE). Guanfacine and clonidine are 2 adrenergic agonists differing in receptor specificity: clonidine is a non-selective alpha-2 adrenergic agonist binding to 2A, B, and C subtypes of adrenergic receptors, while guanfacine acts preferentially at post-synaptic noradrenergic 2A receptors. Both guanfacine and clonidine strengthen prefrontal cortex (PFC) network connectivity by acting on -2A receptors, which mediate inattentiveness, hyperactivity, and impulsivity in the PFC [5, 6]. Viloxazine is a multimodal serotonergic and noradrenergic modulating agent (SNMA) with a unique profile exerting its activity on NET and serotonin receptors [7] .

While meta-analytic evidence on the efficacy and tolerability of ADHD medications in adults has been summarised in the past, e.g. in [8], an updated meta-analytic synthesis focusing on all currently approved nonstimulants for adults with ADHD is missing.

The objectives of this systematic review and meta-analysis were to address this gap and provide an updated systematic review and meta-analysis of randomised controlled trials (RCTs) on the efficacy, tolerability and acceptability of nonstimulant medications in the treatment of adults with ADHD.

# MATERIALS AND METHODS

## Data sources and searches, and study selection.

Data sources, searches, and study selection for this meta-analysis were based on a previously published network meta-analysis (NMA) of RCTs by Cortese et al. [1], which search has been updated yearly up to 30th March 2022, using the same strategy/syntax reported in the original paper [1]. Specifically, the original search was conducted on PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials, EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov. In the original study, Cortese et al., [1] used the following search terms: “adhd” OR “hkd” OR “addh” OR “hyperkine\*” OR “attention deficit\*” OR “hyper-activ\*” OR “hyperactiv\*” OR “overactive” OR “inattentive” OR “impulsiv\*” combined with a list of ADHD medications (Supplement). The US Food and Drug Administration (FDA), European Medicines Agency (EMA), and relevant drug manufacturers’ websites, and references of previous systematic reviews and guidelines, were hand-searched for additional information. Study authors and drug manufacturers were contacted to gather unpublished information and data.

The full lists of RCTs included up to the last update (30th March 2022) and those excluded in Cortese et al. [1], were screened to identify double-blind RCTs with a placebo arm, lasting at least one week, including adults (≥18 years) with a diagnosis of ADHD based on DSM-III, DSM-III-R, DSM-IV(TR), DSM-5, ICD-9 or 10; and reporting data on efficacy, tolerability and acceptability of guanfacine, clonidine, or atomoxetine. Considering that viloxazine ER has been recently approved by the FDA as a non-stimulant medication for ADHD, we also manually searched RCTs reporting data on this medication in adults. Seventeen RCTs were retained from the original search (Cortese et al. [1]), while one study was included from the list of papers retrieved via annual updates (up to March 2022) based on the original search strategy. No study, amongst those initially excluded in the original NMA [1], was found eligible to be included in this meta-analysis. One RCT on viloxazine ER in adults [11] was retrieved from the search conducted in August 2022 and was included in the review. No RCT on clonidine ER in adults was retrieved

The protocol for this systematic review and meta-analysis was uploaded on OSF (https://osf.io/5vnmt/?view\_only=2bf87ed12ba94645babedceeee4c0120). Supplement 1 reports the PRISMA Checklist.

## Outcome, data extraction and quality assessment

Three main outcome measures were investigated in the present study, for medication and placebo arms: (a) efficacy, defined as the mean change in ADHD symptom severity from baseline to endpoint; (b) tolerability, defined as the dropout rate due to side effects. Data were extracted by at least two independent investigators; and (c) acceptability, defined as the dropout rate due to any cause. The risk of bias of individual RCTs was assessed using Cochrane Risk of Bias tool (see Table S11 in the Supplementary appendix of Cortese et al., [4].

## Data synthesis and analysis

For RCTs that resulted eligible to be included in the meta-analysis, we calculated Hedge’s g as the standardized mean difference of the change in ADHD symptom severity between medication and placebo arms. We then calculated the proportion of participants who dropped out from the study because of any cause (acceptability) and because of side effects (tolerability), and calculated log-odds to be inputted in two separate meta-analyses. Random-effects meta-analyses were used to estimate the pooled effect size by using *metafor* [9] in *R 4.1.2* [10], whenever at least two studies reported at least one of the outcomes. Effect sizes were nested within studies in multilevel models for those that reported multiple effect sizes (e.g., at week 12 and week 26), using the Restricted Maximum-Likelihood estimator. Cross-study heterogeneity was tested with Cochran Q. Funnel plots and the rank correlation test for funnel plot asymmetry assessed publication bias and were followed up (where applicable) by trim and fill analyses, to estimate the number of missing studies due to publication bias. Meta-regressions were conducted to investigate potential moderating effects of (a) Assessor (clinician vs. self-report) and (b) Week of assessment. A qualitative synthesis is provided for studies that could not be included in the meta-analysis.

# RESULTS

Sixteen RCTs on atomoxetine (4103 patients in total; 50.5% randomized to medication), two RCTs on guanfacine (235 patients in total; 50.2% randomized to medication), and one on viloxazine ER (374 patients in total; 50.8% randomized to medication) were included in the systematic review (19 studies in total; 4712 patients in total; 50.5% randomized to medication; mean age: 34.7 years; 58.8% males) (Table 1). Amongst the 18 studies reporting data on the efficacy of non-stimulants (15 for atomoxetine, two for guanfacine and one for viloxazine ER, which however was not included in the meta-analysis), all reported the outcomes of assessment conducted in the first 12/14 weeks after the start of the intervention (average: 8.2 weeks) and three also reported data for assessment conducted around the 26th week after the start of the intervention (average: 25.3 weeks). Further information about study characteristics is available in Table 1.

## Atomoxetine

Fifteen studies were included in the meta-analysis investigating the efficacy of atomoxetine vs. placebo (Kay 2009 did not provide usable data). The meta-analysis (on 32 effect sizes) showed that atomoxetine produced significantly larger reductions in ADHD symptoms, than placebo (Hedge’s g = -0.4807, SE = 0.0763, 95% CI = [-0.6362; -0.3251], *t* = -6.3032, *p* < 0.0001; Figure 1). Heterogeneity was significant (Q = 113.6320; *p* < 0.0001), while publication bias was not detected (Kendall's tau = -0.1426, *p* = 0.2556; Figure 2). Meta-regressions investigating potential moderators found no moderating effect of Assessor (clinician vs. self: F1,30 = 0.0308, *p* = 0.8618) or Week of assessment (F1,30 = 0.5934, *p* = 0.4471).

Average dropout rates due to all causes (acceptability) were 34.9% and 27.6% for atomoxetine and placebo, respectively, while dropout rates due to side effects (tolerability) were 9.3% and 3.6% for atomoxetine and placebo, respectively. The meta-analyses (16 studies, 16 effect sizes) investigating acceptability and tolerability of atomoxetine vs. placebo, showed that this type of non-stimulant was less well tolerated (pooled OR = 1.43, 95% CI = [1.25; 1.64]; logOR = 0.3572, SE = 0.0693, 95% CI = [0.2213; 0.4930], *z* = 5.1536, *p* < 0.0001; Figure 3) and less acceptable (pooled OR = 2.70, 95% CI = [1.87; 3.90]; logOR = 0.9923, SE = 0.1876, 95% CI = [0.6247; 1.3599], *z* = 5.2907, *p* < 0.0001; Supplement Figure 1) than placebo. Heterogeneity was not statistically significant for either the meta-analysis on tolerability (Q = 14.6955, *p* = 0.4736) or that on acceptability (Q = 19.5667, *p* = 0.1892). No publication bias was detected for both meta-analyses (tolerability: Kendall's tau = 0.0500, *p* = 0.8248; acceptability: Kendall's tau = -0.0833, *p* = 0.6901) (Figure 4 and Supplement Figure 2).

## Guanfacine

Two studies provided sufficient data for a meta-analysis to be conducted to investigate the efficacy of guanfacine vs. placebo. We found that guanfacine was more effective, than placebo, in reducing ADHD symptoms (Hedge’s g = -0.6606, SE = 0.1435, 95% CI = [-0.9419; -0.3793], *t* = -4.6022, *p* < 0.0001; Figure 5). Heterogeneity was not significant (Q = 0.0012; *p* = 0.9723) and publication bias was not detected (Figure 6). Meta-regressions investigating the moderating effect of Assessor (clinician vs. self) or Week of assessment could not be carried out due to scarcity of studies.

Meta-analyses investigating the acceptability/tolerability of this type of medication could not be carried out, since only one study (Iwanami et al., 2020) reported data on acceptability/tolerability, as follows: dropout rates due to all causes were 21.8% and 7.0% for guanfacine and placebo, respectively, while dropout rates due to side effects were 19.8% and 3.0% for guanfacine and placebo, respectively.

## Viloxazine ER

One RCT [11] was deemed eligible for inclusion in the systematic reviewIt found that viloxazine ER was superior to placebo in improving ADHD symptoms (as measured by the AISRS and CGI-Improvement). Given that only one is RCT available, meta-analyses investigating the acceptability/tolerability of viloxazine ER could not be carried out. The same study reported the following data on acceptability and tolerability, concluding that viloxazine ER was well tolerated: 33.2% and 23.9% for viloxazine ER and placebo, respectively, for dropout rates due to all causes; 8.9% and 4.9% for viloxazine ER and placebo, respectively, for dropout rates due to side effects.

# DISCUSSION

We have presented an updated quantitative synthesis of evidence on the efficacy, acceptability and tolerability of nonstimulant medications in the treatment of adults with ADHD. All medications were significantly more efficacious than placebo in the treatment of ADHD; the comparative efficacies of atomoxetine, guanfacine and viloxazine ER are presented in Figure 7. Although guanfacine had the greatest efficacy effect size, followed by atomoxetine and viloxazine ER, the overlap in 95% confidence intervals indicates that the three drugs do not differ significantly in efficacy. With respect to tolerability, all investigated medications - compared to placebo - were less well tolerated and had a higher overall dropout rate. We did not find any evidence for publication bias, although the small number of guanfacine studies precludes strong conclusions on that issue.

Previously, Cortese et al.'s [1] network meta-analysis concluded that the evidence would support methylphenidate as the first-choice medication for children and adolescents, and amphetamine as the first line treatment for adults. However, there are no clear guidelines on preferred nonstimulant medication for the treatment of adults with ADHD. Here, we show that all investigated nonstimulant medications in the treatment of ADHD were better than placebo and, based on their confidence intervals, did not differ significantly from one another (Figure 7), even though conducting a network meta-analysis to compare these drugs was beyond the scope of this work. The same was the case when compared to the effect size of simulants and their CIs reported elsewhere [1]. Although amphetamines from all investigated medications have the greatest effect size in adults, there was still CI overlap with atomoxetine and guanfacine. In adults with ADHD, methylphenidate and atomoxetine had comparable effect size in terms of symptom reduction rated by clinician [1]. This overlap in confidence intervals limits the ability to interpret if any of these nonstimulant medications is more effective than the others.

Importantly, as this meta-analysis focused on aggregate-level data, it cannot provide information that are informative at the individual patient level. Until more studies are available, when choosing nonstimulant medications clinicians should consider the individual characteristics of patients and other potential clinical effects of the medication. Atomoxetine has been used off-label for treatment-resistant depression [12]. Although viloxazine ER has recently been approved for the treatment of ADHD in the USA, it has been marketed since 1970s as an antidepressant in immediate release (IR) formulation in Europe [13]. IR viloxazine has shown clinical efficacy in the treatment of depressive disorder [14, 15] and in treating concomitant symptoms of anxiety in patients with depression [16-18]. Guanfacine ER has blood pressure-lowering properties and could be a suitable option for patients with comorbid ADHD and hypertension or insomnia [19]. In youth, it is commonly used for patients with both ADHD symptoms and anxiety symptoms such as insomnia.

Potential drug adverse reactions vary between individual patients but may provide some guidance in clinical decision making regarding non-stimulant choice. Atomoxetine and viloxazine ER can both cause nausea and abdominal pain due to their serotonergic effects. Guanfacine and atomoxetine differ in their effects on blood pressure given the former is lowering and the latter has the potential to raise blood pressure. Guanfacine ER is often used in clinical practice given its ability to be effective faster than other nonstimulant choices and our results show it is more effective than placebo. All have the potential to be sedating which can limit use or be helpful for patients with co-morbid anxiety.

This study also found similar effect sizes for non-stimulants in adults as has been documented in children in atomoxetine and guanfacine for clinician-rated ADHD symptoms [1]. However, atomoxetine appears less well tolerated in adults compared with children; in children and adolescent, there was no difference found between placebo and atomoxetine in a recent meta-analysis [1]. Just as with children and adolescents, more studies are need with Viloxazine ER in adults to estimate effect size, although it appears well tolerated. Lastly, there is insufficient data on Clonidine in adults (for whom it is not approved by FDA or other regulatory agencies), whereas in children and adolescents, this medication has been shown to have a similar effect size to guanfacine with wide confidence interval and good tolerability [1]. Of note, the effect size of stimulants in the network meta-analysis by Cortese et al. (2018), when referring to clinician’s ratings of efficacy, in adults [methylphenidate: 0.49 (95% CI: 0.35;0.64); amphetamines: 0.79 (0.58;0.99) were lower than the corresponding effect size in children (methylphenidate: 0.78 (0.62;0.93); amphetamines: 1.02 (0.85;1.19)]. These effect sizes in adults are in line with those found in other pairwise meta-analyses.

When it comes to acceptability and tolerability, placebo was favored than all nonstimulants discussed here. Due to limited studies available on guanfacine and viloxazine ER, we were only able to do a meta-analysis on the tolerability and acceptability of atomoxetine. Our data are in line with previous studies demonstrating that atomoxetine had lower acceptability and tolerability than placebo, but similar tolerability effect size to amphetamines and methylphenidate [1]. Amphetamines in adults with ADHD are the only medication that had better acceptability than placebo [1]. Although there was insufficient data for meta-analysis and direct comparison, limited data available suggests guanfacine ER may not be as tolerable or acceptable as other non-stimulant medications, findings consistent with a meta-analysis that included children and adolescents by Cortese et al. [1]. Future studies are needed to compare the acceptability and tolerability of all nonstimulants in the treatment of adults with ADHD.

This study inherits all the limitations of the constituent studies. As mentioned, we are further limited because we analyzed aggregate level rather than individual data. Additionally, some reported studies are from the same laboratories hence unclear how much the participants from these studies are totally different. Another limitation is that there are only two available studies on guanfacine and one on viloxazine ER. Only one RCT on guanfacine reported acceptability and tolerability data, hence we were not able to perform meta-analysis on these aspects of the medication. One study [20] on guanfacine did not specify if immediate or extended-release guanfacine was studied, but referred to the medication as short-acting implying immediate release formulation. Although we attempted to include all non-stimulant medications, no RCT on clonidine ER was available for adults with ADHD. Additionally, we could not address how variability in dosing could have affected the results.

CONCLUSION

All investigated nonstimulant medications had similar efficacy and were more effective than placebo. The tolerability of atomoxetine was comparable to previously available data on stimulants, and future studies are needed to establish tolerability of guanfacine and viloxazine ER. Despite some limitations, our findings represent an additional resource to assist clinicians and patients in balancing the decision-making process when choosing nonstimulant medication in the treatment of ADHD, either as a monotherapy or as an adjunct to stimulants. Studies are underway to compare the nonstimulant to stimulant medications and non-pharmacological options [21]. In the near future, we welcome the implementation of precision psychiatry approaches in the field, which will provide data informative at the patient, rather than group level [22, 23].

References

1. Cortese, S., et al., *Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis.* Lancet Psychiatry, 2018. **5**(9): p. 727-738.

2. Faraone, S.V., et al., *Attention-deficit/hyperactivity disorder.* Nat Rev Dis Primers, 2015. **1**: p. 15020.

3. Strohl, M.P., *Bradley's Benzedrine studies on children with behavioral disorders.* Yale J Biol Med, 2011. **84**(1): p. 27-33.

4. National Institute for Health Care and Excellence (NICE), *Attention Deficit Hyperactivity Disorder: Diagnosis and Management (NG87).* NICE Guidelines, 2018.

5. Cortese, S., *Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder.* N Engl J Med, 2020. **383**(11): p. 1050-1056.

6. Faraone, S.V., *The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities.* Neurosci Biobehav Rev, 2018. **87**: p. 255-270.

7. Findling, R.L., et al., *Viloxazine in the Management of CNS Disorders: A Historical Overview and Current Status.* CNS Drugs, 2021. **35**(6): p. 643-653.

8. De Crescenzo, F., et al., *Pharmacological and non-pharmacological treatment of adults with ADHD: a meta-review.* Evid Based Ment Health, 2017. **20**(1): p. 4-11.

9. Viechtbauer, W., *Conducting Meta-Analyses in R with the metafor Package.* Journal of Statistical Software, 2010. **36**(3): p. 1 - 48.

10. Team, R.C., *A Language and Environment for Statistical Computing.* R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/, 2020.

11. Nasser, A., et al., *A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder.* CNS Drugs, 2022. **36**(8): p. 897-915.

12. Shim, S.H., et al., *Comparison between Atomoxetine and OROS Methylphenidate as an Adjunctive to SSRIs in Attention-deficit/Hyperactivity Disorder Adults with Comorbid Partially Responsive Major Depressive Disorder: A Head-to-head, 12-week, Randomized, Rater-blinded Clinical Trial.* Clin Psychopharmacol Neurosci, 2022. **20**(1): p. 143-153.

13. Mathew, B. and M. Pellegrini, *Treasure Island (FL).* StatPearls [Internet], 2022. **https://www.ncbi.nlm.nih.gov/books/NBK576423/**.

14. Pinder, R.M., et al., *Viloxazine: a review of its pharmacological properties and therapeutic efficacy in depressive illness.* Drugs, 1977. **13**(6): p. 401-21.

15. Ban, T.A., J.P. McEvoy, and W.H. Wilson, *Viloxazine: a review of the literature.* Int Pharmacopsychiatry, 1980. **15**(2): p. 118-23.

16. Kabes, J., et al., *Multicentre study with viloxazine (Vivalan) in depressed patients.* Int Pharmacopsychiatry, 1980. **15**(4): p. 228-39.

17. Bayliss, P.F.C., et al., *A Double-Blind Controlled Trial of ‘Vivalan’ (Viloxazine Hydrochloride) and Imipramine Hydrochloride in the Treatment of Depression in General Practice.* Journal of International Medical Research, 1974. **2**(4): p. 260-264.

18. Bayliss, P.F.C., et al., *An Open Study of Two Dose Levels of ‘Vivalan’ (Viloxazine Hydrochloride ICI 58 834) in Depression in General Practice.* Journal of International Medical Research, 1974. **2**(4): p. 253-259.

19. Posey, D.J. and C.J. McDougle, *Guanfacine and guanfacine extended release: treatment for ADHD and related disorders.* CNS Drug Rev, 2007. **13**(4): p. 465-74.

20. Taylor, F.B. and J. Russo, *Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder.* J Clin Psychopharmacol, 2001. **21**(2): p. 223-8.

21. Cortese, S., et al., *Pharmacological and non-pharmacological interventions for adults with ADHD: protocol for a systematic review and network meta-analysis.* BMJ Open, 2022. **12**(3): p. e058102.

22. Buitelaar, J., et al., *Toward Precision Medicine in ADHD.* Front Behav Neurosci, 2022. **16**: p. 900981.

23. Cortese, S., *Setting the Foundations of Developmental Precision Psychiatry for ADHD.* Am J Psychiatry, 2021. **178**(8): p. 677-679.

# FIGURE CAPTIONS

## Figure 1 Forest plot of effect sizes for studies investigating the efficacy of atomoxetine vs. placebo

**Figure 2** Funnel plot of studies investigating the efficacy of atomoxetine vs. placebo

**Figure 3** Forest plot of effect sizes for studies investigating the tolerability of atomoxetine vs. placebo

**Figure 4** Funnel plot of studies investigating the tolerability of atomoxetine vs. placebo

**Figure 5** Forest plot of effect sizes for studies investigating the efficacy of guanfacine vs. placebo

## Figure 6 Funnel plot of studies investigating the efficacy of guanfacine vs. placebo (note: the funnel plot should be interpreted with caution given the limited number of studies)

## Figure 7 Efficacy of nonstimulant medications in adults with ADHD. Effect sizes for individual drugs are represented by black squares, with bars representing the corresponding 95% CIs.Note.  Considering that Hedge’s G, in relation to efficacy, has been calculated as the difference between the mean change in ADHD symptom severity from baseline to endpoint for medication vs. placebo, more negative values indicate larger efficacy for medication than placebo. As illustrated in this Figure, mean efficacy is larger for Guanfacine compared to Atomoxetine, and larger for Atomoxetine compared to Viloxazine. However, the overlapping 95% confidence intervals indicate that all these drugs do not differ significantly in relation to efficacy.

# TABLES

## Table 1 Characteristics of studies included in the review

| **Study** | **Type of non-stimulant** | **N patients randomized & Mean Age** | **Tool used for assessment of ADHD symptoms and time of assessment** | **Dropout rates (all causes); % and OR** | **Dropout rates (side effects): % and OR** |
| --- | --- | --- | --- | --- | --- |
| Adler 2008a | Atomoxetine | Medication: 271 (37.1 years), Placebo: 139 (36.0 years). | Clinician-report (CAARS-INV:SV) 26 weeks;  Self-report (CAARS-S-S) 9 weeks and 26 weeks;  CGI-Improvement 26 weeks | Medication: 61.6%, Placebo: 51.1%. OR: 1.54 | Medication: 14%, Placebo: 2.2%. OR: 7.39 |
| Adler 2009a | Atomoxetine | Medication: 224 (37.9 years), Placebo: 218 (38.1 years). | Clinician-report (CAARS-INV:SV) 14 weeks | Medication: 43.3%, Placebo: 37.2%. OR: 1.29 | Medication: 10.3%, Placebo: 8.3%. OR: 1.27 |
| Adler 2009b | Atomoxetine | Medication: 250 (37.7 years), Placebo: 251 (37.4 years). | Clinician-report (AISRS) 10 weeks and 26 weeks; Self-report (ASRS) 10 weeks and 26 weeks | Medication: 62.4%, Placebo: 55.4%. OR: 1.34 | Medication: 17.2%, Placebo: 5.6%. OR: 3.52 |
| Bain 2013 | Atomoxetine | Medication: 50 (36.2 years), Placebo: 225 (36.2 years). | Clinician-report (CAARS-INV:SV) 4 weeks | Medication: 12%, Placebo: 8%. OR: 1.57 | Medication: 6%, Placebo: 0.4%. OR: 14.3 |
| Durell 2013 | Atomoxetine | Medication: 220 (24.7 years), Placebo: 225 (24.7 years). | Clinician-report (CAARS-INV:SV) 12 weeks; Self-report (CAARS-S:S) 12 weeks | Medication: 47.7%, Placebo: 42.2%. OR: 1.25 | Medication: 9.5%, Placebo: 2.7%. OR: 3.85 |
| Goto 2017 | Atomoxetine | Medication: 195 (32.8 years), Placebo: 196 (31.7 years). | Clinician-report (ADHD-RS Total) 4 and 10 weeks | Medication: 20.5%, Placebo: 12.8%. OR: 1.77 | Medication: 5.1%, Placebo: 1.5%. OR: 3.48 |
| Iwanami 2020 | Guanfacine ER | Medication: 101 (33.8 years), Placebo: 100 (31.1 years). | Clinician-report (ADHD-RS Total) 10 weeks | Medication: 21.8%, Placebo: 7%. OR: 3.7 | Medication: 19.8%, Placebo: 3%. OR: 7.98 |
| Kay 2009b | Atomoxetine | Medication: 8 (22.4 years), Placebo: 8 (22.4 years). | No usable data | Medication: 25%, Placebo: 0%. OR: 6.54 | Medication: 12.5%, Placebo: 0%. OR: 3.4 |
| Lin 2016 | Atomoxetine | Medication: 12 (27.8 years), Placebo: 12 (32.5 years). | Self-report (ASRS) 8 weeks | Medication: 0%, Placebo: 0%. OR: 1 | Medication: 0%, Placebo: 0%. OR: 1 |
| McRae-Clark 2010 | Atomoxetine | Medication: 39 (29.4 years), Placebo: 39 (30.4 years). | Self-report (CAARS-S:L) 12 weeks; CGI-Improvement 12 weeks | Medication: 51.3%, Placebo: 51.3%. OR: 1 | Medication: 0%, Placebo: 0%. OR: 1 |
| Michelson 2003 (cohort 1) | Atomoxetine | Medication: 141 (40.2 years), Placebo: 139 (40.3 years). | Clinician-report (CAARS-INV:SV) 4 and 10 weeks; Self-report (CAARS-S:L) 10 weeks | Medication: 27.7%, Placebo: 23%. OR: 1.28 | Medication: 7.8%, Placebo: 4.3%. OR: 1.88 |
| Michelson 2003 (cohort 2) | Atomoxetine | Medication: 129 (43.0 years), Placebo: 127 (41.2 years). | Clinician-report (CAARS-INV:SV) 4 and 10 weeks; Self-report (CAARS-S:L) 10 weeks | Medication: 36.4%, Placebo: 25.2%. OR: 1.7 | Medication: 9.3%, Placebo: 2.4%. OR: 4.24 |
| Nasser 2022 NCT04016779 | Viloxazine ER | Medication: 190 (34.1 years), Placebo: 184 (35.4 years). | Clinician-report (AISRS) 6 weeks; CGI-Improvement 6 weeks | Medication: 33.2%, Placebo: 23.9%. OR: 1.58 | Medication: 8.9%, Placebo: 4.9%. OR: 1.91 |
| Spencer 1998 | Atomoxetine | Medication: 22 (34.0 years), Placebo: 22 (34.0 years). | Clinician-report (ADHD-RS Total) 3 weeks | Medication: 4.5%, Placebo: 0%. OR: 3.14 | Medication: 4.5%, Placebo: 0%. OR: 3.14 |
| Sutherland 2012 NCT00174226 | Atomoxetine | Medication: 97 (37.0 years), Placebo: 47 (37.0 years). | Clinician-report (AISRS) 7 weeks; Self-report (BADDS-adults) 7 weeks | Medication: 27.8%, Placebo: 42.6%. OR: 0.52 | Medication: 11.3%, Placebo: 14.9%. OR: 0.73 |
| Taylor 2001 | Guanfacine-unspecified | Medication: 17 (41.2 years), Placebo: 17 (41.2 years). | Self-report (ADHD Behavior Checklist for Adults) 2 weeks | Not reported | Not reported |
| Weisler 2012 | Atomoxetine | Medication: 74 (34.6 years), Placebo: 74 (33.4 years). | Clinician-report (ADHD-SRS total) 6 weeks | Medication: 27%, Placebo: 14.9%. OR: 2.12 | Medication: 10.8%, Placebo: 2.7%. OR: 4.36 |
| Wilens 2008 | Atomoxetine | Medication: 72 (34.3 years), Placebo: 75 (34.8 years). | Clinician-report (ADHD-SRS total) 12 weeks; Self-report (ASRS) 12 weeks; CGI-Improvement 12 weeks | Medication: 55.6%, Placebo: 36%. OR: 2.22 | Medication: 9.7%, Placebo: 2.7%. OR: 3.93 |
| Young 2011 | Atomoxetine | Medication: 268 (41.2 years), Placebo: 234 (41.4 years). | Clinician-report (CAARS-INV:SV) 12 weeks, (CAARS-O:L) 24 weeks | Medication: 55.6%, Placebo: 42.7%. OR: 1.68 | Medication: 21.3%, Placebo: 9.4%. OR: 2.6 |

## Table 2 Effect size estimates (efficacy of medication vs. placebo) for all RCTs included in the review

| **Effect size** | **Type of non-stimulant** | **Assessor (ADHD symptoms)** | **Weeks of assessment** | **Hedge's g** | **Standard Error (g)** | **Variance (g)** | **Lower 95% CI (g)** | **Upper 95% CI (g)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Adler 2008a.1 | Atomoxetine | Self | 9 | -0.1711 | 0.1072 | 0.0115 | -0.3811 | 0.039 |
| Adler 2008a.2 | Atomoxetine | Clinician | 26 | -0.0084 | 0.1207 | 0.0146 | -0.2451 | 0.2282 |
| Adler 2008a.3 | Atomoxetine | Self | 26 | -0.1398 | 0.1071 | 0.0115 | -0.3497 | 0.0701 |
| Adler 2008a.4 | Atomoxetine | Clinician | 26 | 0.0936 | 0.107 | 0.0115 | 0.3034 | -0.1162 |
| Adler 2009a | Atomoxetine | Clinician | 14 | -0.3094 | 0.099 | 0.0098 | -0.5034 | -0.1153 |
| Adler 2009b.1 | Atomoxetine | Clinician | 10 | -0.4254 | 0.1027 | 0.0105 | -0.6267 | -0.2242 |
| Adler 2009b.2 | Atomoxetine | Self | 10 | -0.4202 | 0.0916 | 0.0084 | -0.5998 | -0.2406 |
| Adler 2009b.3 | Atomoxetine | Clinician | 26 | -0.4346 | 0.138 | 0.019 | -0.7051 | -0.1642 |
| Adler 2009b.4 | Atomoxetine | Self | 26 | -0.4001 | 0.0915 | 0.0084 | -0.5795 | -0.2207 |
| Bain 2013 | Atomoxetine | Clinician | 4 | -1.4029 | 0.1862 | 0.0347 | -1.7679 | -1.0379 |
| Durell 2013.1 | Atomoxetine | Clinician | 12 | -0.5207 | 0.1281 | 0.0164 | -0.7717 | -0.2696 |
| Durell 2013.2 | Atomoxetine | Self | 12 | -0.3933 | 0.1028 | 0.0106 | -0.5948 | -0.1918 |
| Goto 2017.1 | Atomoxetine | Clinician | 4 | -0.4652 | 0.1032 | 0.0106 | -0.6674 | -0.2629 |
| Goto 2017.2 | Atomoxetine | Clinician | 10 | -0.5487 | 0.1037 | 0.0108 | -0.752 | -0.3455 |
| Iwanami 2020 | Guanfacine ER | Clinician | 10 | -0.6628 | 0.1572 | 0.0247 | -0.9709 | -0.3548 |
| Lin 2016 | Atomoxetine | Self | 8 | -0.5332 | 0.416 | 0.173 | 0.282 | -1.3485 |
| McRae-Clark 2010.1 | Atomoxetine | Self | 12 | -0.318 | 0.3266 | 0.1067 | -0.9581 | 0.322 |
| McRae-Clark 2010.2 | Atomoxetine | Clinician | 12 | -0.6566 | 0.4005 | 0.1604 | 0.1285 | -1.4416 |
| Michelson\_2003\_cohort 1.1 | Atomoxetine | Clinician | 4 | -0.1163 | 0.1225 | 0.015 | -0.3564 | 0.1238 |
| Michelson\_2003\_cohort 1.2 | Atomoxetine | Clinician | 10 | -0.3596 | 0.1234 | 0.0152 | -0.6014 | -0.1177 |
| Michelson\_2003\_cohort 1.3 | Atomoxetine | Self | 10 | -0.4414 | 0.1239 | 0.0153 | -0.6842 | -0.1986 |
| Michelson\_2003\_cohort 2.1 | Atomoxetine | Clinician | 4 | -0.2112 | 0.1274 | 0.0162 | -0.4608 | 0.0384 |
| Michelson\_2003\_cohort 2.2 | Atomoxetine | Clinician | 10 | -0.3739 | 0.1281 | 0.0164 | -0.625 | -0.1228 |
| Michelson\_2003\_cohort 2.3 | Atomoxetine | Self | 10 | -0.3369 | 0.1279 | 0.0164 | -0.5876 | -0.0862 |
| Nasser2022.1 | Viloxazine ER | Clinician | 6 | -0.3158 | 0.107 | 0.0114 | -0.5255 | -0.1062 |
| Nasser2022.2 | Viloxazine ER | Clinician | 6 | -0.2507 | 0.1067 | 0.0114 | -0.4599 | -0.0415 |
| Spencer 1998 | Atomoxetine | Clinician | 3 | -0.9115 | 0.3248 | 0.1055 | -1.5481 | -0.2748 |
| Sutherland 2012.1 | Atomoxetine | Clinician | 7 | -1.3904 | 0.1959 | 0.0384 | -1.7743 | -1.0065 |
| Sutherland 2012.1 | Atomoxetine | Self | 7 | -0.389 | 0.1792 | 0.0321 | -0.7402 | -0.0377 |
| Taylor 2001 | Guanfacine (unspecified) | Self | 2 | -0.6494 | 0.3524 | 0.1242 | 0.0412 | -1.34 |
| Weisler 2012 | Atomoxetine | Clinician | 6 | -0.4897 | 0.168 | 0.0282 | -0.819 | -0.1604 |
| Wilens 2008.1 | Atomoxetine | Clinician | 12 | -0.4625 | 0.1672 | 0.028 | -0.7902 | -0.1348 |
| Wilens 2008.2 | Atomoxetine | Self | 12 | -0.3561 | 0.1663 | 0.0277 | -0.682 | -0.0301 |
| Wilens 2008.3 | Atomoxetine | Clinician | 12 | -0.2655 | 0.2314 | 0.0536 | 0.1881 | -0.7191 |
| Young 2011.1 | Atomoxetine | Clinician | 12 | -0.3778 | 0.0908 | 0.0082 | -0.5557 | -0.1999 |
| Young 2011.2 | Atomoxetine | Clinician | 24 | -0.524 | 0.0915 | 0.0084 | -0.7034 | -0.3446 |