Comparative efficacy and acceptability of pharmacological, psychological, and neurostimulatory interventions for ADHD in adults: a systematic review and component network meta-analysis

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Summary

Background The comparative benefits and harms of available interventions for ADHD in adults remain unclear. We aimed to address these important knowledge gaps.

Methods In this systematic review and component network meta-analysis (NMA), we searched multiple databases for published and unpublished randomised controlled trials (RCTs) investigating pharmacological and non-pharmacological interventions for ADHD in adults from database inception to Sept 6, 2023. We included aggregate data from RCTs comparing interventions against controls or any other eligible active intervention for the treatment of symptoms in adults (ages ≥18 years) with a formal diagnosis of ADHD. Pharmacological therapies were included only if their maximum planned doses were considered eligible according to international guidelines. We included RCTs of at least 1-week duration for medications, of at least four sessions for psychological therapies, and of any length deemed appropriate for neurostimulation. For RCTs of medications, cognitive training, or neurostimulation alone, we included only double-blind RCTs. At least two authors independently screened the identified records and extracted data from eligible RCTs. Our primary outcomes were efficacy (change in ADHD core symptom severity on self-rated and clinician-rated scales at timepoints closest to 12 weeks) and acceptability (all-cause discontinuation). We estimated standardised mean differences (SMDs) and odds ratios (ORs) using random effects pairwise and component NMA, dismantling interventions into specific therapeutic components. This study was registered with PROSPERO (CRD42021265576). People with relevant lived experience were involved in the conduct of the research and writing process.

Findings Of 32 416 records, 113 unique RCTs encompassing 14 887 participants were eligible for analysis (6787 [45·6%] females, 7638 [51·3%] males, 462 [3·1%] sex not reported). The RCTs encompassed pharmacological therapies (63 [55·8%] of 113 RCTs; 6875 participants), psychological therapies (28 [24·8%] of 113 RCTs; 1116 participants), neurostimulatory therapy and neurofeedback (ten [8·8%] of 113 RCTs; 194 participants), and control conditions (97 [85·8%] of 113 RCTs; 5770 participants). For reduction of ADHD core symptoms at 12 weeks on both self-reported and clinician-reported rating scales, atomoxetine (self-reported scale SMD –0·38, 95% CI –0·56 to –0·21; clinician-reported scale –0·51, –0·64 to –0·37) and stimulants (0·39, –0·52 to –0·26; –0·61, –0·71 to –0·51) had higher efficacy than placebo (Confidence in Network Meta-Analysis [CINeMA] ranging between very low and moderate). Cognitive behavioural therapy (–0·76, –1·26 to –0·26), cognitive remediation (–1·35, –2·42 to –0·27), mindfulness (–0·79, –1·29 to –0·29), psychoeducation (–0·77, –1·35 to –0·18), and transcranial direct current stimulation (–0·78; –1·13 to –0·43) were better than placebo only on clinician-reported measures. Regarding acceptability, all therapeutic components were similar to placebo other than atomoxetine (OR 1·43, 95% CI 1·14 to 1·80; CINeMA moderate) and guanfacine (3·70, 1·22 to 11·19; high), which had lower acceptability compared with placebo. Baseline severity of self-reported ADHD core symptoms, year of publication, percentage of male individuals, and percentage of individuals with ADHD and another mental health condition did not explain the heterogeneity observed in unadjusted non-component models of self-reported ADHD core symptoms. Treatment length had little effect on heterogeneity.

Interpretation Stimulants and atomoxetine were the only interventions with evidence of beneficial effects in terms of reducing ADHD core symptoms in the short term, supported by both self-reported and clinician-reported ratings. However, atomoxetine was less acceptable than placebo. Medications for ADHD were not efficacious on additional relevant outcomes, such as quality of life, and evidence in the longer term is underinvestigated. The effects of non-pharmacological strategies were inconsistent across different raters. Our network meta-analysis represents the most comprehensive synthesis of available evidence to inform future guidelines in the field.

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Research in context

Evidence before this study

Pharmacological interventions for ADHD in adults have a prominent role in clinical guidelines to date. However, in the past decade, an increasing number of randomised controlled trials (RCTs) of non-pharmacological options for adults with ADHD have been published. Given the concerns around the safety of ADHD medications, there is a pressing need to better understand the comparative efficacy and tolerability or safety of medications and non-pharmacological interventions for the management of ADHD in adults. Before conducting our systematic review and network meta-analysis, we searched in May, 2022, and again on March 17, 2024, PubMed, PsycINFO, and Embase for network meta-analyses (NMAs) on interventions for ADHD in adults using the search terms "network", "adult", "ADHD" , "meta-analysis", and related terms as keywords. We found three NMAs on pharmacological interventions, but none encompassed both pharmacological and non-pharmacological strategies for the management of ADHD in adults. For our systematic review and NMAs, we searched for potentially eligible records from database or website inception to Sept 6, 2023, with no language limitations. We included aggregate data from RCTs comparing pharmacological and non-pharmacological interventions against controls or any other eligible active intervention for the treatment of adults (ages ≥18 years) with a formal diagnosis of ADHD.

Added value of this study

To our knowledge, this is the first component NMA on ADHD in adults that jointly synthesises comparative effects for pharmacological, psychological, and neurostimulatory interventions within a single network. Our study is also, to our knowledge, the first study to provide comparative meta-analytic evidence showing that stimulants and atomoxetine, among all available pharmacological and non-pharmacological interventions for ADHD, are the only ones to be rated as efficacious in terms of ADHD core symptoms according to both self-reported and clinician-reported scales. However, ADHD medications are not well tolerated by everyone, there is no evidence that they significantly improve outcomes that are important to individuals with ADHD such as quality of life, and their long-term effects are under investigation. We also provide, for the first time, comparative meta-analytic evidence that the efficacy in the short term and longer term for several non-pharmacological strategies, cognitive behavioural therapy, neurofeedback, and relaxation therapy varies across types of raters and show that long-term data are scarce.

Implications of all the available evidence

Our study provides the most comprehensive comparative evidence on the effects of pharmacological and non-pharmacological therapies for ADHD in adults to date. Clinical decision making should be based on a careful weighing of benefits and harms, considering the findings from this NMA and other sources of evidence. Overall, further longer-term studies on alternative medications, non-pharmacological strategies, and their combinations available to date are needed to better inform the care of ADHD in adults.

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Introduction

ADHD is characterised according to DSM-5-TR as a persistent and pervasive pattern of inattention, hyperactivity–impulsivity, or both, that interferes with functioning or development.[1] ADHD is the most common neurodevelopmental disorder, affecting around 5% of school-aged children (ages 6–18 years) worldwide between 1990 and 2019.[2] Impairing symptoms of ADHD persist into adulthood in up to 75% of people with ADHD, with an estimated global prevalence of ADHD in adults at around 2·5% in 2020.[3] ADHD often co-occurs with other disorders (including mood, anxiety, and addictions) or dysfunctions (eg, emotional dysregulation and executive dysfunction).[4] In terms of societal burden, in 2018, the excess cost attributable to ADHD was estimated at US$122·8 billion ($14092 per adult) in the USA.[5]

Pharmacological and non-pharmacological interventions are available to support people with ADHD. Medications—stimulants and non-stimulants—have an important role in available clinical guidelines to help manage ADHD in adults.[6] However, the 2018 guidelines from the UK National Institute for Health and Care Excellence (NICE) recommended considering non-pharmacological support if that is the informed choice of the patient, if medications are not well tolerated or are ineffective, or if regular adherence to medication is difficult.[7]

Given concerns about the safety of ADHD medications, including their possible cardiovascular effects, and the increasing number of trials of non-pharmacological treatments in the past few years, gaining insights into the efficacy and safety of all available interventions for ADHD in adults is crucial.[8] Furthermore, it is still unclear how to best treat co-occurring dysfunctions frequently associated with ADHD in adults.[9] To address these knowledge gaps, we did a systematic review and component network meta-analysis (NMA) comparing pharmacological and non-pharmacological interventions in terms of changes in core ADHD symptoms (efficacy) and associated dysfunctions, as well as acceptability and tolerability in adults with ADHD.

Methods

Search strategy and eligibility criteria

For this systematic review and component NMA, we searched for published and unpublished randomised

controlled trials (RCTs) in CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, the EU Clinical Trials Register, the WHO International Clinical Trials Registry Platform, and websites of regulatory agencies and pharmaceutical companies, from inception to Sept 6, 2023, without any a priori restrictions. The full search strategy is reported in the appendix (S2; pp 33–77). The PRISMA checklist and its extension for NMAs are reported in the appendix (S37; pp 1192–99).

See Online for appendix

We included RCTs comparing interventions against placebos or other controls or any other eligible active intervention for the treatment of symptoms in adults (aged ≥18 years) with a formal diagnosis of ADHD according to the DSM-III onwards, the ICD-10, or the ICD-11. For medications, we included stimulants (amphetamines, including lisdexamfetamine, and methylphenidate), atomoxetine, bupropion, clonidine, guanfacine extended release, modafinil, and viloxazine to reflect licensed and unlicensed medications that are commonly used in clinical practice.[10] Pharmacological therapies were included only if their maximum planned doses were considered eligible according to international guidelines (appendix S3; pp 78–80). We included RCTs of at least 1-week duration for medications, of at least four sessions for psychological therapies, and of any length deemed appropriate by the original study authors for neurostimulation (appendix S4; p 81). For RCTs of medications, cognitive training, or neurostimulation alone, we included only double-blind RCTs. Crossover studies were eligible, but only data collected before the crossover phase contributed to analyses to avoid the carry-over effect.[11] Aggregate-level data were collected. We systematically contacted investigators to supplement incomplete reports and obtain unpublished information and summary estimates. Deviations from the protocol, with reasons, are reported in the appendix (S1.2; p 32). EGO, MS, CZ, LCF, and AT independently screened the records and extracted the relevant data. Conflicts were resolved via discussion with SC and AC.

Data analysis

Primary outcomes were the severity of ADHD core symptoms according to self-rated and clinician-rated scales at timepoints closest to 12 weeks, and acceptability (all-cause discontinuation rate). We estimated effect sizes from pairwise meta-analyses and NMAs using standardised mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes, together with their 95% CIs and 95% prediction intervals (PIs). For continuous outcomes, we estimated SMDs between endpoint scores and, when these were not available, based on changes from baseline scores.[12] Secondary outcomes were severity of ADHD core symptoms according to self-rated and clinician-rated scales at timepoints closest to 26 weeks and 52 weeks; tolerability (proportion of participants discontinuing treatment due to adverse events); severity of emotional dysregulation; severity of executive dysfunction; and quality of life. Additional details on measuring these outcomes are in the appendix (S1.1; p 20).

We evaluated the assumption of transitivity by comparing the across-comparison distribution of the following potential effect modifiers: duration of intervention, mean age, proportion of male participants, co-occurrence of a mental disorder, pharmacological intervention at a stable dose, percentage of medication-naive participants, and medication resistance.[11] As prespecified in our protocol, stimulants were included as a single node to allow for the comparison of pharmacological and non-pharmacological interventions, and other medications were included as independent nodes.[11] Control groups were included as separate nodes, consistent with previous NMAs of psychotherapies.[13] We did a series of NMAs using a random-effects model within a frequentist setting, assuming equal heterogeneity across all comparisons and accounting for correlations induced by multi-arm RCTs. For networks including combinations of eligible treatments, we did a component NMA assuming additivity of treatment effects, in line with previous component NMAs.[14] We refer to combinations of interventions as interventions (eg, A plus B), and to specific components as therapeutic components (eg, A, B). We reported the effect size of therapeutic components against the control group most represented across the identified RCTs in the network. We assessed the plausibility of the additivity assumption by evaluating study-specific outcome estimates across different study designs. We also explored the effects of the additivity assumption by evaluating the coherence of estimates from additive and non-additive NMAs. Furthermore, we assessed the incoherence between direct and indirect sources of evidence using a design-by-treatment test (global approach) and a separate indirect-from-direct-design evidence method (local approach). We assessed statistical heterogeneity for each pairwise comparison and NMA comparison using τ^2. These analyses were done across all the identified networks (or subnetworks if fragmented). For standard and component NMAs, we estimated the p score ranking (appendix S15; pp 989–1005, S2; 1091–107). For our primary outcomes, we did Bayesian random-effects network meta-regressions using the following variables as covariates: self-reported baseline ADHD core symptom score, clinician-reported baseline ADHD core symptom score (only for acceptability), percentage of participants with co-occurrence of another mental disorder, percentage of male participants, intervention duration in weeks, and year of publication (appendix S25–30; pp 1148–65).

We assessed the risk of bias of RCTs on each coprimary outcome separately with the Cochrane Risk of Bias version 2.0.[15] If at least ten relevant RCTs were available, we assessed the presence of small-study effects bias for active treatments compared against a control group

using a contour-enhanced funnel plot. We assessed the certainty of evidence using the Confidence in Network Meta-Analysis (CINeMA) framework. As component NMA models cannot be evaluated by the CINeMA framework, we evaluated the certainty of evidence of comparisons within each subnetwork (appendix S24; pp 1142–47).[16] We conducted the following sensitivity analyses: only non-industry-sponsored studies, only studies lasting less than 12 weeks, only studies rated as low bias, and splitting stimulants into amphetamines and methylphenidate (appendix S31–34; pp 1166–74). Additional information on subgroup and sensitivity analyses is available in the protocol.[11] To facilitate the communication of benefits and harms across multiple outcomes and competing treatments, we used Vitruvian plots to visualise results.[17]

As we did in another project,[18] people with lived experience were involved in all phases of the study, from study design and funding application (particularly providing input on the study questions and selection of outcomes) to study reporting, advising on the selection of outcomes for the Vitruvian plots, prioritisation of outcomes, and interpretation of the findings. A representative (AB) of an association of people with lived experience of ADHD liaised with members of the association, reported their views to the writing team, and coauthored this Article.

We did the analyses in R (version 4.3.1) using the netmeta package. The published protocol was pre-registered in PROSPERO (CRD42021265576, S1.1).[11] Ethical approval and participant consent were not required because we analysed aggregate data.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit it for publication.

Results

Of 32 416 records identified from our searches, 113 unique RCTs were eligible for inclusion in the systematic review and meta-analysis (figure 1). The lists of included and excluded RCTs, with reasons for exclusion, are reported in the appendix (S5–6; pp 82–787). The included RCTs recruited a total of 14 887 participants (6787 [45·6%] female, 7638 [51·3%] male, and 462 [3·1%] sex not reported) with a median age of 35·6 years (IQR 33·5–38·5; mean of means 35·1 years, range 19·6–44·0; appendix S7.1; pp 788–808). Ethnicity data were reported only by 47 (41·6%) of 113 studies, using inconsistent definitions and categorisations (appendix S7.3; pp 830–38).

We identified 50 treatments, dismantled into one or more interventions: pharmacological therapies (63 [55·8%] of 113 RCTs; 6875 participants), psychological therapies (28 [24·8%] RCTs; 1116 participants), neurostimulatory therapy and neurofeedback (ten [8·8%] RCTs; 194 participants), and control conditions (97 [85·8%] RCTs; 5770 participants). 24 trials included comparisons of active interventions, and 16 of these did not include any control conditions (appendix S7.5; pp 877–78). Additional characteristics of the included RCTs are available in the appendix (S7; pp 788–78). Most RCTs contributed to at least one component NMA at timepoints closest to 12 weeks (87 RCTs and 13 680 participants) rather than at longer timepoints of 26 weeks (17 RCTs and 3282 participants) or 52 weeks (five RCTs and 801 participants). None of the included RCTs of non-pharmacological therapies

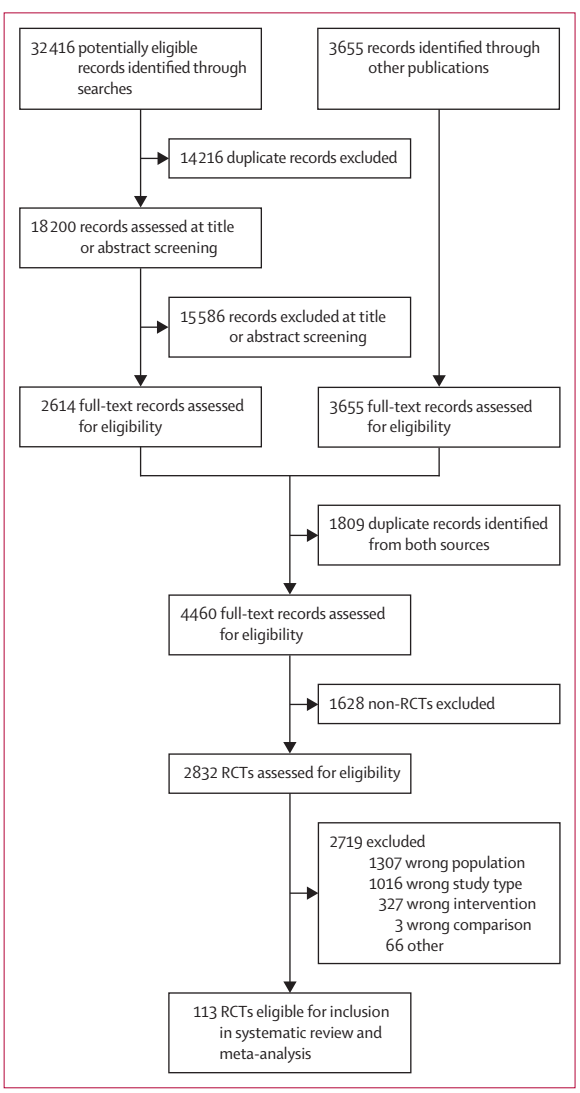


Figure 1: **Study selection process**
In total, 113 RCTs were included in one or more network meta-analyses. For the primary outcomes, 56 trials (8083 participants) were analysed for self-reported ADHD core symptoms at 12 weeks after random assignment, and 77 trials (13 008 participants) were analysed for acceptability (any-cause discontinuation). Additional details on exclusions are in the appendix (S6; 138–787). For the full list of websites of regulatory agencies and pharmaceutical companies searched, see the appendix (S2; pp 33–34). RCTs=randomised controlled trials.

ATO	1·62§ (0·43 to 6·08)	4·39 (0·82 to 23·66)	**4·93 (1·07 to 22·71)**	3·12 (0·64 to 15·26)	0·39† (0·13 to 1·20)	3·38 (0·46 to 24·72)	0·78 (0·32 to 1·93)	4·05 (0·35 to 47·03)	**1·43† (1·14 to 1·80)**	3·64 (0·50 to 26·60)	1·63 (0·14 to 19·37)	**1·59† (1·18 to 2·15)**	1·03 (0·06 to 16·95)	0·93 (0·03 to 28·08)	2·13 (0·15 to 30·79)	2·93 (0·22 to 39·77)
–0·18§ (–0·78 to 0·42)	**BUP**	2·71 (0·33 to 22·46)	3·04 (0·41 to 22·32)	1·93 (0·25 to 14·8)	0·24 (0·04 to 1·32)	2·08 (0·20 to 22·21)	0·48§ (0·10 to 2·31)	2·49 (0·16 to 39·7)	0·88§ (0·24 to 3·24)	2·24 (0·21 to 23·90)	1·00 (0·06 to 16·31)	0·98§ (0·26 to 3·66)	0·64 (0·03 to 13·82)	0·58 (0·02 to 21·85)	1·32 (0·07 to 25·4)	1·80 (0·10 to 33·01)
0·1 (–0·64 to 0·84)																
0·93 (0·22 to 1·64	**1·11 (0·21 to 2·01)**	**CBT**	1·12 (0·44 to 2·86)	0·71§ (0·29 to 1·73)	**0·09 (0·01 to 0·65)**	0·77§ (0·23 to 2·59)	0·18 (0·03 to 1·17)	0·92§ (0·15 to 5·48)	0·33 (0·06 to 1·73)	0·83§ (0·25 to 2·70)	0·37§ (0·06 to 2·28)	0·36 (0·07 to 1·90)	0·24 (0·02 to 2·93)	0·21 (0·01 to 5·12)	0·49 (0·04 to 5·25)	0·67 (0·07 to 6·73)
–0·26 (–0·77 to 0·26)	–0·36 (–1·15 to 0·44)															
0·40 (–0·68 to 1·48)	0·58 (–0·64 to 1·79)	–0·53§ (–1·41 to 0·35)	**CTr**	0·63 (0·30 to 1·34)	**0·08 (0·01 to 0·51)**	0·68 (0·17 to 2·82)	**0·16 (0·03 to 0·91)**	0·82 (0·11 to 6·15)	0·29 (0·06 to 1·32)	0·74 (0·18 to 3·03)	0·33 (0·04 to 2·54)	0·32 (0·07 to 1·44)	0·21 (0·02 to 2·36)	0·19 (0·01 to 4·21)	0·43 (0·04 to 4·20)	0·59 (0·07 to 5·36)
..	..	..														
0·89 (0·20 to 1·58)	**1·07 (0·19 to 1·95)**	–0·04‡ (–0·40 to 0·33)	0·49§ (–0·42 to 1·40)	**DBT**	**0·12 (0·02 to 0·85)**	1·08§ (0·27 to 4·31)	0·25 (0·04 to 1·51)	1·30§ (0·18 to 9·52)	0·46 (0·10 to 2·20)	1·16§ (0·29 to 4·62)	0·52§ (0·07 to 3·94)	0·51 (0·11 to 2·42)	0·33 (0·03 to 3·87)	0·30 (0·01 to 6·85)	0·68 (0·07 to 6·90)	0·94 (0·10 to 8·84)
0·31 (–0·08 to 0·69)	0·21 (–0·51 to 0·92)	0·56 (–0·02 to 1·15)	..													
–0·29§ (–1·00 to 0·41)	–0·11§ (–1·01 to 0·78)	**–1·22 (–2·18 to –0·26)**	–0·69 (–1·95 to 0·57)	**–1·18 (–2·13 to –0·24)**	**GUA**	8·72 (0·90 to 84·1)	2·02† (0·49 to 8·27)	10·45 (0·72 to 152·66)	**3·70* (1·22 to 11·19)**	9·39 (0·98 to 90·52)	4·21 (0·28 to 62·74)	**4·11* (1·33 to 12·65)**	2·67 (0·13 to 53·60)	2·41 (0·07 to 85·81)	5·51 (0·31 to 98·24)	7·55 (0·45 to 127·46)
0·11 (–0·37 to 0·59)	0·01 (–0·85 to 0·87)	0·37 (–0·27 to 1·00)	..	–0·20 (–0·73 to 0·34)												
0·46 (–0·28 to 1·19)	0·64 (–0·28 to 1·55)	**–0·47‡ (–0·85 to –0·09)**	0·06§ (–0·87 to 0·99)	**–0·43§ (–0·86 to –0·01)**	0·75 (–0·23 to 1·73)	**MIND**	0·23 (0·03 to 2·01)	1·20§ (0·14 to 10·38)	0·42 (0·06 to 3·07)	1·08§ (0·45 to 2·58)	0·48§ (0·05 to 4·29)	0·47 (0·07 to 3·37)	0·31 (0·02 to 4·73)	0·28 (0·01 to 7·92)	0·63 (0·05 to 8·57)	0·87 (0·07 to 11·05)
–0·29 (–0·80 to 0·23)	–0·39 (–1·18 to 0·40)	–0·03 (–0·61 to 0·55)	..	**–0·59 (–1·18 to –0·01)**	–0·40 (–1·03 to 0·24)											
0·14† (–0·28 to 0·55)	0·31‡ (–0·38 to 1·00)	**–0·79 (–1·58 to –0·01)**	–0·26 (–1·39 to 0·87)	–0·76 (–1·52 to 0·01)	0·43‡ (–0·35 to 1·21)	–0·32 (–1·13 to 0·48)	**MOD**	5·17 (0·39 to 69·12)	1·83† (0·77 to 4·37)	4·65 (0·54 to 40·29)	2·08 (0·15 to 28·42)	2·03† (0·83 to 4·97)	1·32 (0·07 to 24·50)	1·19 (0·04 to 39·73)	2·72 (0·17 to 44·76)	3·73 (0·24 to 57·98)
0·63 (0·15 to 1·12)	0·53 (–0·33 to 1·39)	**0·89 (0·25 to 1·53)**	..	0·32 (–0·22 to 0·86)	0·52 (–0·14 to 1·18)	**0·92 (0·28 to 1·56)**										
1·04 (0·11 to 1·97)	**1·22 (0·14 to 2·29)**	0·11§ (–0·49 to 0·70)	0·64§ (–0·42 to 1·70)	0·15§ (–0·55 to 0·85)	**1·33 (0·20 to 2·46)**	0·58‡ (–0·13 to 1·29)	0·90 (–0·08 to 1·89)	**NEU**	0·35 (0·03 to 4·07)	0·90§ (0·11 to 7·65)	0·40§ (0·03 to 5·13)	0·39 (0·03 to 4·49)	0·26 (0·01 to 9·07)	0·23 (0·00 to 13·41)	0·53 (0·02 to 16·95)	0·72 (0·02 to 22·20)
..	..	..	..	..	..	..	..									
0·38† (0·21 to 0·56)	0·56† (–0·02 to 1·14)	–0·55 (–1·24 to 0·14)	–0·02 (–1·08 to 1·05)	–0·51 (–1·17 to 0·16)	0·67† (–0·01 to 1·36)	–0·08 (–0·79 to 0·64)	0·25† (–0·13 to 0·63)	–0·66 (–1·57 to 0·25)	**Placebo**	2·54 (0·35 to 18·33)	1·14 (0·10 to 13·38)	1·11† (0·91 to 1·36)	0·72 (0·04 to 11·72)	0·65 (0·02 to 19·46)	1·49 (0·10 to 21·29)	2·04 (0·15 to 27·49)
0·51 (0·37 to 0·64)	0·40 (–0·32 to 1·13)	**0·76 (0·26 to 1·26)**	..	0·20 (–0·17 to 0·57)	0·39 (–0·07 to 0·86)	**0·79 (0·29 to 1·29)**	–0·13 (–0·59 to 0·34)	..								
0·52 (–0·29 to 1·34)	0·70 (–0·28 to 1·68)	–0·41† (–0·90 to 0·08)	0·12§ (–0·86 to 1·11)	–0·37§ (–0·92 to 0·18)	0·82 (–0·22 to 1·85)	0·06§ (–0·35 to 0·48)	0·39 (–0·49 to 1·26)	–0·52‡ (–1·29 to 0·25)	0·14 (–0·65 to 0·94)	**PSY**	0·45§ (0·05 to 3·91)	0·44 (0·06 to 3·13)	0·28 (0·02 to 4·39)	0·26 (0·01 to 7·35)	0·59 (0·04 to 7·95)	0·80 (0·06 to 10·25)
–0·26 (–0·86 to 0·34)	–0·36 (–1·21 to 0·49)	0·00 (–0·59 to 0·58)	..	–0·57 (–1·22 to 0·09)	–0·37 (–1·08 to 0·33)	0·03 (–0·39 to 0·45)	**–0·89 (–1·60 to –0·18)**	..	**–0·77 (–1·35 to –0·18)**							
1·24 (0·43 to 2·05)	**1·42 (0·44 to 2·40)**	0·31‡ (–0·09 to 0·72)	0·84§ (–0·12 to 1·81)	0·35§ (–0·18 to 0·88)	**1·53 (0·50 to 2·57)**	**0·78† (0·25 to 1·31)**	**1·11 (0·23 to 1·98)**	0·20§ (–0·52 to 0·92)	**0·86 (0·07 to 1·65)**	**0·72† (0·10 to 1·34)**	**REL**	0·98 (0·08 to 11·41)	0·64 (0·03 to 14·21)	0·57 (0·01 to 22·36)	1·31 (0·07 to 26·15)	1·80 (0·09 to 34·00)
0·27 (–0·51 to 1·04)	0·16 (–0·82 to 1·15)	0·52 (–0·06 to 1·11)	..	–0·04 (–0·87 to 0·78)	0·15 (–0·71 to 1·02)	0·55 (–0·27 to 1·38)	–0·37 (–1·23 to 0·50)	..	–0·24 (–1·01 to 0·53)	0·52 (–0·30 to 1·35)						
–0·01§ (–0·23 to 0·21)	0·17§ (–0·42 to 0·76)	**–0·94 (–1·62 to –0·26)**	–0·41 (–1·47 to 0·65)	**–0·90 (–1·55 to –0·25)**	0·28§ (–0·40 to 0·96)	–0·47 (–1·17 to 0·23)	–0·15† (–0·54 to 0·25)	**–1·05 (–1·95 to –0·15)**	**–0·39§ (–0·52 to –0·26)**	–0·53 (–1·32 to 0·25)	**–1·25 (–2·03 to –0·47)**	**STIM**	0·65 (0·04 to 10·48)	0·59 (0·02 to 17·42)	1·34 (0·09 to 19·02)	1·84 (0·14 to 24·57)
–0·10 (–0·27 to 0·06)	–0·20 (–0·94 to 0·53)	0·15 (–0·36 to 0·66)	..	**–0·41 (–0·79 to –0·03)**	–0·21 (–0·69 to 0·26)	0·18 (–0·32 to 0·69)	**–0·73 (–1·21 to –0·26)**	..	**–0·61 (–0·71 to –0·51)**	0·16 (–0·43 to 0·75)	–0·37 (–1·14 to 0·41)					
0·08 (–1·31 to 1·46)	0·25 (–1·23 to 1·74)	–0·85 (–2·13 to 0·42)	–0·32 (–1·84 to 1·19)	–0·81 (–2·08 to 0·45)	0·37 (–1·16 to 1·89)	–0·38 (–1·67 to 0·91)	–0·06 (–1·48 to 1·36)	–0·96 (–2·49 to 0·57)	–0·31 (–1·68 to 1·07)	–0·45 (–1·78 to 0·89)	–1·17 (–2·50 to 0·17)	0·09 (–1·28 to 1·45)	**tDCS**	0·90§ (0·05 to 17·33)	2·06§ (0·26 to 16·29)	2·83§ (0·39 to 20·67)
–0·27 (–0·64 to 0·10)	–0·37 (–1·08 to 0·33)	–0·02 (–0·59 to 0·56)	..	**–0·58 (–1·04 to –0·12)**	–0·38 (–0·91 to 0·14)	0·01 (–0·56 to 0·59)	**–0·90 (–1·43 to –0·37)**	..	**–0·78 (–1·13 to –0·43)**	–0·01 (–0·66 to 0·64)	–0·54 (–1·36 to 0·28)	–0·17 (–0·53 to 0·19)				
0·86 (–0·41 to 2·13)	1·04 (–0·35 to 2·43)	–0·07 (–1·23 to 1·09)	0·46 (–0·95 to 1·88)	–0·03 (–1·17 to 1·11)	1·15 (–0·27 to 2·58)	0·40 (–0·77 to 1·58)	0·73 (–0·59 to 2·04)	–0·18 (–1·61 to 1·25)	0·48 (–0·78 to 1·74)	0·34 (–0·89 to 1·56)	–0·38 (–1·60 to 0·84)	0·87 (–0·38 to 2·13)	0·79§ (–0·64 to 2·21)	**TMS (bilateral)**	2·29§ (0·13 to 39·00)	3·14§ (0·19 to 50·56)
..	..	..	..	..	..	..	..	..	..	..	..	..	..			
0·75 (–0·27 to 1·78)	0·93 (–0·23 to 2·09)	–0·18 (–1·05 to 0·70)	0·35 (–0·84 to 1·55)	–0·14 (–1·00 to 0·72)	1·05 (–0·16 to 2·26)	0·30 (–0·60 to 1·19)	0·62 (–0·46 to 1·69)	–0·29 (–1·50 to 0·93)	0·37 (–0·64 to 1·38)	0·23 (–0·73 to 1·19)	–0·49 (–1·45 to 0·47)	0·76 (–0·24 to 1·76)	0·68§ (–0·53 to 1·89)	–0·11§ (–1·19 to 0·97)	**TMS (left)**	1·37§ (0·30 to 6·37)
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..		
–0·21 (–1·26 to 0·83)	–0·04 (–1·21 to 1·14)	**–1·14 (–2·04 to –0·25)**	–0·61 (–1·82 to 0·60)	**–1·10 (–1·98 to –0·22)**	0·08 (–1·15 to 1·30)	–0·67 (–1·59 to 0·25)	–0·35 (–1·44 to 0·74)	**–1·25 (–2·48 to –0·02)**	–0·59 (–1·62 to 0·43)	–0·74 (–1·72 to 0·25)	**–1·46 (–2·43 to –0·48)**	–0·20 (–1·22 to 0·82)	–0·29§ (–1·52 to 0·94)	–1·07§ (–2·18 to 0·03)	**–0·97§ (–1·59 to –0·34)**	**TMS (right)**
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	

provided evidence that participants were not eligible for pharmacological interventions.

Figure 2 shows the primary results of the component NMAs. Among active therapeutic components, we found evidence that atomoxetine (self-rated symptoms SMD –0·38, 95% CI –0·56 to –0·21, 95% PI –0·82 to 0·06; clinician-rated symptoms SMD –0·51, –0·64 to –0·37, –0·91 to –0·10) and stimulants (self-rated symptoms –0·39, –0·52 to –0·26, –0·81 to 0·03; clinician-rated symptoms –0·61, –0·71 to –0·51, –1·00 to –0·21) were better than placebo in reducing ADHD core symptoms at timepoints closest to 12 weeks on both self-reported (56 studies, 7375 participants) and clinician-reported (54 studies, 9742 participants) rating scales (CINeMA range very low to moderate; appendix S12.1–12.2; pp 934–35, S24; 1142–47). Relaxation therapy (0·86, 0·07 to 1·65, –0·04 to 1·76) did worse than placebo in reducing ADHD core symptoms at timepoints closest to 12 weeks for self-rating scales only. Cognitive behavioural therapy (CBT; –0·76, –1·26 to –0·26, –1·41 to –0·12), cognitive remediation (–1·35, –2·42 to –0·27, –2·52 to –0·18), mindfulness (–0·79, –1·29 to –0·29, –1·43 to –0·15), psychoeducation (–0·77, –1·35 to –0·18, –1·48 to –0·05), and transcranial direct current stimulation (tDCS; –0·78; –1·13 to –0·43, –1·31 to –0·25) were better than placebo in reducing ADHD core symptoms on clinician-reported scales, but not self-reported scales. For the remaining therapeutic components, we did not find evidence of a difference compared with placebo for both clinician-reported and self-reported rating scales. In the sensitivity analysis, amphetamines and methylphenidate did not materially differ in efficacy (appendix S34; pp 1173–74).

Regarding acceptability (77 studies, 13 008 participants), we found evidence that atomoxetine (OR 1·43, 95% CI 1·14–1·80, 95% PI 0·71–2·87; CINeMA moderate) and guanfacine (3·70, 1·22–11·19, 1·00–13·66; high) were less acceptable than placebo (appendix S12.7; p 940 and S24.2; p 1147).

At timepoints closest to 26 weeks, we found evidence that atomoxetine was more efficacious than placebo (SMD –0·35, 95% CI –0·67 to –0·03, 95% PI –0·97 to 0·28) according to self-reported ratings only (16 studies, 2379 participants), whereas mindfulness (–0·63, –1·23 to –0·03, –2·25 to 0·99) and stimulants (–0·31, –0·61 to –0·01, –1·47 to 0·85) were more efficacious than placebo on clinician-reported scales only (eight studies, 1732 participants; appendix S12.3–12.4; pp 936–37). We identified only five studies contributing to the network at timepoints closest to 52 weeks using either self-reported scales (five studies: 523 participants) or clinician-rated scales (two studies: 313 participants), including CBT, dialectical behavioural therapy (DBT), neurofeedback, relaxation therapy, and stimulants. There was no evidence of a difference between active therapeutic components and placebo for clinician-reported ratings of symptoms, but CBT (–1·09, –1·77 to –0·42, –5·62 to 3·43), neurofeedback (–1·10, –1·94 to –0·26, –6·64 to 4·44), and relaxation therapy (–1·00, –1·77 to –0·24, –6·08 to 4·07) were more efficacious than placebo on self-reported scales (appendix S12.5–12.6; pp 938–39).

We found evidence of lower tolerability for atomoxetine (OR 2·43, 95% CI 1·89–3·12, 95% PI 1·88–3·14), guanfacine (7·98, 2·29–27·83, 2·22–28·69), modafinil (3·99, 1·60–9·94, 1·57–10·16), and stimulants (2·15, 1·61–2·88, 1·60–2·90) compared with placebo (61 studies, 11 987 participants; appendix S12.17; p 950).

Regarding secondary efficacy outcomes, for effects on emotional dysregulation at timepoints closest to 12 weeks (14 studies, 2296 participants), we found evidence that atomoxetine (SMD –0·36, 95% CI –0·67 to –0·04, 95% PI –1·00 to 0·29) and stimulants (–0·38, –0·62 to –0·14, –0·97 to 0·20) were more efficacious than placebo (appendix S12.8; p 941). At 26 weeks, we found no evidence of a difference in emotional dysregulation between active therapeutic components and placebo, with only three RCTs identified (433 participants; appendix S12.9; p 942), whereas at 52 weeks (two studies, 277 participants) we found evidence that stimulants were more efficacious than placebo (–0·41, –0·67 to –0·15, –0·67 to –0·15; appendix S12.10; p 943). In terms of executive dysfunction, we found no evidence of difference between active therapeutic components and placebo on processing speed at timepoints closest to 12 weeks (seven studies, 349 participants), apart from mindfulness (–0·45, –0·79 to –0·12, –2·63 to 1·72; appendix S12.13; p 946). We found no evidence of a difference between active therapeutic components and placebo in terms of quality of life at timepoints closest to 12 weeks (six studies, 1472 participants, standard NMA), and later timepoints (four RCTs on CBT, DBT, hypnotherapy, and relaxation therapy; appendix S17.14–16; pp 1043–45).

Figure 2: **Component network meta-analysis of the self-rated and clinician-rated severity of core symptoms at about 12 weeks and acceptability (any-cause discontinuation) outcomes**

Therapeutic components are listed in alphabetical order. Comparative estimates (reported as standardised mean differences for ADHD severity score and odds ratios for acceptability, with corresponding 95% CIs) are located at the intersection between the therapeutic component defined by the column and the therapeutic component defined by the row. The lower left triangle contains self-rated (light violet) and clinician-rated (dark violet) ADHD core symptoms at about 12 weeks and estimates above 0 (positive) favour the intervention defined by the column. The upper right triangle contains acceptability (any-cause discontinuation; orange) and estimates above 1 favour the intervention defined by the column (ie, lower any-cause discontinuation). All active therapeutic components and the most investigated control group with data available for both primary outcomes (self-rated ADHD core symptoms and acceptability) are listed (additional details in the appendix S14; pp 972–88). The certainty of the evidence (according to Confidence in Network Meta-Analysis [CINeMA] framework) for the coprimary outcomes is detailed using footnotes. Bold data indicate a statistically significant difference. ATO=atomoxetine. BUP=bupropion. CBT=cognitive behavioural therapy. CTr=cognitive training. DBT=dialectical behavioural therapy. GUA=guanfacine. MIND=mindfulness. MOD=modafinil. NEU=neurofeedback. PSY=psychoeducation. REL=relaxation therapy. STIM=stimulants. tDCS=transcranial direct current stimulation. TMS=transcranial magnetic stimulation.*High certainty of evidence. †Moderate certainty of evidence. ‡Low certainty of evidence. §Very low certainty of evidence.

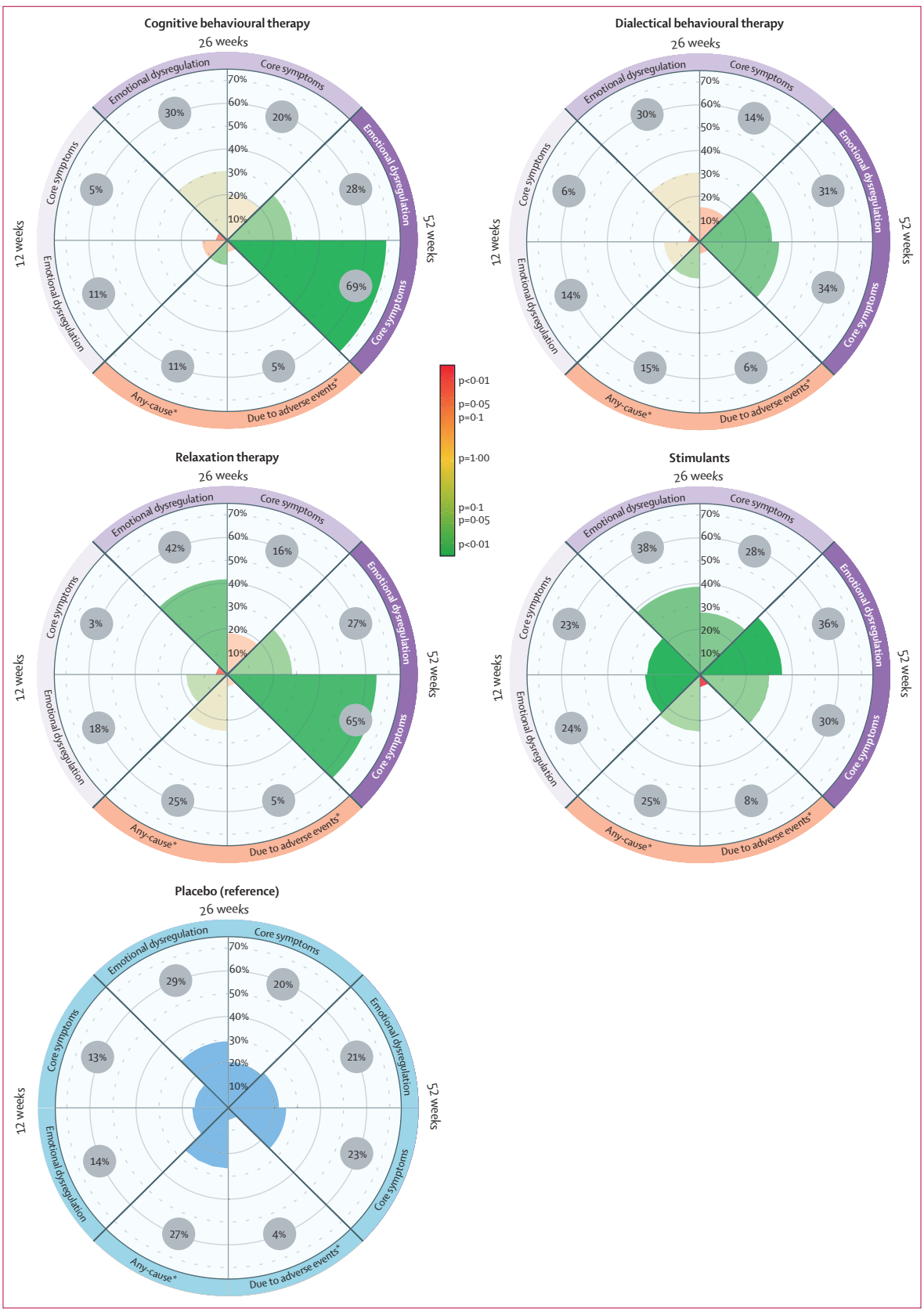


Figure 3: **Vitruvian plots of competing active therapeutic components with data for all prioritised outcomes**

The four competing active therapeutic components with available data for all the eight outcomes prioritised by the representative of people with lived experience of ADHD are summarised here. For each plot: the left quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 12 weeks; the top quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 26 weeks; the right quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 52 weeks; and the bottom quadrant includes acceptability (any-cause discontinuation) and tolerability (discontinuation due to adverse event). Colour indicates the relative performance of the active therapeutic component of interest and the precision of the estimate in comparison with pill placebo (blue), from green (component better than placebo), to yellow (unclear whether the component performs better or worse than placebo), and then red (component worse than placebo). The more precise the estimate (narrow confidence interval), the brighter the colour. Experimental and control event rates are expressed as the estimated probability of an outcome, calculated from the component network meta-analysis. Further details are available in the appendix (S38; pp 1200–01). For the originally submitted figure see appendix (S41; p 1205). *Discontinuation from trials.

Figure 3 shows a visual summary of the Vitruvian plots of the three active therapeutic components with data for the outcomes selected by people with lived experience of ADHD as being the most important to people with ADHD, and figure 4 shows the seven active therapeutic components with partial data availability (appendix S38; pp 1200–01).

We observed unbalanced distribution for some potential effect modifiers (appendix S8; pp 879–80) that we explored further in subgroup analyses and network meta-regressions (appendix S25–34; pp 1148–74). We observed incoherence in one subnetwork of clinician-reported ADHD core symptoms at 12 weeks (four of seven comparisons; appendix S11; pp 916–33). Only one comparison (right transcranial magnetic stimulation *vs* sham treatment; self-reported ADHD core symptoms at 12 weeks) was rated a major concern in terms of the effect of the additivity assumption on the model estimates, but overall the additivity assumption was considered plausible (appendix S22; pp 1132–37). We did not find evidence that higher values of baseline severity of self-reported ADHD core symptoms, year of publication, percentage of male individuals, or percentage of individuals with ADHD with another mental disorder affected the results. These parameters did not explain the heterogeneity observed in the unadjusted model (appendix S25–30; pp 1148–65). In the subnetwork that included the pharmacological interventions, we observed that the increase in treatment length in weeks yielded an increase in any-cause treatment discontinuation with little effect on heterogeneity (unadjusted model τ^2 1·13; adjusted model τ^2 1·11; appendix S25–30; pp 1148–65).

When restricting the analyses to studies at low risk of bias for self-reported ADHD core symptoms (11 studies, 2281 participants) and acceptability (34 studies, 9480 participants), we found evidence that atomoxetine (SMD –0·36, 95% CI –0·58 to –0·14), bupropion (–0·57, –1·12 to –0·02), and stimulants (–0·43, –0·64 to –0·23) were more efficacious than placebo at reducing self-reported symptoms, whereas atomoxetine (OR 1·54, 95% CI 1·23 to 1·94) was associated with lower acceptability compared with placebo (appendix S31–34; pp 1166–74).When restricting the network to non-industry-sponsored studies, studies up to 12 weeks, and when dividing stimulants into amphetamines and methylphenidate, we did not observe material changes from the main results (appendix S31–34; pp 1166–74).

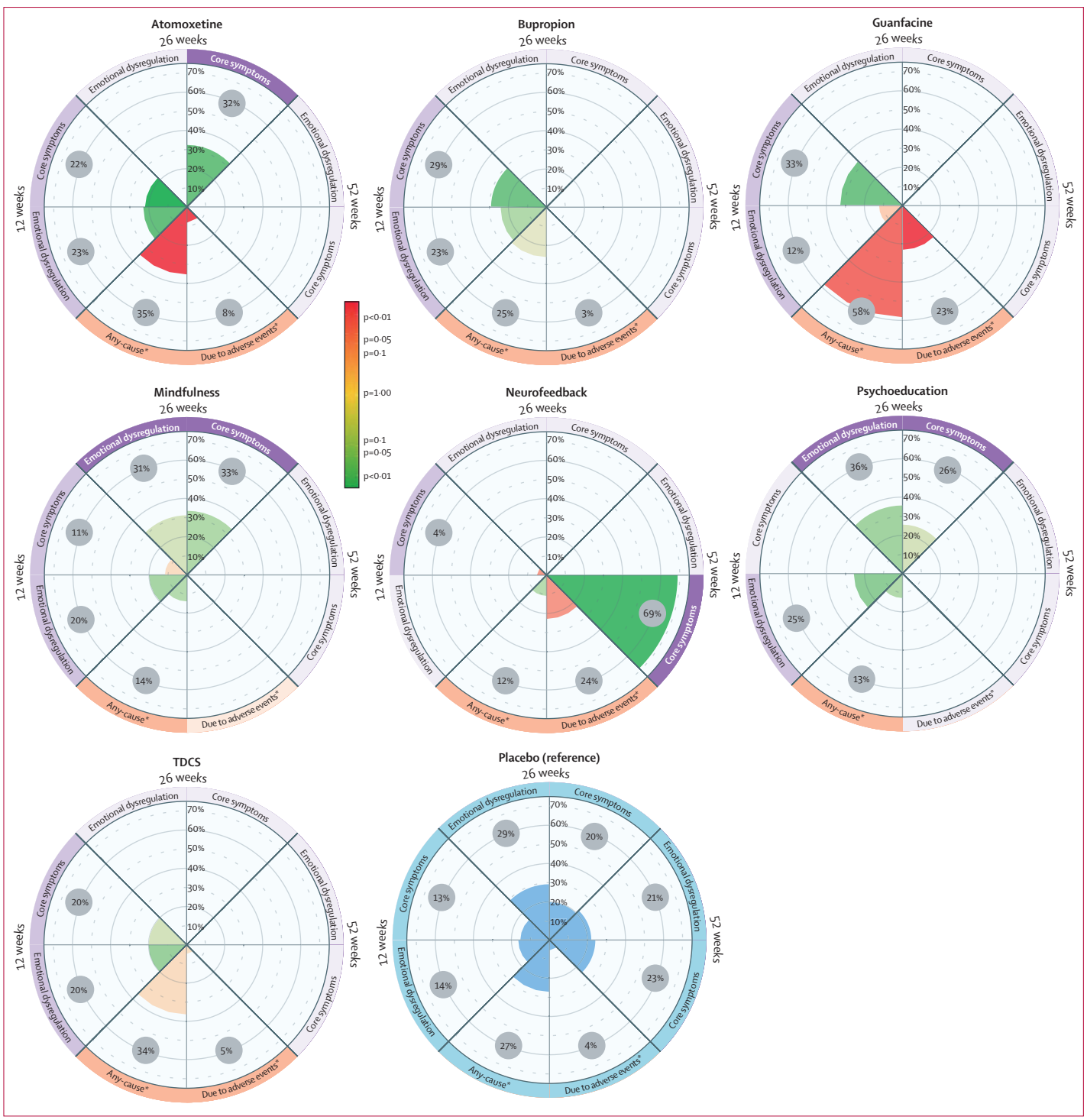
Discussion

We conducted the first NMA comparing pharmacological, psychological, and neurostimulatory interventions for ADHD in adults, to our knowledge. Our findings were based on 113 RCTs, including 14887 participants, and indicated that stimulants were the only intervention that was supported by evidence of efficacy in the short term (ie, at timepoints closest to 12 weeks) for core symptoms of ADHD in adults (both self-reported and clinician-reported) and was associated with good acceptability (all-cause discontinuation). Atomoxetine was efficacious but with worse overall acceptability than placebo. However, we found a paucity of studies on the medium-term to long-term effects of medications on ADHD core symptoms. Some non-pharmacological therapeutic components (ie, CBT, neurofeedback, and relaxation therapy) achieved beneficial effects on ADHD core symptoms over longer timeframes, yet with discordant results across types of raters and based on a small body of evidence.

Our findings on the pharmacological interventions were based on a larger body of evidence and support those of a previous NMA showing that amphetamines, atomoxetine, and methylphenidate were more efficacious than placebo on both self-based and clinician-based scales of ADHD symptoms at timepoints closest to 12 weeks.[10] Few RCTs have examined medication effects on core symptoms beyond 12 weeks. Future RCTs should assess long-term outcomes or, when not feasible, randomised discontinuation trials should be done to help evaluate long-term effects. Given the scarcity of randomised discontinuation trials on ADHD medications in adults, more are needed to better estimate long-term outcomes.[19,20] Observational studies, especially using the target trial emulation approach focusing on more pragmatic outcomes (eg, treatment discontinuation and adverse events), could provide an important complementary source of evidence on longer-term effects.

The efficacy of non-pharmacological interventions varied according to whether the individual with ADHD or their clinician was rating the ADHD core symptoms. Although we are not aware of any NMA comparing various non-pharmacological interventions, previous pairwise meta-analyses have reported beneficial effects of CBT on ADHD core symptoms when conflating self-reported and clinician-reported ratings, but meta-analyses focusing on self-reported and clinician-reported ratings separately align with our findings.[21,22] Our component NMA adds to the literature by extending these findings to other non-pharmacological interventions, including cognitive training, psychoeducation, and tDCS. The rationale behind the observed discrepancy according to the type of raters should be further explored in future studies. We cannot exclude that different raters might capture different aspects of the complexity of ADHD symptoms (eg, minimal important difference *vs* just noticeable difference) or might be differently affected by the fluctuating course of ADHD.[23] Our findings highlight how both individuals with ADHD and clinicians should be considered as sources of evidence, with ratings of symptoms by both groups measured in RCTs. As suggested by our representative with lived experience, participants in RCTs might report positive effects of the

active intervention to please the interviewer (the Hawthorne effect), or might not correctly report the perceived effects of interventions (especially when they feel under pressure from the clinicians and have difficulties with executive function, as is often the case in people with ADHD). Thus, self-report of ADHD core symptoms is valuable. Similar discrepancies between self-reported outcomes and external raters have been found for the treatment of panic disorders,[24] and lower improvement in symptoms was observed when participants with major depressive and psychotic disorders were actively told not to please the rater.[25] More



effort should be put into disentangling the complex relationship between different raters. The characteristics that influence the discrepancy in the rating of symptom severity by individuals with ADHD and clinicians, and the possible added value of objective biological measures in subjective reasoning should be investigated.

With regard to acceptability, all pharmacological and non-pharmacological therapeutic components were similar to placebo, except for atomoxetine and guanfacine, which were found to be less acceptable than placebo. Individuals with ADHD might discontinue an intervention due to insufficient perceived improvement in the symptoms that they find challenging, intolerable adverse events, or both. In our analyses on tolerability, atomoxetine, modafinil, guanfacine, and stimulants were associated with higher rates of discontinuation due to adverse events compared with placebo, which was consistent with previous findings.[10] High rates of co-occurring physical conditions in adults (eg, obesity) might contribute to overall poor tolerability of stimulants in adults.[26] Our findings on tolerability complemented those of long-term observational studies showing an increased risk of hypertension with cumulative use of stimulants for up to 14 years, especially at high doses.[8,27] In some individuals, the perceived benefits might outweigh the effects of non-serious adverse events associated with ADHD medications, but in other people, specific adverse events might lead to discontinuation of the intervention.[6] Overall, the trade-off between potential benefits and harms should be carefully considered in a shared decision-making process.

Regarding secondary outcomes, only stimulants were efficacious for emotional dysregulation, with small to moderate effect sizes in both the short term and long term. We did not observe an effect of DBT, which is at odds with its expected effects on the regulation of emotion. As difficulty with regulation of emotions is often a highly impairing symptom that some argue should be regarded as part of the core symptoms of ADHD,[28] additional evidence to support its management is a pressing need. Unlike findings in children,[29] we found that neither medications nor cognitive training were efficacious in improving executive dysfunction in adults. Given the high frequency and impairing nature of executive dysfunction associated with ADHD in adults, effective interventions and support are urgently needed.

Finally, regarding quality of life, we found little evidence at 12 weeks to support any intervention-specific effects, and data at later timepoints were extremely scarce. Although it could be expected that a longer timeframe (generally more than 1 year) is required when measuring outcomes to appreciate any positive effects of medications on quality of life, a 2024 meta-analysis of RCTs found beneficial effects of medication on the quality of life in the short-to-medium term in children with ADHD.[30] With the similar effects of continuing and discontinuing medications on reported quality of life in a few randomised discontinuation trials,[31] available evidence does not support medications as standalone treatments in providing satisfactory benefits on the quality of life of adults with ADHD, who might face additional challenges in their daily lives compared with children. The effects of multimodal approaches should therefore be explored in the future.

Overall, considering our findings across outcomes, although atomoxetine and stimulants had similar short-term efficacies, acceptability in relation to placebo was more favourable for stimulants. However, both atomoxetine and stimulants were found to be less tolerated than placebo. These results should inform future guidelines, which should account for the complexity of findings across outcomes and raters. Comparative evidence, such as that provided by our component NMA, was not available to inform previous guidelines for for the treatment of adults with ADHD (eg, the NICE guidelines,[7] the Canadian ADHD Resource Alliance, and the 2022 Australian ADHD Professionals Association guidelines).[32] Our work should inform upcoming guidelines, such as those from the American Professional Society of ADHD and Related Disorders,[33] providing guidance to health-care professionals and empowering individuals with ADHD in making informed decisions about their health.

Our study has limitations. Although we endeavoured to include all available trials and retrieved unpublished data, we cannot rule out the possibility of missing information. We found few data collected at 26 weeks and even less at 52 weeks after random assignment. This paucity of data partly reflects the ethical, practical, and cost constraints associated with conducting long-term placebo-controlled

Figure 4: **Vitruvian plots of competing active therapeutic components with partial data availability for prioritised outcomes**

The seven competing active therapeutic components with available data for four to seven of the eight outcomes prioritised by the representative of people with lived experience of ADHD are summarised here. For each plot: the left quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 12 weeks; the top quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 26 weeks; the right quadrant includes changes of self-reported ADHD core symptoms and emotional dysregulation at about 52 weeks; and the bottom quadrant includes acceptability (any-cause discontinuation) and tolerability (discontinuation due to adverse event). Colour indicates the performance from component network meta-analyses of the active therapeutic components of interest and the precision of the estimate in comparison with pill placebo (blue), from green (component better than placebo), to yellow (unclear whether the component performs better or worse than placebo), and then red (component worse than placebo). The more precise the estimate (narrow confidence interval), the brighter the colour. Experimental and control event rates are expressed as the estimated probability of an outcome, calculated from the component network meta-analysis. Coloured wedge titles indicate availability of data for the analyses. Purple=efficacy data. Brown=acceptability and tolerability data. No colour=no available data. For the originally submitted figures see appendix (S42; p 1205). Further details are available in the appendix (S38; pp 1200–01). pp 1200–01). TDCS=transcranial direct stimulation. For the originally submitted figure see the appendix (S42; p 1205). *Discontinuation from trials.

For the **Canadian ADHD Resource Alliance** see https://www.caddra.ca/

RCTs of efficacious interventions. Altogether, our findings can reliably inform only the choice of short-term intervention for ADHD in adults. Regarding medications, due to the network geometry, we could not separate methylphenidate and amphetamines in the main analyses. However, in our sensitivity analysis we did not find evidence of substantial difference in efficacy between these two compounds, in line with a previous NMA in adults.[10]

Our findings require the additivity assumption of the identified components to hold. When testing its plausibility and effects, overall we did not find violations to this assumption. We categorised specific interventions in therapeutic components based on the definitions of the original trialists, but future evidence synthesis studies could encompass alternative definitions of specific components to capture the complexity and nuances of specific therapeutic mechanisms of action or delivery. Future studies should also explore the effects of multimodal interventions involving different therapeutic components, to validate our findings and support the additive value of multimodal interventions. As specified in the published protocol, we included pharmacological and non-pharmacological interventions in a single network, as a trial including all these strategies could be, hypothetically, designed.[11]

Because masking for psychological interventions is not possible, we downgraded unmasked interventions in the risk of bias and confidence in the available evidence assessments. To explore potential violations of the transitivity assumption, we checked the distribution of potential effect modifiers across comparisons. We identified incoherent estimates of clinician-rated ADHD core symptoms at 12 weeks only in a subnetwork including DBT and stimulants or placebo combinations when using a non-additive model.

Finally, our findings are applicable at a group level only. Future approaches should use individual-level data to stratify treatment effects across subgroups of individuals with ADHD.

To conclude, stimulants and atomoxetine were the only interventions with evidence of effectively reducing core ADHD symptoms in the short term, based on both self-reported and clinician-reported ratings, although atomoxetine was less well tolerated than placebo. However, ADHD medications had no significant effects on broader outcomes, such as quality of life, and there is little long-term evidence on their effects. Non-pharmacological strategies showed inconsistent results across different evaluators. Our results are the best available evidence base to date to inform future guidelines considering benefits and harms of available interventions for ADHD in adults.

For the **dataset and analysis code** see https://github.com/EGOstinelli/cNMA_on_adults_with_ADHD/

Contributors

SC and AC conceptualised and designed the study. EGO, MS, CZ, LCF, and AT collected the data. EGO and CDG did the analyses. EGO, MS, CZ, LCF, AT and SC verified the data. EGO and SC wrote the first draft of the report. SRC, AP, SY, PJC, AB, and AC provided crucial input into the interpretation, analysis, and presentation of the data. All authors critically reviewed the report. EGO, AC, and SC coordinated and directed the project. All authors had full access to all the data in this study and provided final approval to submit the manuscript for publication.

Declaration of interests

EGO has received research and consultancy fees from Angelini Pharma. AT has received research and consultancy fees from the Italian Network for Paediatric Trials (INCiPiT), Angelini Pharma, and Takeda, and acts as a clinical advisor for Akrivia Health outside this work. CDG has received research support from the Multiple Sclerosis International Federation. SRC receives honoraria from Elsevier for journal editorial work and his research is funded by the National Health Service (NHS). AP served on advisory boards for, gave lectures for, did phase 3 studies for, and received travel grants within the past 5 years from MEDICE Arzneimittel Pütter, Takeda, Boehringer Ingelheim, and Janssen-Cilag; receives royalties from books published by Elsevier, Hogrefe, MWV, Kohlhammer, Karger, Oxford University Press, Thieme, Springer, and Schattauer; is a member of the German ADHD Guideline Group; and is an author of the Updated European Consensus Statement. SY has received honoraria for consultancy and educational talks from Janssen, Medice, and Takeda; is author of the ADHD Child Evaluation (ACE) and ACE+ for adults; and is lead author of three psychological treatment programmes (R&R2 for ADHD Youths and Adults, the Young–Bramham Programme, and the Young–Smith Programme). PJC holds a patent on behalf of Oxford University for the use of ebselen in patients with resistant depression. AC has received research and consultancy fees from INCiPiT, Fondazione Cariplo, Lundbeck, and Angelini Pharma outside of the submitted work. SC has received reimbursement for travel and accommodation expenses in relation to lectures delivered for the Association for Child and Adolescent Central Health, the Canadian ADHD Alliance Resource, and the British Association of Psychopharmacology, and has received honoraria from MEDICE. All other authors declare no competing interests.

Data sharing

The dataset and analysis code are available at Github.

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