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Review article

Treatments in the pipeline for attention-deficit/hyperactivity disorder (ADHD) in adults

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ABSTRACT

To provide an overview of treatments in the pipeline for adults with attention-deficit/hyperactivity disorder (ADHD), we searched https://clinicaltrials.gov/and and https://www.clinicaltrialsregister.eu/ from 01/01/2010–10/18/2023 for ongoing or completed phase 2 or 3 randomised controlled trials (RCTs), assessing pharmacological or non-pharmacological interventions for adults with ADHD with no current regulatory approval. We found 90 eligible RCTs. Of these, 24 (27 %) reported results with statistical analysis for primary efficacy endpoints. While several pharmacological and non-pharmacological interventions had evidence of superiority compared to the control condition from a single RCT, centanafadine (norepinephrine, dopamine, and serotonin re-uptake inhibitor) was the only treatment with evidence of efficacy on ADHD core symptoms (small effect size=0.28–0.40) replicated in at least one additional RCT, alongside reasonable tolerability. Overall, the body of ongoing RCTs in adults with ADHD is insufficient, without any intervention on the horizon to match the efficacy of stimulant treatment or atomoxetine and with better tolerability profile. Additional effective and well tolerated treatments for adults with ADHD require development and testing.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterised by developmentally inappropriate and impairing inattention plus hyperactivity and/or impulsivity (Faraone et al., 2024). ADHD is the most common neurodevelopmental disorder, affecting around 5 % of school-aged children worldwide according to a re-analysis of the Global Burden of Disease (GBD) data (Cortese et al., 2023) and 8 %, with an

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uneven gender distribution of 10 % for males and 5 % for females, based on an umbrella review including five systematic reviews and meta-analyses (57 unique primary studies) (Ayano et al., 2023).

Impairing symptoms of ADHD persist into adulthood in up to 75 % of the cases (Sibley et al., 2016), with an estimated prevalence of ADHD in adults at around 2.5 % (Song et al., 2021). ADHD is often comorbid with other disorders, including mood, anxiety, and substance use disorders, or dysfunctions, such as emotional dysregulation and executive dysfunction (Faraone et al., 2021), as well as physical disorders, including obesity and asthma (Arrondo et al., 2022).

Treatment options proposed for ADHD include pharmacological - encompassing stimulant and non-stimulant medications - and non-pharmacological interventions (Cortese, 2020). In currently available guidelines, pharmacotherapy plays an important role in the management of ADHD in adults. For instance, the 2018 (updated in 2019) National Institute for Healthcare and Excellence (NICE) guidelines (National Institute For Health and Care Excellence (NICE), 2019) suggested that medication (stimulants as first line, followed by the non-stimulant atomoxetine) should be offered after environmental modifications (such as reducing noise or distractions) have been implemented but ADHD symptoms are still impairing. Current medications for ADHD in adults are efficacious, albeit with lower effect sizes compared to children, especially in relation to stimulants for which effects sizes have been found to be high in children and medium in adults (Cortese et al., 2018). However, there are concerns around the safety of currently available ADHD medications, including their possible cardiovascular effects (Cortese and Fava, 2024) and limited abuse potential - even though the risk-benefit profile in general favours the use of medications, as recently highlighted by the ADDUCE project, a naturalistic, longitudinal, controlled study in 27 European child and adolescent mental health centres (e.g., Buitelaar et al., 2022). Therefore, there is a need for additional efficacious and safer medications for adults with ADHD.

In addition to pharmacological treatments, current guidelines include also non-pharmacological options. For instance, the NICE guidelines recommend considering non-pharmacological treatments if they are the preferred choice by the patient, medications are not well tolerated or ineffective, or regular adherence to medication is difficult. It remains unclear to what extent non-pharmacological options are efficacious and effective to tackle ADHD core symptoms or associated problems, such as emotional dysregulation. Of note, an increasing number of randomised controlled trials (RCTs) are testing the efficacy of non-pharmacological treatments, including psychotherapy, diet changes, cognitive training, and neurostimulation, for adult ADHD. Therefore, gaining insight into promising pharmacological and non-pharmacological treatment for adults with ADHD is crucial to inform future guidelines.

A previous study systematically reviewed 939 phase 2 or 3 RCTs testing medications for adults with mental health conditions, but ADHD was outside the scope of that work (Correll et al., 2023). Another study (Cortese et al., 2023b) systematically reviewed 234 phase 2 or 3 RCTs of medications without regulatory approval in the US, Europe or Asia, including also RCTs of dietary interventions/probiotics, as well as phase 4 RCTs of agents targeting unlicensed indications for children/adolescents with mental health disorders, including ADHD, but was limited to children and to pharmacological treatments. The present review builds on those two previous studies and complements them by systematically searching for phase 2, 3, 4 RCTs of non-approved pharmacological and non-pharmacological interventions for adults with ADHD. The present review is expected to provide a comprehensive overview of treatments in the pipeline for adult ADHD inform future research priorities in the field.

2. Methods

The study protocol is available in Open Science Framework, OSF (https://osf.io/dnmr7/).

2.1. Search strategy

We searched https://clinicaltrials.gov/and and https://www.clinicaltrialsregister.eu/ from 01/01/2010–10/18/2023. The time frame is very similar to the one considered in a recent similar review on phase 2/3 RCTs of psychopharmacological agents in adults (Correll et al., 2023). We also conducted an additional systematic targeted search in PubMed to check if identified RCTs for which results were not available in the clinical trials platforms had been published. The following filters were used for the search in clinicaltrials.gov: 1) study type: interventional studies (Clinical Trials); 2) recruitment: any available option (not yet recruiting/recruiting/enrolling by invitation/active, not recruiting/terminated/completed/unknown status); 3) age group: "adults"; 4) phase: phase 2/phase 3 or 4; 5) study start: From 01/01/2010 (assuming that if studies initiated $\geq$13 years ago and results had not been published or no additional studies were ongoing that this trial program had been discontinued). Likewise, the following filters were used for the search in https://www.clinicaltrialsregister.eu/: 1) select trial status: completed/ongoing/restarted; 2) age range: adults; 3) select trial phase: phase two/phase three/phase four; and 4) select date range: 01/01/2010–10/18/2023 (with the same reasoning for the cut-off date as mentioned for clinicaltrials.gov).

2.2. Inclusion and exclusion criteria

We included ongoing or completed phase 2 or 3 RCTs, regardless of their level of blinding, assessing pharmacological or non-pharmacological interventions for adults with ADHD that had to the best of our knowledge no regulatory approval in the US, Europe (through EMA licensing procedures, not those approved by individual countries through national licensing procedures) or Asia as of 10/18/2023. We also aimed to include any phase 4 RCTs of non-pharmacological treatments and, for pharmacological treatments, of medications, if any, already approved for adults with ADHD but targeting a currently unapproved indication (e.g., emotional dysregulation as primary outcome).

2.3. Classification of the mechanisms of action of the tested medications

To describe the possible mechanisms of action of the tested medications, we referred, whenever possible to the Neuroscience based Nomenclature (NbN) website (https://nbn2r.com/).

2.4. Evaluation of the chances of success

After summarizing the search results, we highlighted those interventions that were considered to be most promising based on the current level of evidence with regard to i) positive phase 2 and/or phase 3 or 4 clinical trials indicating superiority vs. placebo/other control. In particular, we assessed i) whether there were treatments with at least two positive RCTs (on the primary outcomes) without any negative RCTs (on the primary outcomes); ii) magnitude of the observed effect, with reference to the benchmarks suggested by Cohen (Cohen, 1988): 0.2: small; 0.5: medium; 0,8: large effect size; iii) demonstration of minimum requirements for safety/tolerability, in terms of lack of severe adverse events as defined by the Food and Drug Administration (FDA), i.e., those: resulting in death, or life threatening, or requiring inpatient hospitalisation or causing prolongation of existing hospitalisation, or resulting in persistent or significant disability/incapacity, or contributing to a congenital anomaly/birth defect, or requiring intervention to prevent permanent impairment or damage.

3. Results

3.1. Overview of included RCTs

We initially identified 115 potentially eligible RCTs (Table S1). However, 25 of the RCTs of pharmacological treatments tested medications already approved for adults with ADHD for core symptoms of ADHD (Table S2), which will not be discussed further in the present article. Of the remaining 90 RCTs, around 27 % (n = 24) reported results with statistical analysis for primary efficacy endpoints; in the rest (73 %, n = 66), results with statistical analysis of significance were not reported/available (ongoing trials: 38 %, completed trials: 38 %, unknown status: 14 %, terminated: 4 %, not yet recruiting: 6 %).

Completed RCTs with positive results on at least one primary outcome (n = 26) and those with negative results on every primary outcome (n = 8) are reported in Table 1 (pharmacological treatment) and Table 2 (non-pharmacological treatment). When available, Tables 1–2 report also data on tolerability, in terms of percentage of participants who dropped out due to adverse events or those who experienced adverse events defined as serious by the study authors, in line with the above-mentioned FDA classification.

3.2. Pharmacological treatments

Agents for which results of statistical analysis were available are descried below, in alphabetical order.

3.2.1. Centanafadine

Centanafadine is a compound that acts by inhibiting the reuptake of norepinephrine, dopamine, and serotonin. Its sustained release (SR) formulation was investigated in two phase III, multicentre studies conducted contemporaneously (Adler et al., 2022). In the first trial (NCT03605680), 466 (48.7 % females) adults with ADHD were randomised, following a 1-week single-blind run-in period, to receive centanafadine SR 200 mg/day, 400 mg/day, or placebo. At day 42, efficacy was assessed according to the change from baseline in the ADHD Investigator Symptom Rating Scale (AISRS). Both active arms showed superiority against placebo. Least Square mean differences (95 % CI) versus placebo for the 200 mg/day and 400 mg/day groups were, respectively, −3.1 ([-5.79, −0.51]; p = 0.0193; effect size = −0.28) and −2.74 ([-5.35, −0.14]; p = 0.0392; effect size = −0.24).

The second trial (NCT03605836) utilised the same design and had a total of 440 participants (47 % females) randomised to treatment. Measurement of change from baseline in AISRS total score at the end of week six also showed superiority of centanafadine SR over placebo for both 200 mg/day and 400 mg/day dose groups. Respectively, LS mean differences were reported as −4.01 ([-6.55, −1.46]; p = 0.0021; effect size = −0.37) and −4.47 ([-7.02, −1.82]; p = 0.0009; effect size = −0.40).

In both studies, adverse effects (AEs) were more frequent in the active groups (200 mg/day = 25.2 %; 400 mg/day = 31.8 %) than in controls (17.6 %), although most were mild or moderate in severity. Of the AEs deemed to be possibly related to centanafadine, the most common AEs were decreased appetite, headache, dry mouth, and nausea. Discontinuation due to treatment-emergent AEs (TEAEs) was also higher in the active (200 mg/day = 4.8 %; 400 mg/day = 6.2 %) than in the placebo arm (1.4 %).

An earlier, phase IIb study (NCT02547428), reported in Wigal et al. (2020), had previously evaluated the efficacy of centanafadine SR in 85 adults (44 % females) with ADHD utilising a crossover design. Patients were allocated to either placebo or centanafadine SR (400–800 mg/day) and received three weeks of treatment before crossing over to the opposite treatment assignment. Change in ADHD Rating Scale-IV (ADHD-RS-IV) score from baseline to week 3 showed superiority of centanafadine SR against placebo (LS mean difference [CI 95 %]: −8.1 [-11.0, −5.1]; p < 0.001; effect size = 0.66). Eighty percent of patients receiving centanafadine SR experienced an AE, compared with 68 % in the placebo group. In the centanafadine SR group, TEAEs were, in descending order of occurrence, decreased appetite, headache, and nausea. Out of the twelve patients that discontinued treatment due to a TEAE (centanafadine: n = 11; placebo: n = 1), ten had received 600 mg or more of centanafadine SR within one day of AE onset.

3.2.2. Dasotraline

A multicentre RCT including 636 adults (39.6 % females) with ADHD (NCT02276209) (Adler et al., 2021) investigated the efficacy of dasotraline, a pharmacologic agent that potently inhibits dopamine and norepinephrine transporters presynaptically (Adler et al., 2021). Subjects were allocated on a 1:1:1 ratio to treatment with dasotraline 4 or 6 mg/day, or placebo. At the end of week 8, change in severity of ADHD symptoms as measured by the ADHD Rating Scale, Version IV, total score showed no significant improvement in the active groups when compared to placebo when corrected using Hochberg's procedure ([dasotraline 4 mg/day vs. placebo: −15.0 vs. −13.9; p = n.s.; effect size: 0.09]; [dasotraline 6 mg/day vs. placebo: −16.5 vs. −13.9; $P = 0.074$; effect size: 0.23]). For non-adjusted p-values, dasotraline 6 mg/day was significantly better than placebo (p = 0.037). AEs were more common in the combined dasotraline dose group (80.1 %) than in the placebo arm (62.6 %). The most common AEs in the former group were insomnia, decreased appetite, dry mouth, and anxiety. Psychosis and mania-related events happened in two patients in the dasotraline 4 mg/day group, four patients in the Dasotraline 6 mg/day group and two in those taking placebo.

3.2.3. L-methylfolate supplementation

L-methylfolate is a folate derivative which is transported across the blood brain barrier and acts as an important factor in the synthesis of monoaminergic neurotransmitters such as norepinephrine and dopamine (Lam et al., 2022). A pilot study (NCT01853280) evaluated the effect of L-methylfolate supplementation to OROS-methylphenidate pharmacotherapy in adults with ADHD. Following randomisation, 44 patients (61.4 % females) received treatment with either 15 mg/day of L-methylfolate plus OROS methylphenidate or OROS methylphenidate with matched placebo comparator, for a period of twelve weeks. The mean change in score from baseline in the AISRS at week 12 was slightly greater in the treatment (-22.9, with a standard deviation of 10.4) than in the control arm (-20.8, with a standard deviation of 11.3); however, no additional statistical analyses were reported. No serious adverse events were reported. Other (not serious) adverse events that included headache, insomnia, mucosal dryness, decreased appetite and nausea, vomiting and diarrhoea were reported in 20/22 and 19/22 of the participants in the active and control group, respectively.

3.2.4. Mazindol

One study (NCT02808104) (Wigal et al., 2018) investigated the efficacy of a controlled-release (CR) formulation of mazindol, a drug previously marketed for short-term treatment of obesity which acts by blocking the reuptake of dopamine and noradrenaline, for adult ADHD. Seventy-five patients (57 % females) completed six weeks of treatment with either placebo or 1–3 mg/day of mazindol CR. At the end of week 6, a significant decrease in the ADHD-RS-DSM5 score was seen in the intervention group when compared to placebo (-18.9 vs. −5.7; LS mean difference [95 % CI]: −13.2 [-18.7, −7.6]; $p < 0.001$), with an overall placebo-corrected effect size of 1.09 in the intention-to-treat population. The group taking mazindol CR experienced more dry mouth, nausea, fatigue, increased heart rate, decreased appetite and constipation than the one allocated to placebo, with no serious treatment-emergent adverse events.

3.2.5. Metadoxine

The efficacy of metadoxine - a selective antagonist of the serotonin receptor subtype 5-HT 2b - in decreasing ADHD symptoms in

Table 1
Completed RCTs of pharmacological treatments with positive results on at least one primary outcome and those with negative results on every primary outcome.

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
Treatment of Cannabis Use Disorder Among Adults With Comorbid Attention-Deficit/ Hyperactivity Disorder (MJ-ADHD)	Adderall-XR [80 mg/day]	dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	2 arms: placebo vs Adderall-XR	placebo	33	18 Years to 65 Years (Adult, Older Adult)	12w	New York State Psychiatric Institute	2;3	NCT02803229	United States	2016.07	COMPLETED WITH RESULTS	Superior	Serious adverse events: 7.69 % (n = 1) in Adderall-XR group
Real-World Evidence of Duration of Effect of Adhansia XR (Extended-Release) for Treatment of Attention-Deficit/ Hyperactivity Disorder (ADHD) (RE-DAX)	Adhansia XR - Methylphenidate extended-release capsules taken once daily [25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg]	dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	2 arms: Adhansia XR vs Concerta	Cconcerta, once daily (18 mg, 27 mg, 36 mg, and 54 mg)	267	12 Years and older (Child, Adult, Older Adult)	8w	Purdue Pharma LP	4	NCT04507204	United States	2020.07	COMPLETED WITH RESULTS	Superior	Serious adverse events: 2.26 % (n = 3) in Adhansia XR group; 2.99 % (n = 4, including one death) in Concerta group
Adult Attention Deficit Hyperactivity Disorder (ADHD) Study With Amphetamine Sulfate	Amphetamine Sulfate [20 mg/ day, 40 mg/day]	dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	3 arms 1) 20 mg/ day Amphetamine Sulfate arm; 2) 40 mg/day Amphetamine Sulfate arm 3) Placebo	placebo	320	18 Years to 55 Years (Adult)	5w	Arbor Pharmaceuticals, Inc.	3	NCT03659929	United States	2018.09	COMPLETED	Superior: $p < 0.001$ for both 20 mg/ day and 40 mg/day	
Atomoxetine in Veterans With Comorbid ADHD/ PTSD	Atomoxetine [80 MG]	norepinephrine reuptake inhibitor (NET)	2 arms, Atomoxetine 80 MG vs placebo	placebo	44	20 Years to 60 Years (Adult)	10w	VA Office of Research and Development	4	NCT02287038	United States	2014.10	COMPLETED WITH RESULTS	Superior: $p = 0.017$	Discontinuation of treatment due to side effects: n = 1 atomoxetine phase Serious adverse events: nil observed
A Trial Evaluating the Efficacy, Safety, & Tolerability of Centanafadine Sustained-release Tablets in Adults With Attention-deficit/ Hyperactivity Disorder	Centanafadine [Centanafadine SR 200 mg; Centanafadine SR 400 mg]	inhibits the reuptake of norepinephrine, dopamine, and serotonin	4 arms: 1)Single-blind treatment with Placebo; 2) Double-blind Treatment with Centanafadine SR 200 mg; 3) Double-blind Treatment with Centanafadine SR 400 mg; 4) Double-blind Treatment with Placebo	placebo	604	18 Years to 55 Years (Adult)	6w	Otsuka Pharmaceutical Development & Commercialization, Inc.	3	NCT03605680; PMID: 35652746	United States	2019.01	COMPLETED WITH RESULTS	Superior: 200 mg/day: $p = 0.0193$, effect size −0.28; 400 mg/day: $p = 0.0392$, effect size −0.24	Discontinuation of treatment due to side effects (results pooled with study NCT3605836): 4.8 % (n = 14) in centanafadine 200 mg/day group, 6.2 % (n = 18) in centanafadine 400 mg/day group, 1.4 % (n = 4) in placebo group Serious adverse events (NCT03605680 only): 1.34 % (n = 2) in centanafadine 200 mg/day group

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Table 1 (*continued*)

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
A Trial to Evaluate the Efficacy, Safety, and Tolerability of Centanafadine Sustained-release Tablets in Adults With Attention-deficit/ Hyperactivity Disorder	Centanafadine [Centanafadine SR 200 mg; Centanafadine SR 400 mg]	inhibits the reuptake of norepinephrine, dopamine, and serotonin	4 arms:1) Single-blind tretament with Placebo, 2) Double-blind Treatment with Centanafadine SR 200 mg, 3)Double-blind Treatment with Centanafadine SR 400 mg, 4) Double-blind Treatment with Placebo	placebo	590	18 Years to 55 Years (Adult)	6w	Otsuka Pharmaceutical Development & Commercialization, Inc.	3	NCT03605836; PMID: 35652746	United States	2019.01	COMPLETED WITH RESULTS	Superior: 200 mg/day: $p = 0.0021$, effect size −0.37; 400 mg/day: $p = 0.0009$, effect size −0.40	Discontinuation of treatment due to side effects (results pooled with study NCT03605680): 4.8 % (n = 14) in centanafadine 200 mg/day group, 6.2 % (n = 18) in centanafadine 400 mg/day group, 1.4 % (n = 4) in placebo group Serious adverse events (NCT03605836 only): 0.69 % (n = 1) in centanafadine 200 mg/day group
Safety and Efficacy Study of Centanafadine Sustained-Release (CTN SR) in Adults With Attention-Deficit Hyperactivity Disorder (ADHD)	Centanafadine Sustained-Release (CTN SR) [CTN SR tablets starting at a dose of 100 or 200 milligrams (mg) on Day 1. Dose was up titrated up to 800 mg daily dose for up to 3 weeks in Period 1. The dose was decreased based on safety and tolerability based on Investigator's discretion, followed by a washout Period of 1 week followed by matching-placebo for up to 3 weeks in Period 2. The most common total daily dose (TDD) was 400 mg/day.]	inhibits the reuptake of norepinephrine, dopamine, and serotonin	2 arms: 1) Experimental: CTN SR First, Then Placebo; 2) Experimental: Placebo First, Then CTN SR	placebo	82	18 Years to 60 Years (Adult)	7w	Otsuka Pharmaceutical Development & Commercialization, Inc.	2	NCT02547428; PMID: 32606695	United States	2015.08	COMPLETED WITH RESULTS	Superior: $p < 0.001$; effect size = 0.66.	Discontinuation of treatment due to side effects: 13.9 % (n = 11) in centanafadine group, 1.4 % (n = 1) in placebo group Serious adverse events: nil observed
Dasotraline Adult ADHD Study	Dasotraline [4 Mg, 6 mg]	serotonin-norepinephrine-dopamine reuptake inhibitor	3 arms: Dasotraline 4 mg vs Dasotraline 6 mg vs placebo	placebo	636	18 Years to 55 Years (Adult)	8w	Sumitomo Pharma America, Inc.	3	NCT02276209; PMID: 33724251	United States	2014.12	COMPLETED	Not superior for primary outcome: Dasotraline 4 mg/day: p = n.s.; effect size: 0.09;	Discontinuation of treatment due to side effects: 17.1 % in Dasotraline 4 mg/ day group, 23.2 % in Dasotraline 6 mg/ day group, 3.2 % in placebo group

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Table 1 (*continued*)

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
														Dasotraline 6 mg/day: p = 0.074; effect size: 0.23	Serious adverse events: n = 2 in Dasotraline 4,g/day group, n = 2 in Dasotraline 6 mg/ day group, n = 1 in placebo group
L-methylfolate Supplementation to OROS-Methylphenidate Pharmacotherapy in ADHD Adults	L-methylfolate supplementation to OROS-Methylphenidate pharmacotherapy. L-Methylfolate [15 mg of L-Methylfolate (Deplin®) daily for 12 weeks as a supplement to OROS-Methylphenidate],	Methylfolate is a cofactor required for the synthesis of serotonin, norepinephrine, and dopamine. Methylphenidate is a dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE).	2 arms: L-Methylfolate as a supplement to OROS-Methylphenidate vs placebo with OROS-Methylphenidate	placebo with OROS-Methylphenidate	47	18 Years to 55 Years (Adult)	12w	Massachusetts General Hospital	2 and 3	NCT01853280	United States	2014.05	COMPLETED WITH RESULTS	Superior	Serious adverse events: nil observed
Shire SCT: Lisdexamfetamine Treatment for ADHD and SCT	Lisdexamfetamine [30 mg with allowed adjustments in increments of 10 mg or 20 mg at weekly intervals. Subjects are initiated on these doses and then they were titrated up by 20 mg with a maximum dose of 70 mg].	prodrug to dextroamphetamine; norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	2 arms: Lisdexamfetamine first, then placebo second; placebo first, then Lisdexamfetamine second	placebo	38	18 Years to 60 Years (Adult)	10w	NYU Langone Health	2	NCT02635035; PMID: 34232582	United States	2015.11	COMPLETED WITH RESULTS	Superior Block 1: p= 0.01, effect size 0.97; Block 2: p= 0.007, effect size 0.91	Discontinuation of treatment due to side effects: n = 1 in the placebo phase, after having done the Lisdexamphetamine phase Serious adverse events: nil observed
Efficacy of Lisdexamfetamine Dimesylate for Promoting Occupational Success in Young Adults With ADHD	Lisdexamfetamine Dimesylate [40 mg]	prodrug to dextroamphetamine; norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	2 arms: Lisdexamfetamine Dimesylate vs Placebo	Placebo	22	16 Years to 25 Years (Child, Adult)	2d	Gregory Fabiano	4	NCT03446885; PMID: 32297783	United States	2018.04	COMPLETED WITH RESULTS	Superior for completion of work-related tasks: p < 0.05; effect size 0.39	Serious adverse events: nil observed
Mazindol Controlled Release in Adults With Attention Deficit Hyperactivity Disorder (ADHD)	Mazindol [Dosage starting at 1 mg increasing or decreasing in increments of 1 mg depending on efficacy and tolerability. Maximum dose	releases and blocks reuptake of dopamine and noradrenaline	2 arms: mazindol vs placebo	placebo	84	18 Years to 65 Years (Adult, Older Adult)	6w	NLS Pharmaceutics	2	NCT02808104; PMID: 29557078	United States	2016.08	COMPLETED	Superior: p < 0.001, effect size 1.09	Discontinuation of treatment due to side effects: n = 2 in placebo group Serious adverse events: nil observed

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Table 1 (*continued*)

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
	during the study is 3 mg taken once daily]														
A 6 Week Study of MG01CI 1400 mg Compared With Placebo in Adults With ADHD (Attention Deficit/ Hyperactivity)	MG01CI (Metadoxine Immediate-release/Slow-release, Bilayer Caplet) [1400 mg]	increases acetaldehyde dehydrogenase activity, ethanol and acetaldehyde plasma clearance, and urinary elimination of ketones	2 (MG01CI vs placebo)	placebo	300	18 Years to 55 Years (Adult)	6w	Alcobra Ltd.	2 and 3	NCT02059642	United States	2014.03	COMPLETED WITH RESULTS	Not superior: $p = 0.13$	Serious adverse events: 0.68 % (n = 1) in placebo group
The Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/ Hyperactivity Disorder	OPC-64005 [During the titration period, participants received OPC-64005 two 10 milligram (mg) tablets, and one OPC-64005-matching placebo tablet along with two atomoxetine-matching placebo capsules, orally, once daily (QD), from Day 1 up to Day 4. During the treatment period, participants received OPC-64005 three 10 mg tablets, and two atomoxetine-matching placebo capsules, orally, QD, from Day 5 up to Day 56. The dose was reduced to 20 mg if the 30 mg dose in the treatment period was not tolerable.]	OPC-64005: triple reuptake (SERT, NET, and DAT) inhibitor	3 arms: OPC-64005 vs Atomoxetine vs Placebo	placebo	239	18 Years to 55 Years (Adult)	8w	Otsuka Pharmaceutical Development & Commercialization, Inc.	2	NCT03324581	United States	2017.11	COMPLETED WITH RESULTS	Superior against placebo: $p = 0.0101$	Serious adverse events: 1.30 % (n = 1) in OPC-65005 group
PRC-063 Adult Laboratory Classroom Study in Adults With Attention-Deficit/ Hyperactivity Disorder (ADHD)	PRC-063 [25, 35, 45, 55, 70, 85, or 100 mg]	dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	2 arms: 1) Treatment with PRC-063 (25, 35, 45, 55, 70, 85, or 100 mg) vs Placebo	placebo	288	18 Years to 60 Years (Adult)	1w	Purdue Pharma, Canada	3	NCT03618030	United States	2018.08	COMPLETED WITH RESULTS	Superior: $P = 0.0003$	Discontinuation of treatment due to side effects: nil during double-bling phase. 2.5 % (n = 7) during open-label, dose optimization phase

(*continued on next page*)

Table 1 (*continued*)

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
															Serious adverse events: 0.35 % (n = 1) during open-label, dose optimization phase
Experimental Medicine in ADHD - Cannabinoids (EMA-C)	Sativex	NA	2 arms Sativex Oromucosal Spray vs Placebo	placebo	30	18 Years to 55 Years (Adult)	6w	King's College London	NA	NCT02249299; PMID: 28576350	United Kingdom	2014.08	COMPLETED	Not superior for primary outcome: p = 0.16	Discontinuation of treatment due to side effects: 6,67 % (n = 1) in Sativex group, 6,67 % (n = 1) in placebo group Serious adverse events: 6,67 % (n = 1) in Sativex group, 6,67 % (n = 1) in placebo group
A Controlled Study of Solriamfetol for ADHD in Adults	Solriamfetol [75 mg, 150 mg]	dopamine and norepinephrine reuptake inhibitor	2 arms: Solriamfetol vs Placebo	placebo	60	18 Years to 65 Years (Adult, Older Adult)	6w	Massachusetts General Hospital	2 and 3	NCT04839562; PMID: 37819836	United States	2021.08	COMPLETED	Superior. p =.0012, effect size = 1.09	Adverse effects in Solriamfetol group with a minimum 10 % difference when compared to placebo: decreased appetite, headache, gastrointestinal, insomnia, increased energy, cardiovascular, and neurologic symptoms.
Safety and Efficacy Study of SHP465 in Adults Aged 18–55 Years With Attention-deficit/ Hyperactivity Disorder (ADHD)	SHP465 [12.5 mg up to 37.5 mg]	dopamine, norepinephrine reuptake inhibitor (DAT, NET), releaser (DA, NE)	3 arms: SHP465 12.5 mg; SHP465 37.5 mg; Placebo	placebo	275	18 Years to 55 Years (Adult)	4w	Shire	3	NCT02604407	United States	2015.11	COMPLETED WITH RESULTS	Superior: 12.5 mg/ day: p < 0.001, effect size = 0.67; 37.5 mg/ day: - p < 0.001, effect size = 1.11	Discontinuation of treatment due to side effects: 7.6 % (n = 7) in 12.5 mg/day SHP465 group, 5.6 % (n = 5) in 37.50 mg/day SHP465 group Serious adverse events: nil observed
Evaluation of SPN-812 (Viloxazine Extended-release Capsule) in Adults With ADHD	SPN-812 (Viloxazine Extended-release Capsule)	serotonin norepinephrine modulating agent	2 arms: SPN-812 vs placebo	placebo	374	18 Years to 65 Years (Adult, Older Adult)	6w	Supernus Pharmaceuticals, Inc	3	NCT04016779; PMID: 35896943	United States	2019.11	COMPLETED WITH RESULTS	Superior: p = 0.0040	Discontinuation of treatment due to side effects: 9.0 % (n = 17) in Viloxazine ER group, 4.9 % (n = 9) in placebo group Serious adverse events: 1.1 % (n = 2) in placebo group
Investigating the Effect of Vortioxetine in	vortioxetine [10 mg, 20 mg tablet]	serotonin reuptake inhibitor, receptor partial agonist (5-	3 arms: vortioxetine 10 mg tablet vs	placebo	227	18 Years to 55	12w	H. Lundbeck A/S	2	NCT02327013; PMID: 30843450	United States	2014.12	COMPLETED WITH RESULTS	Not superior: Vortioxetine 10 mg: p =	Discontinuation of treatment due to side effects: 4.3 % (n = 2)

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Table 1 (*continued*)

title	Intervention (dose)	mechanism of action	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT/EudraCT number	country	start date	status	descriptive results (primary outcome)	Tolerability
Adult ADHD Patients		HT1A), receptor antagonist (5-HT3)	vortioxetine 20 mg tablet vs Placebo tablet			Years (Adult)								0.972; Vortioxetine 20 mg: p = 0.601	in Vortioxetine 10 mg/day group, 9.1 % (n = 4) in Vortioxetine 20 mg/ day group, 1.6 % (n = 2) in placebo group Serious adverse events: 2.1 % (n = 1) in Vortioxetine 10 mg/day group, 1.1 % (n = 1) in placebo group

NA: not applicable

comparison to placebo was investigated in an RCT (NCT02059642) with 249 adults (53 % females). Groups were randomly assigned to receive either a once-daily dose of metadoxine 1400 mg or placebo, for six weeks. At the end of week 6, no statistically significant change in total ADHD symptom score with adult prompts of the Conners Adult ADHD Rating Scale was seen in the two groups (Metadoxine vs. Placebo: −12.0 vs. −9.9; LS mean difference [95 % CI]: −2.1 [-4.87–0.66]; p = 0.1358).

3.2.6. OPC-64005

OPC-64005 is a triple reuptake (serotonin transporter, norepinephrine transporter, and dopamine transporter) inhibitor whose efficacy and safety in the treatment of adults with ADHD were assessed in a phase II, multicentre clinical trial (NCT03324581). A total of 239 participants (53.1 % females) were randomly assigned to eight weeks of treatment with OPC-64005 (20–30 mg/day), atomoxetine (active comparator; 40–80 mg/day), or placebo. For the primary outcome, measured as the change from baseline in Conners' Adult ADHD Rating Scales-Observer: Screening Version (CAARS-O:SV), OPC-64005 was superior to placebo (-19.4 vs. −10.3; mean difference [95 % CI]: −6.61 [-11.6, −1.60]; p = 0.0101, effect size: not reported), however no significant difference was seen between the OPC-64005 and the atomoxetine arms (19.4 vs. −20.2; mean difference [95 % CI]: 0.81 [-4.30, 5.92]; p = 0.7554).

3.2.7. Sativex

One study (NCT02249299) (Cooper et al., 2017) evaluated the efficacy of cannabinoids in 30 adults (50 % females) with ADHD. Following a six-week period of treatment with either placebo or Sativex, an oromucosal spray containing 2.7 mg delta-9-tetrahydrocannabinol and 2.5 mg cannabidiol per 100 microlitres, measurement of cognitive performance and activity level were carried out utilising the Quantitative Behavioural Test (QbTest). Each participant followed a dosing schedule comprised of a 14-day titration period to find the optimal dose (up to maximum of 14 sprays per day), followed by another 28 days of daily administration of the titrated dose. However, no statistically significant changes in QbTest performance from baseline to day 42 were found between the two groups (estimated reduction in scores = −0.17 [95 % CI −0.40–0.07]; p = 0.16). Mild adverse events were experienced by three patients on the sativex group, including two reports of light-headedness and one of diarrhoea, all of whom were able to resume and complete treatment. One active group participant reported sudden onset of muscular seizures/spasms and stopped Sativex.

3.2.8. Solriamfetol

Solriamfetol, a dopamine and norepinephrine reuptake inhibitor most commonly used for treatment of sleep disorders, was evaluated in a study with 60 adults (48.3 % females) with ADHD (NCT04839562) (Surman et al., 2023). Subjects were randomised to receive placebo or Solriamfetol (75–150 mg/day) for six weeks. Following treatment, patients in the active group had greater improvement in total scores in the ADHD Investigator Symptom Rating Scale (AISRS), starting from week 3 through week 6 (p = 0.0012; week 6 effect size = 1.09). Adverse effects reported by the solriamfetol group with a minimum 10 % difference when compared to placebo included decreased appetite, headache, gastrointestinal, insomnia, increased energy, cardiovascular, and neurologic symptoms.

3.2.9. Vortioxetine

Vortioxetine, a multimodal antidepressant, which acts as a serotonin reuptake inhibitor, receptor agonist (5-HT_{1A}), receptor partial agonist (5-HT_{1B}), and a receptor antagonist (5-HT_3), was investigated as a potential treatment for ADHD in a twelve week, two-stage study (NCT02327013) (Biederman et al., 2019). Stage I, completed by 181 adults, comprised of six weeks of treatment with vortioxetine 10 or 20 mg/day, or placebo (randomised in a 1:1:3 ratio). Placebo non-responders (n = 59) were then re-allocated in stage II to another six weeks of vortioxetine 10 or 20 mg/day, or placebo (randomised in a

1:1:1 ratio). A total of 151 subjects completed the study. The primary efficacy endpoint, measured as mean scores on Adult ADHD Investigator Symptom Rating Scale (AISRS), did not reveal any significant differences between the groups (vortioxetine 10 mg vs. placebo = −0.1 [SE = 1.4; p = 0.972]; vortioxetine 20 mg vs placebo = 1.0 [SE = 1.9; p = 0.601). TEAEs were more common in the vortioxetine 20 mg group, with nausea and fatigue being the most frequently reported ones in either active group. Suicidal ideation reported by one patient was the only serious adverse event in the active groups.

3.2.10. Compounds in RCTs with results of statistical analysis not reported

Non-FDA approved compounds for ADHD core symptoms or other outcomes in RCTs with results of statistical analysis not reported included: TAK-137 (AMPA receptor potentiator) (note: RCT terminated), vayarin (which acts on restoring brain lipid imbalance), metadoxine (a selective antagonist of the serotonin receptor subtype 5-HT 2b, in addition to the RCT above- in a RCT that was terminated), centanafadine (inhibitor of norepinephrine, dopamine, and serotonin reuptake, in addition to the two positive RCTs above- in a RCT that was terminated), probiotic, melatonin, oxytocin, tolcapone (specific inhibitor of cathechol-O-methyltransferase), contrave (combination of naltrexone, an opioid antagonist, and bupropion, an inhibitor of the neuronal reuptake of dopamine and norepinephrine in a study that was withdrawn), solriamfetol (dopamine and norepinephrine reuptake inhibitor, in addition to a study with positive results reported above), MM-120 (a tartrate salt form of lysergide, which is a partial 5-HT2A agonist), PDC-1421 (inhibitor of the norepinephrine plasma membrane transport protein), cannabis oil (note: RCT terminated), zantiva (selective inhibition of presynaptic norepinephrine reuptake), and NRCT-101SR (adrenergic receptor agonist).

3.3. Non-pharmacological interventions

Interventions for which results with statistical analysis were available are descried below, grouped by type and presented in alphabetical order.

3.3.1. Dietary interventions

A study (NCT03342469) investigated the effects of artificial food colours (AFCs) on ADHD symptoms in 29 students with ADHD (aged 18–24 years, 21 females), following a stable medication dose and frequency (ADHD medication or otherwise) for at least 3 months. The dietary intervention consisted of ingesting six of the most common AFCs (Red 40, Red 3, Yellow 5, Yellow 6, Blue 1 and Blue 2) mixed in chocolate biscuits or a placebo of chocolate biscuits. The participants underwent an electroencephalogram (EEG) and a cognitive test (Adult ADHD Self-Report Scale-V1). Exposure to AFC did not result in any significant changes in ADHD symptoms.

3.3.2. Neurostimulation

Of the studies identified, three used neurostimulation as a non-pharmacological treatment for adults with ADHD. One of these trials (NCT03663179) used transcranial magnetic stimulation (TSM), a non-invasive technique for electromagnetic stimulation of brain tissue. Specifically, the study investigated whether 20 sessions of active TMS targeting the left dorsal prefrontal cortex (DLPFC) could improve executive cognitive function in adults with ADHD compared to 20 sessions of sham TMS. To evaluate the efficacy of TSM as an alternative treatment for ADHD, only patients who were not receiving pharmacological treatment for ADHD were included. Of the 27 participants (9 males, mean [SD] age: 34.4 [13.0] years), 14 were assigned to active TSM and 13 to sham TSM. The study showed that active TSM did not significantly improve ADHD symptoms, as measured by the Conners Adult ADHD Rating Scale—Self-Report: Long Version (t-score, mean [SD]: active TMS −4.4 [9.4] vs. sham TMS −5.1 [7.6]). However, an isolated improvement in sustained attention was found using the Conners Continuous Performance Task (mean [SD]: active TMS −16.2 [17.6] vs. sham TMS −4.8 [18.0]. In this study, no serious adverse events were reported.

Transcranial direct current stimulation (tDCS) was investigated in the other two studies. In the first study (NCT04003740), tDCS was used to improve symptoms of inattention in patients with ADHD. Adults with ADHD (n = 64, 34 males, all without ongoing pharmacological treatment for ADHD; mean [SD] age: 38.3 [9.6] years) participated in the study. Participants were randomised to receive tDCS stimulation with active or sham devices. After the first 4 weeks of daily stimulation, the active tDCS group significantly improved in terms of symptoms of inattention (p <0.001, effect size: not reported) as measured by the clinician administered ADHD Self-Report Scale—Part A, Inattention (CASRS-I), compared to the sham treatment. No serious adverse events were recorded during the study.

In another randomised, sham–controlled, double-blind study (NCT04175028) (Dubreuil-Vall et al., 2021), the cognitive and physiological effects of tDCS were investigated in 40 adults with ADHD (aged 18–67 years). Before and after each session (in which tDCS targeted the left DLPFC, the right DLPFC and was a sham treatment), participants completed tests to measure their response inhibition. For this purpose, the Eriksen-Flanker Task (EFT) or the Stop Signal Task (SST) were performed to assess interference cognitive control or action cancellation, respectively. Behavioral data (reaction time (RT), accuracy) and neurophysiological data (event-related potentials, ERPs) were also recorded. In the EFT, left-sided stimulation resulted in significantly faster RT compared to sham treatment (p <0.0001) and right-sided stimulation (p = 0.0183). In the EFT, left-sided stimulation also modulated physiological measures, resulting in a significant increase in P300 amplitude compared to sham (p = 0.022) and a significant decrease in N200 amplitude compared to right-sided stimulation (p = 0.027). Although a significant correlation was found between the RTs in the EFT and the ERPs (larger P200 amplitude (p = 0.046), and between larger P300 amplitudes (p = 0.046) and faster RT; smaller N200 amplitude and faster RT (p <0.0001)), no significant differences were found in these relationships before vs. after stimulation. This finding suggests that tDCS may not significantly modulate the relationship between RT and ERPs. As for Stop trials in SST, no significant cognitive or physiological changes were found after left-sided stimulation. The authors interpreted these results with the hypothesis that tDCS targeting the left DLPFC could lead to an improvement in cognitive control but not in action cancellation.

3.3.3. Physical activity

A RCT (NCT05049239) (Svedell et al., 2023) investigated the effects of a 12-week exercise program in 14 adults with ADHD (aged 27–54 years). The intervention consisted of a physiotherapist-led, small-group (4–6 participants) mixed exercise program with moderate to high intensity cardio, strength and flexibility exercises, targeting 60 %–90 % of maximum heart rate, taking place for 50 min, three times a week for twelve weeks. When analysing the differences between pre- and post-treatment in the intervention group and the control group (who received usual care), significant improvement was found only in the intervention group. Compared to baseline, the intervention group actually showed a reduction in ADHD symptoms (significant as measured by the ASRS [p=0.036]; non-significant as measured by the CGI-S [p=0.11]), a general and significant improvement (determined by a composite score calculated from the scores of the Adult ADHD Self-Report Scale (ASRS), Clinical Global Impression-Severity (CGI-S), Patient Global Impression-Improvement (PGI-I), Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S) and EQ visual analogue scaler (EQ-VAS) rating scales [p = 0.008]), and an improvement in cognitive functioning (significant, measured by the AX-CPT [p=0.032], non-significant for the Go/NoGo and emotion regulation tasks). Effect sizes were not reported.

Table 2
Completed RCTs of non-pharmacological treatments with positive results on at least one primary outcome and those with negative results on every primary outcome.

title	Intervention	type of intervention (neurostimulation, dietary, psychological, physical activity)	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT number/ PMID	country	start date	status	descriptive results (primary outcome)	tolerability
Food Additives Effects on EEG Profiles in College Students With ADHD	Artificial Food Coloring	dietary	4 arms: 1) ADHD- Artificial food coloring, then placebo; 2) ADHD - Placebo, then artificial food coloring; 3) Controls- Artificial food coloring, then placebo; 4) Controls - Placebo, then artificial food coloring	placebo	29	18 Years to 24 Years (Adult)	6w	American University	NA	NCT03342469	United States	2018.01	COMPLETED WITH RESULTS	Not superior	Serious adverse events: nil observed
Transcranial Magnetic Stimulation for Attention Deficit/ Hyperactivity Disorder (ADHD)	TMS	neurostimulation	2 arms: Active TMS vs Sham TMS	Sham TMS	27	18 Years to 65 Years (Adult, Older Adult)	4w	University of Pennsylvania	NA	NCT03663179	United States	2017.01	COMPLETED WITH RESULTS	Not superior in reducing ADHD symptoms (CAARS-S:L); superior in improving sustained attention (mean [SD]: active TMS −16.2 [17.6] vs. sham TMS −4.8 [18.0]; Conners CPT)	Serious adverse events: nil observed in both arms. Not serious adverse events: 22.22 % in active TMS (Sleep disturbance 5.56 %; allergic reaction 5.56 %; Injury 5.56 %; Depression symptoms 5.56 %), and 7.14 % in sham TMS (Visual disturbance 7.14 %)
TDCS for the Treatment of Inattention Symptoms in Adult ADHD Patients (TUNED)	Home-based tDCS	neurostimulation	2 arms: Active tDCS vs Sham tDCS	Sham tDCS	64	18 Years and older (Adult, Older Adult)	12w	Hospital de Clinicas de Porto Alegre	NA	NCT04003740	Brazil	2019.07	COMPLETED WITH RESULTS	Superior in decreasing inattention ($p < 0.001$; ASRS)	NA
Neuromodulation of Executive Function in the ADHD Brain	tDCS	neurostimulation	2 arms: ADHD vs controls	controls	40	18 Years to 67 Years (Adult, Older Adult)	6w	Massachusetts General Hospital	NA	NCT04175028 PMID: 33549516	United States	2015.07	COMPLETED WITH RESULTS	Effects on executive functions: superior in improving RT in the EFT ($p < 0.0001$); non superior in the SST	NA
Structured Physical Training With and Without Cognitive	Physical training	physical activity	2 arms: Physical training vs TAU	TAU	14	27 Years to 54 Years	12 m	Region Örebro County	NA	NCT05049239; PMID: 37255729	Sweden	2021.02	COMPLETED WITH RESULTS	Superior in reducing ADHD symptoms, as measured by ASRS	100 % of the participants in the experimental arm

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Table 2 (*continued*)

title	Intervention	type of intervention (neurostimulation, dietary, psychological, physical activity)	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT number/ PMID	country	start date	status	descriptive results (primary outcome)	tolerability
Support for Adults With ADHD						(Adult, Older Adult)								(p=0.036), not superior by CGI-S; general improvement (p = 0.008; composite score*), improvement in cognitive functioning (p=0.032; AX-CPT)	considered the intervention physically strenuous, and 50 % of them considered it mentally strenuous. 100 % of trial participants reported overall health improvement.
Training Attentional Awareness and Control in ADHD (SAC-I)	Sustained Attention Control (SAC) Method	psychological	2 arms: SAC Method vs Control	Behavioral learning using the mobile software game "Scrabble")	85	18 Years to 40 Years (Adult)	10w	Think Now Incorporated	NA	NCT02489279	United States	2015.06	COMPLETED WITH RESULTS	Superior in improving sustained attention (p = 0.026; Conners CPT RT Variability), timed reading comprehension (p = 0.014; NDRT), attention (p = 0.000001; ASRS), hyperactivity (p = 0.00018; ASRS)	Adverse events: nil observed
Improving ADHD Teen Driving	PC-based "FOCAL+" training	psychological	2 arms: "FOCAL +" vs Control	modified conventional driver's training	152	16 Years to 19 Years (Child, Adult)	12 m	. Children's Hospital Medical Center, Cincinnati	NA	NCT02848092; PMID: 36449421	United States	2016.12	COMPLETED WITH RESULTS	Superior in improving attention (P < 0.001; reduction in the number of long glances away from the roadway); fewer collisions (RR, 0.60)	Motion sickness is reported during evaluation drives (0 % intervention group, 3 %control group), and during training drives (8 % intervention group, 5 % control group). Frustration with the simulator is reported in 3 % in the intervention group
The Secret Trail of Moon (Serious Videogame) and Chess on ADHD: a Clinal Trial	Cognitive Training with Virtual Reality Videogame (The Secret Trail of Moon) and Cognitive Traning with	psychological	3 arms: Cognitive Training with Virtual Reality Videogame (The Secret Trail of Moon) vs Cognitive Traning with Therapeutic Chess vs Control Group	TAU	105	12 Years to 22 Years (Child, Adult)	3 m	Puerta de Hierro University Hospital	2	NCT04355065; PMID: 37093628	Spain	2019.12	COMPLETED WITH RESULTS	Superior in reducing inattentive symptoms and emotional dysregulation (p < 0.10; CPT-3, ATENTO, BRIEF-2).	NA

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Table 2 (*continued*)

title	Intervention	type of intervention (neurostimulation, dietary, psychological, physical activity)	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT number/ PMID	country	start date	status	descriptive results (primary outcome)	tolerability
	Therapeutic Chess													Not superior in improving executive functions (BRIEF-2).	
Effects of Structured Skills Training Group in Treatment of ADHD in Adults	Structural skills training group	psychological	2 arms: Structural skills training group vs Treatment as usual	TAU	121	18 Years and older (Adult, Older Adult)	8 m	University of Oslo	NA	NCT02685254; PMID: 36443712	Norway	2016.02	COMPLETED	Superior in decreasing ADHD symptoms ($p < 0.001$; ASRS) and improving executive function ($p=0.005$; BRIEF-A). Not superior in improving emotional regulation (DERS)	Adverse events: nil observed
Group Dialectical Behavior Therapy as add-on Treatment for Adults With Attention Deficit/ Hyperactive Disorder	Skill Training Group of the Dialectical Behavior Therapy	psychological	2 arms: Group Dialectical Behavior Therapy vs treatment as usual	TAU	31	18 Years to 60 Years (Adult)	12w	Hospital de Clinicas de Porto Alegre	NA	NCT03326427; PMID: 32880953	Brazil	2018.04	COMPLETED WITH RESULTS	Not superior (ARSR)	NA
The Efficacy of Goal Focused, Non-Pharmacological Treatment for Persons With ADHD/ ADD	Goal Attainment Scaling	psychological	2 arms: Goal Attainment Scaling vs control group	TAU	81	18 Years to 60 Years (Adult)	12w	University Hospital, Akershus	NA	NCT04638283; PMID: 38046113	Norway	2019.08	COMPLETED WITH RESULTS	Not superior in improving executive functioning (BRIEF-A) or reducing ADHD symptoms (ARSR). Superior in decreasing anxiety symptoms ($p = 0.014$)	NA
CBT Through Internet and Smartphones for Adults With ADHD - a Randomized Controlled Trial (Ad5)	iCBT: A skill training internet-based treatment program based on CBT and DBT interventions	psychological	3 arms: iCBT vs iART vs TAU	iART; TAU	104	18 Years to 65 Years (Adult, Older Adult)	60w	Karolinska Institutet	NA	NCT02041884; PMID: 37483263	Sweden	2014.01	COMPLETED WITH RESULTS	Superior ($p<0.01$; ARSR), even 12 months after treatment ($p < 0.001$). No significant difference between iCBT to iART ($p = 0.53$)	In iCBT, 8 % reported stress, 5 % depression, 5 % felt overwhelmed, 3 % felt discomfort. In iART, 11 % stress, 8 % anxiety, 3 % perceived the treatment as unclear, and % experienced somatic problems.

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Table 2 (*continued*)

title	Intervention	type of intervention (neurostimulation, dietary, psychological, physical activity)	total n of arms	control	total n subjects	age range	trial duration	funding/ manufacturer	phase	NCT number/ PMID	country	start date	status	descriptive results (primary outcome)	tolerability
Mindfulness Training in Adults With ADHD	MBCT	psychological	2 arms: MBCT vs TAU	TAU	120	18 Years and older (Adult)	9 m	Radboud University Medical Center	NA	NCT02463396; PMID: 29486807	Netherlands	2014.09	COMPLETED WITH RESULTS	Superior in reducing ADHD symptoms (p = 0.004; CAARS), even 6 months after treatment, and in improving executive functions after 6 months (effect size of d = 0.49).	NA
An Internet-delivered Intervention for Coping With ADHD in Adulthood (MyADHD)	interventional MyADHD	psychological	2 arms: interventional MyADHD vs Psychoeducation	Psychoeducation	120	18 Years and older (Adult, Older Adult)	8w	University of Bergen	NA	NCT04726813; PMID: 36969389	Norway	2021.04	COMPLETED WITH RESULTS	Superior in improving ADHD symptoms (d = 0.70; ASRS) and quality of life (d = 0.53; AAQoL scale)	NA

Abbreviations:
AAQoL: Adult ADHD Quality of Life
ASRS: ADHD Self-Report Scale
ATENTO questionnaire,
BRIEF-2: Behavior Rating Inventory of Executive Function-2
CAARS-INV: SV: Conners' Adult ADHD Rating Scale
CAARS-S:L: Conners Adult ADHD Rating Scale - Self-Report: Long Version
CGI-S: Clinical Global Impression-Severity
Conners CPT RT Variability: Conners Continuous Performance Test Reaction Time Variability
Conners CPT: Conners Continuous Performance Task
CPT-3: Continuous Performance Test 3
EFT: Eriksen flanker task.
FOCAL: Focused Concentration and Attention Learning
iART:internet-based applied relaxation training
iCBT: internet-based cognitive behavioral therapy
MBCT: Mindfulness Based Cognitive Therapy
NA: not applicable
NDRT:Nelson Denny Reading Comprehension test
RT: reaction time
SST: stop signal task
TAU: treatment as usual
tDCS: transcranial direct current stimulation
TMS: Transcranial Magnetic Stimulation
*composite score: calculated from the scores of the ASRS, CGI-S, PGI-I, MADRS-S and EQ-VAS rating scales

3.3.4. Psychological therapies

3.3.4.1. Cognitive training. One RCT (NCT02489279) tested two cognitive training programs on personal mobile devices that were used to assess the attention of 85 adults (58.7 % females, 18–40 years old) with ADHD. Specifically, the Sustained Attention Control (SAC) mobile software, which tests sustained attention skills and self-awareness of attention control, was compared with the software game "Scrabble"," which is used to practice word processing and executive control functions. At the end of the 10-week treatment, significantly greater improvements were found in the SAC group than in the active control group on both primary outcome measures, namely the measure of sustained attention (measured using the Conners Continuous Performance Test Reaction Time Variability ($p = 0.026$)) and timed reading comprehension (using the Nelson-Denny Reading Test ($p = 0.014$)).

In addition, the authors analysed the ADHD symptoms between the two groups using the Adult Attention-Deficit Hyperactivity Disorder Self-Report Scale (ASRS). The participants in the Scrabble group showed a greater improvement on the inattentive subscale ($p = 0.000001$) and the hyperactive subscale ($p = 0.00018$).

A computer-based training program referred to as FOcused Concentration and Attention Learning (FOCAL+) was developed to improve the attention of drivers with ADHD by trying to reduce their long glances ($\geq$2 seconds) away from the roadway. A group of 152 participants (38 % females) aged 16–19 years *(note; this study was included, as the sample encompassed individuals aged 18 or older)* were randomised to either this intervention group or the sham comparison group, which consisted of computerised training on traffic rules, laws, and regulations (NCT02848092) (Epstein et al., 2022)). Both the experimental and control training took place weekly for 5 weeks. During simulated driving after training, a significant reduction in the number of long glances away from the roadway was observed in the intervention group compared to the sham group after 1 month ($P < 0.001$) and after 6 months ($P < 0.001$). In addition, the rate of collisions and near-collisions during real driving was significantly lower in the intervention group one year after training (relative risk: 0.60).

Executive functions and emotional regulation were investigated in a group of 105 patients with ADHD (21.5 % females, aged 12–22 years) who received either cognitive training with a virtual reality video game (The Secret Trail of Moon, TSTM group) or cognitive training with therapeutic chess (TC) or no cognitive intervention (control group, CG) (NCT04355065 (Rodrigo-Yanguas et al., 2023)). Notably statistical threshold was set and reported in this study at $p < 0.10$. Compared to the CG group, the TC group performed significantly better in terms of emotional control, emotional regulation, and inattention ($p < 0.10$). On the other hand, the TSTM group showed significantly better improvements compared to the CG group ($p < 0.10$) on the measures of emotional regulation, inattention, and school context.

3.3.4.2. Dialectical behavioural therapy-based group treatment. A study investigated the effects of 14 weeks of Dialectical Behavioural Therapy-based Group Treatment (DBT-bGT) compared to treatment as usual (TAU) on executive functions and emotional regulation in adults with ADHD ($n = 121$, 56 % females) (NCT02685254) (Halmøy et al., 2022). Although emotional regulation (measured with the Difficulties in Emotion Regulation Scale, DERS) did not differ significantly between the groups, significant improvements in executive functions were found in the DBT-bGT group using the Behaviour Rating Inventory of Executive Function (BRIEF-A) ($p = 0.005$). Compared to participants receiving TAU, those assigned to DBT-bGT reported significant improvement in ADHD core symptoms (ASRS total score, $p < 0.001$), depressive symptoms (BDI total score, $p < 0.001$), and quality of life (AAQol total score, $p = 0.004$). However, DBT-bGT was not superior to TAU in reducing anxiety symptoms. The authors also found that these observed symptom reductions persisted in the DBT-bGT group at the 6-month follow-up. Effect sizes were not reported.

The efficacy of the Dialectical Behavior Therapy Skill Training Group (DBT-ST) was compared as an add-on treatment to ADHD medication vs to treatment as usual (TaU) in another study (NCT03326427) (Moritz et al., 2021)) involving 31 adults with ADHD (aged 18 and 60 years). After participating in 12 weeks of DBT-ST or TaU, ADHD symptoms were assessed using the ADHD Self-Rating Scale (ASRS). No significant difference was found between the groups in ASRS scores over time.

3.3.4.3. Goal management training. Goal Management Training (GMT) was compared with Treatment as usual (TAU) in improving executive functions and reducing ADHD symptoms and comorbidity (NCT04638283) (Hanssen et al., 2023). In this study, the active intervention consisted of 16 hours of GMT and psychoeducation plus 4 individual sessions focusing on specific goals. Adults with ADHD ($n = 81$; aged 18–55 years; 58 % women; 23.5 % diagnosed with anxiety) were randomly assigned to either GMT or TAU. In both groups, executive functions, psychological well-being, and ADHD symptoms were assessed from baseline to 8-month follow-up. A significantly greater decrease in anxiety symptoms was found in the GMT compared to the TAU group ($p = 0.014$, measured with HSCL-25, anxiety; $p = 0.048$ with HSCL-25, total). Conversely, no statistically significant difference was found between the two groups in improvement in daily executive functioning (BRIEF-A) or reduction in ADHD symptom intensity (ASRS-v1.1).

3.3.4.4. Internet-based cognitive behavioural therapy. In 2104 adults (18–65 years) with ADHD (69 % females), internet-based cognitive behavioural therapy (iCBT) was compared to internet-based applied relaxation training (iART) and treatment as usual (TAU) (NCT02041884) (Nasri et al., 2023). The change in scores on the Adult ADHD Self-Report Scale (ASRS), consisting of the two subscales of inattention and hyperactivity/impulsivity, was tested after 12 weeks of treatment (post-treatment) and 3 and 12 months after the end of treatment. ASRS scores improved significantly more with both iCBT ($p < 0.01$; Cohen's $d = 0.42$ at post-treatment and 0.67 at 3 months) and iART ($p < 0.01$; Cohen's $d = 0.57$ at post-treatment and 0.66 at 3 months) than with TAU. These improvements persisted over 12 months with both iCBT ($p < 0.001$) and iART ($p < 0.001$). However, no significant differences were found between the iCBT and iART groups.

3.3.4.5. Mindfulness-based cognitive therapy. Mindfulness-based cognitive therapy (MBCT), consisting of an 8-week group therapy with meditation exercises, psychoeducation, and group discussion, in addition to treatment as usual (TAU, i.e., pharmacotherapy and/or psychoeducation), was compared with TAU only in terms of core symptom reduction in one RCT (NCT02463396) involving 120 participants (Janssen et al., 2019). In the experimental arm (MBCT + TAU), a significant decrease in ADHD symptoms was observed after treatment ($p = 0.004$), and this significant difference remained stable during the 6-month follow-up period. In addition, more patients in the MBCT + TAU group showed a symptom reduction of $\geqslant$30 % ($p = 0.001$) or symptomatic remission ($p = 0.039$) compared to the TAU group. Although patients in the MBCT + TAU group reported no improvement in executive functions immediately after treatment compared to the TAU group, the difference between the groups became significant over the 6-month follow-up period (effect size: $d = 0.49$).

3.3.4.6. Self-guided psychological internet-delivered intervention. The efficacy of a self-guided psychological internet-delivered intervention on ADHD symptom severity and quality of life in adults with ADHD was compared with a control intervention consisting of an online psychoeducation module (NCT04726813) (Kenter et al., 2023)). A sample with

self-reported ADHD diagnoses (N = 120, 80 % females) was randomly assigned to one of these two groups. When comparing the two groups, a moderate to large improvement in ADHD symptoms (d = 0.70) and quality of life (d = 0.53) was found for the Self-guided psychological internet-delivered intervention, these effects also persisted at the 3-month follow-up (d = 0.76 and d = 0.52).

3.3.5. Non-pharmacological treatments in RCT with results of statistical analysis not reported

Non-pharmacological treatments in RCTs (other than those described above) with results of statistical analysis not reported for ADHD core symptoms or other outcomes included: *psychological therapies*: CBT (3 RCTs) (2 RCTs), iCBT (2 RCTs), working memory training, cognitive training, programme aimed at strengthening resilience, contingency management, structural skills training (2 RCTs), psychoeducation (in 2 RCTs), psychoeducation+Brief Motivational Interviewing and Behavioral Activation, dCBTi, occupational Therapy, training via videogame, Mindfulness (3 RCTs), Acceptance and Commitment-Therapy, neurofeedback (3 RCts), digital self-help, Goal Attainment Scaling, online self-compassion intervention, FOCUS ADHD App, cognitive behavioral therapy and Motor Learning Techniques; *lifestyle*: tai chi and exercise, structured aerobic exercise, Bright light therapy, physical exercise (2 RCTs), fidget ball, transdiagnostic sleep and circadian treatment; *dietary interventions*: highly unsaturated omega-3 fatty acids (RCT terminated), fish oil, Rhodiola rosea (2 RCTs), oligopin; *neurostimulation:* rTMS, tDCS (6 RCTs), home-based transcranial direct current stimulation, Magnetic EEG/ ECG-Guided Resonance Therapy (MeRT), active transcranial photobiomodulation (t-PBM) (2 RCTs), and functional near-infrared spectroscopy (fNIRS)-based neurofeedback (NF).

4. Discussion

To our knowledge, this is the first systematic review of ongoing or completed (in the last decade) RCTs of pharmacological or non-pharmacological treatments for ADHD in adults, providing an overview on recent developments in the field and treatments in the pipeline. When considering the overall body of RCTs of interventions for adult ADHD that have been registered over the past decade, it is striking that only around 30 % tested a pharmacological treatment, while the majority (nearly 70 %) explored the efficacy/safety of non-pharmacological options. This situation likely reflects two main aspects. First, the notion that currently available medications for the management of ADHD are quite effective for ADHD symptoms but have a symptomatic, rather than curative, action. Second, concerns around possible side effects of medications, in particular stimulants, including cardiovascular safety and abuse potential. However, it is interesting to note that amphetamines in adults have been found to have better acceptability than placebo in network meta-analytic evidence (Cortese et al., 2018). Furthermore, in relation to the potentially most concerning side effect of stimulant, i.e., cardiovascular safety, recent evidence from the large observational study with the longest follow-up indicated that longer cumulative use of methylphenidate for up to 14 years was correlated with a statistically significant but overall small increased risk of hypertension and arterial disease, but not of other serious cardiovascular conditions, such as heart failure (Zhang et al., 2024).

From the body of 90 RCT eligible for the present review (after discarding 25 RCTs of pharmacological compounds approved by the FDA and hence used in clinical practice) identified in clinical trial registries, about 27 % (n = 24) reported results with statistical analysis. From these RCTs, positive results in single trials for ADHD core symptoms were identified, in relation to pharmacological treatments, for centanafadine, mazindol, OPC-64005, solriamfetol, and, regarding non-pharmacological options, for rTMS, tDCS, physical activity, DBT, iCBT, mindfulness and self-guided support. However, when considering positive results replicated in at least one additional independent RCT, only centanafadine had this level of evidence, and the effect sizes were small (0.24, 0.28, 0.37, and 0.40) across the 4 active arms with positive results.

Focusing on pharmacological treatments, more specifically, the effect size found for non- stimulant compounds were generally small, with two isolated trials having large effect sizes of 1.1 (mazindol, solriamfetol isazol), but without replication (mazindol) or even with a trial without results reported (solriamfetol isazol), likely indicating non-significant or small effect. While it would be desirable to have compounds with effect size as high as those of stimulants (one of the highest effect sizes across psychiatry and more generally medicine, at least in the short term), being 0.79 for amphetamines and for 0.49 methylphenidate in adults (Cortese et al., 2018), and better tolerability profile, this has not been achieved yet. This state of affairs is not dissimilar from the situation in relation to medications in the pipeline for children. In the previous review focused on recent (last 10 years) registered phase II, III, or IV RCTs in children (Cortese et al., 2023b), only dasotraline had positive evidence, replicated in at least one additional RCT, of superiority versus placebo, with a small-moderate effect size (~0.4). In contrast, dasotraline was not superior in the trial in adults with ADHD when correcting for multiple comparisons, as summarized above.

An interesting development in the field, that may eventually lead to even more effective, well tolerated and possibly curative pharmacological treatments is represented by research on the so-called *druggable genome*, which refers to as a selection of genes that are potential targets for pharmacological interventions. Interestingly, through the analysis of data derived from genome-wide analyses (GWA) of ADHD, it has been discovered that none of the genes responsible for the primary targets of first-line pharmacotherapeutics for ADHD exhibited significant association with the disorder (Hegvik et al., 2021). This finding implies that FDA-approved ADHD medications might operate through mechanisms distinct from those underlying ADHD. Remarkably, three specific loci on chromosomes 1, 4, and 12 exhibited significant association with ADHD and harbored nine genes susceptible to pharmacological intervention, five of which encode well-established drug targets for conditions such as malignancies, autoimmune disorders, and neurodevelopmental disorders (Hegvik et al., 2021).

While we excluded from this review RCTs on compounds that are FDA approved, we highlight that an important area of research is represented by the additional development of formulations of already approved compounds that can have a longer duration of action and/or that can lead to a better adherence (such as liquid or chewable formulations), as well as formulations that are active in the early hours of the day, or patches. Indeed, adherence is a crucial issue in the pharmacological treatment of ADHD. During the 12-month follow-up periods examined in multiple studies within a systematic review of 91 original studies (Gajria et al., 2014), the mean duration of stimulant treatment was found to be 136 days for children and 230 days for adults. Notably, the highest rates of medication discontinuation were observed among individuals aged 15–21 years (Zetterqvist et al., 2013). Reasons cited for discontinuation encompassed side effects, perceived inefficacy, aversion to medication intake, determination of unnecessary treatment, social stigma, and challenges associated with transitioning from paediatric to adult healthcare services. Another issue to consider in future RCTs is around the length of the RCT. As the average length of currently available or planned RCTs is usually limited to a few weeks, the evidence they generate is not suitable to inform clinical decision making in the longer-term. While longer-term RCTs may be challenging due to logistic and ethical reasons (in terms of randomising participants to placebo over a sustained period of time when active medication is superior to placebo), discontinuation RCTs, where individuals treated with active medication for months or years are randomised for a short period to continuation of active treatment or switch to placebo should be encouraged. Another important aspect to bear in mind when planning future RCTs is sex/gender balance in terms of recruitment. We note that, compared to RCTs in children, those in adults have in general a more balanced recruitment in terms sex/gender, probably reflecting the more

balanced sex/gender ratio in the diagnosis of ADHD in adults compared to children. In fact, while, due to a referral bias, boys, who tend to be more hyperactive than girls, are referred more frequently to clinical services for ADHD, in adulthood women who struggle mainly with inattentive presentation of ADHD are more prone to consult an ADHD specialist due to the impact of inattention and additional comorbidities that are highly frequent in adulthood (Cortese et al., 2016).

Finally, future RTs will need to address placebo effects, that have been shown to be present also in RCTs of medications for ADHD (Faraone et al., 2022). Evidence primarily derived from RCTs in schizophrenia indicates that certain factors enhance the likelihood of distinguishing between drug and placebo effects. These factors have led to the following recommendations: refrain from incorporating an open-label lead-in phase prior to randomization in general; minimize the number of study sites, active treatment arms, and participants; randomly allocate more participants to the placebo group, thereby reducing the expectancy bias associated with receiving an active intervention; consider employing an extended wash-out period after discontinuation of previous medication, if feasible and ethically sound given the condition; utilize validated diagnostic and symptom rating tools; conduct trials lasting longer than four weeks in acute settings; and include individuals severely affected by the condition as well as those experiencing a first episode or with shorter illness durations (Cortese et al., 2024; Correll et al., 2023). Additionally, regarding placebo, we suggest that researchers will need to consider possible ethical implications of testing active medications vs placebo when efficacious treatments are already available in the market.

Regarding non-pharmacological treatments, even though no individual treatment had evidence of superiority versus control for ADHD core symptoms in more than one RCT, the field looks forward to the results of an increasing body of ongoing RCTs on a variety of non-pharmacological interventions, spanning from psychological to dietary treatments and neurostimulation. Two possible developments in the field are of potential interest. First, the development of digital delivery, arguably fostered by the COVID-19 pandemic, of approaches traditionally delivered face-to-face, such as iCBT, which, however, needs additional evidence. Second, the development of more sophisticated or alternative versions of existing treatments, such as, just to cite two examples: 1) novel and unusual types of psychotherapy, such as brief motivational interviewing and behavioral activation, or acceptance and commitment-therapy; 2) functional near-infrared spectroscopy (fNIRS)-based neurofeedback (NF). However, after decades of research on neurofeedback, there is no solid evidence that it can significantly change ADHD core symptoms when considering blinded outcomes (Coghill et al., 2023) (Sonuga-Barke et al., 2013), reflecting the findings in relation to other non-pharmacological approaches, such as cognitive training (Westwood et al., 2023) and behavioral interventions (Daley et al., 2014) in children. It is possible that novel neurofeedback approaches and protocol are more efficacious, but this possibility needs rigorous RCT and meta-analytic evidence.

Notably, for some non-pharmacological treatments it is challenging or virtually impossible to blind the trial. A series of meta-analyses by the European ADHD Guidelines Group (EAGG) (Sonuga-Barke et al., 2013; Westwood et al., 2023; Daley et al., 2014; Cortese et al., 2015; Cortese et al., 2016) focused on children with ADHD has established that, while, when considering probably blinded outcomes many non-pharmacological treatments are not more efficacious than control in terms of ADHD core symptoms, they may be efficacious for some outcomes, such as executive dysfunction for cognitive training (Westwood et al., 2023), or parenting for parent training behavior (Daley et al., 2014). Future RCTs of non-pharmacological treatments of adults with ADHD should take this possible discrepancy into account, by carefully assessing effects on core and non-core symptoms. While some unusual outcomes of interest have been recently examined (such as the number of long glances away from the roadway (Epstein et al., 2022)) with a computerized skills-training program, which significantly reduced the relevant endpoint of accidents, other increasingly relevant outcomes, such as quality of life, remain still underrepresented in ADHD RCTs (both of pharmacological and non-pharmacological treatments).

In addition to shorter-term RCTs, mainly aimed at obtaining regulatory approval, like those included in the present review, the field will need also pragmatic, longer-term RCTs, withdrawal RCTs and, crucially, comparative studies including pharmacological and non-pharmacological options, as well as RCTs examining the most effective sequencing or combination(s) of pharmacological and non-pharmacological treatments.

This study should be considered in light of some limitations. First, we systematically searched https://clinicaltrials.gov/and and https://www.clinicaltrialsregister.eu/ but not other national registries, which would have been unpractical. Second, we limited the search to 01/01/2010–10/18/2023, to cover a recent time span, but other search dates would have been also an option. Third, it was beyond the scope of the present work to systematically contact study authors or pharmaceutical companies to inquiry about the status of the trials and their results. Lastly, we did not systematically check any discrepancy between data reported in the publication and what was planned, which is the focus on another ongoing work from our group.

Despite these limitations, this review provided the currently most rigorous overview of RCTs of pharmacological and non-pharmacological treatments for adults with ADHD. Since to date no treatments more efficacious and safer the stimulants have been identified and given the frequency and relevance of ADHD in adults, it is important to continue developing and testing additional treatments for adults with ADHD seeking other effective and well tolerated treatments, and possibly curative intervention strategies.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105774.

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