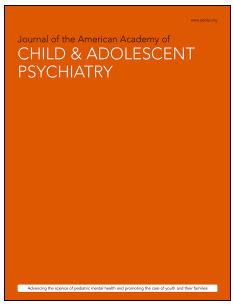
Journal Pre-proof



Systematic Review and Meta-Analysis: Effects of Pharmacological Treatment for Attention-Deficit/Hyperactivity Disorder on Quality of Life

Alessio Bellato, PhD, Nadia J. Perrott, MSc, Lucia Marzulli, PhD, Valeria Parlatini, MD, PhD, David Coghill, MD, Samuele Cortese, MD, PhD

PII: S0890-8567(24)00304-6

DOI: https://doi.org/10.1016/j.jaac.2024.05.023

Reference: JAAC 4635

To appear in: *Journal of the American Academy of Child & Adolescent Psychiatry*

Received Date: 5 February 2024

Revised Date: 15 May 2024

Accepted Date: 15 May 2024

Please cite this article as: Bellato A, Perrott NJ, Marzulli L, Parlatini V, Coghill D, Cortese S, Systematic Review and Meta-Analysis: Effects of Pharmacological Treatment for Attention-Deficit/Hyperactivity Disorder on Quality of Life, *Journal of the American Academy of Child & Adolescent Psychiatry* (2024), doi: https://doi.org/10.1016/j.jaac.2024.05.023.

Systematic Review and Meta-Analysis: Effects of Pharmacological Treatment for Attention-Deficit/Hyperactivity Disorder on Quality of Life

RH = ADHD Medication and Quality of Life

Alessio Bellato, PhD, Nadia J. Perrott, MSc, Lucia Marzulli, PhD, Valeria Parlatini, MD, PhD, David Coghill, MD, Samuele Cortese, MD, PhD

Dr. Bellato and Ms. Perrott contributed equally to this work.

Supplemental Material

Accepted May 23, 2024

Dr. Bellato is with the University of Southampton, Southampton, United Kingdom, and the University of Nottingham Malaysia, Semenyih, Malaysia. Ms. Perrott is with the University of Southampton, Southampton, United Kingdom. Dr. Marzulli is with Università degli Studi di Bari "Aldo Moro", Bari, Italy. Dr. Parlatini is with University of Southampton, Southampton, United Kingdom, King's College London, London, United Kingdom, and Solent NHS Trust, Southampton, United Kingdom. Prof. Coghill is with the University of Melbourne, Melbourne, Australia, and Murdoch Children's Research Institute, Melbourne, Australia. Prof. Cortese is with the University of Southampton, Southampton, United Kingdom, Università degli Studi di Bari "Aldo Moro", Bari, Italy, Solent NHS Trust, Southampton, United Kingdom, and New York University Child Study Center, New York.

The authors have reported no funding for this work.

This work has been prospectively registered: https://osf.io/qvgps/.

Disclosure: Dr. Bellato has declared an honorarium as Joint Editor of *JCPP Advances*. Prof. Coghill has received honoraria or conference support from Novartis, Medice, Takeda, and Servier and royalties from Cambridge University Press and Oxford University Press. Prof. Cortese has declared honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), Medice, and Healthcare Convention for educational activity on ADHD. He has served on the advisory board of the Association for Child and Adolescent Mental Health and the British Association for Psychopharmacology. Drs. Marzulli and Parlatini and Ms. Perrott have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Alessio Bellato, PhD, Building 44, School of Psychology, Highfield Campus, University of Southampton, Southampton, SO17 1BJ, United Kingdom; e-mail: a.bellato@soton.ac.uk

ABSTRACT

Objective: We conducted a systematic review and meta-analysis to quantify the effect of ADHD medication on QoL, and to understand if this effect differs between stimulants and non-stimulants.

Method: From the dataset of a published network meta-analysis (Cortese et al., 2018[1]), updated on 27th February 2023 (https://med-adhd.org/), we identified randomized controlled trials (RCTs) of ADHD medications for individuals aged 6 or more with a diagnosis of ADHD based on *DSM* (from III to 5 editions) or *ICD* (9 or 10), reporting data on QoL (measured with a validated scale). The risk of bias for each RCTs was assessed using the Cochrane Risk of Bias tool 2. Multi-level meta-analytic models were conducted with R 4.3.1.

Results: We included 17 RCTs (5,388 participants in total; 56% randomized to active medication) in the meta-analyses. We found that amphetamines (Hedge's g = 0.51, 95% CI = 0.08, 0.94), methylphenidate (0.38; 0.23, 0.54), and atomoxetine (0.30; 0.19, 0.40) were significantly more efficacious than placebo in improving QoL in people with ADHD, with moderate effect size. For atomoxetine, these effects were not moderated by the length of intervention, nor differed between children/adolescents and adults.

Discussion: In addition to being efficacious in reducing ADHD core symptoms' severity, both stimulant and non-stimulant medications are efficacious in improving QoL in people with ADHD, albeit with lower effect sizes. Future research should explore whether and to what degree combining pharmacological and non-pharmacological interventions is likely to further improve QoL in people with ADHD.

Study preregistration information: Effects of pharmacological treatment for ADHD on quality of life: a systematic review and meta-analysis; https://osf.io/; qvgps.

Keywords: ADHD; stimulants; non-stimulants; quality of life; RCT

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate and impairing inattention and/or hyperactivity-impulsivity, which interfere with overall functioning in everyday life[2]. Indeed, ADHD core symptoms, alongside associated mental and physical problems[3, 4] – especially if not promptly managed – can affect the quality of social interactions and relationships, and overall quality of life, in people with ADHD.

Quality of life (QoL) is a broad concept that is usually defined as a person's satisfaction with their life, and it is measured across several dimensions including psychological, social, health, biological, and economic wellbeing[5]. Specifically, instruments aimed at assessing QoL are usually self-reported (mostly used with adults), while QoL in children and adolescents is sometimes assessed indirectly based on parent- or caregiver-reports. Adults with ADHD have been found to report lower QoL compared to their neurotypical peers[6, 7]. Importantly, a linear association between ADHD symptoms and QoL has been reported, with those displaying more symptoms also showing lower QoL in areas of life such as work productivity, social and family life, and self-esteem[8]. Similar results have been found in children and young people with ADHD, especially in relation to social impairment, strained familial relationships, and difficulties with emotion regulation and communication[9-13].

Medications for ADHD include stimulants (methylphenidate and amphetamines) and non-stimulants (e.g., atomoxetine, clonidine, guanfacine, viloxazine)[14]. As QoL is related to ADHD symptoms' severity, effective management of ADHD via pharmacological or non-pharmacological interventions could have important positive effects not only on core symptoms but also on QoL in people with ADHD. Coghill and colleagues[7] conducted a systematic review to assess such effects. Most of the eligible studies (i.e., those reporting QoL measures before and after pharmacological intervention for ADHD) found significant effects of medication on QoL, in both children/adolescents and adults with the condition. Moreover, a

secondary data analysis of two randomized controlled trials (RCTs) of lisdexamfetamine and guanfacine extended release[15] found associations between medication-related changes in ADHD symptomatology, QoL, and functional outcomes. Although all these outcomes improved with both medications, the correlation between changes in ADHD symptomatology and changes in either QoL or functional outcomes was smaller than the correlation between changes in functional outcomes and QoL. These findings highlight the importance of understanding what specific functional outcomes and/or QoL domains – besides main symptoms – are affected by medication use in people with ADHD.

However, a formal meta-analysis was beyond the scope of the study by Coghill et al. [7]. A systematic review and meta-analysis by Tsujii et al. [16] explored QoL in relation to symptom remission in people who had been treated previously with ADHD medication and continued or discontinued the pharmacological treatments (withdrawal studies). The authors found that children and adolescents (but not adults) who discontinued medication reported having significantly lower QoL than those who continued the treatment. However, the interpretation of withdrawal studies is hampered by selection bias, as a sizeable portion of individuals who have been treated with medication may not be willing to be recruited in withdrawal trials.

Therefore, currently no meta-analytic evidence on the effects of ADHD medications on QoL, based on standard (parallel or cross-over) RCTs, is available. Moreover, it is not clear if stimulant (e.g., methylphenidate, amphetamines) and non-stimulant (e.g., atomoxetine, guanfacine) medications for ADHD have similar or different effects on QoL. We aimed to fill these gaps by conducting a systematic review and meta-analysis of parallel or cross-over RCTs to estimate the effects of ADHD medication on QoL, and secondary analyses to investigate if these effects differed in children/young people versus adults, as well as by class of medications, and if they were moderated by the length of treatment.

METHOD

Data sources, searches, and study selection

We followed the most recent PRISMA guidelines[17] (Table S1, available online, reports the PRISMA Checklist). The protocol was pre-registered in OSF (https://osf.io/qvgps/). We drew on the dataset of a 2018 network meta-analysis of RCTs of ADHD medications (reported in https://med-adhd.org/)[1], which we updated on 27th February 2023, to identify RCTs including people of any age with a diagnosis of ADHD based on DSM (from III to 5 editions) or ICD (9 or 10), and reporting data on QoL (measured with a validated scale). For cross-over RCTs, we only included data at pre-cross-over or – if pre-cross-over data were not available – at endpoint after wash-out (when conducted), to avoid carry-over effect.

The original search in Cortese et al. [1] was conducted in PubMed, BIOSIS Previews, CINAHL, the Cochrane Central Register of Controlled Trials, EMBASE, ERIC, MEDLINE, PsycINFO, OpenGrey, Web of Science Core Collection, ProQuest Dissertations and Theses (UK and Ireland), ProQuest Dissertations and Theses (abstracts and international), and the WHO International Trials Registry Platform, including ClinicalTrials.gov. The US Food and Drug Administration (FDA), European Medicines Agency (EMA), and relevant medication manufacturers' websites, and references of previous systematic reviews and guidelines, were hand-searched for additional information. Study authors and medication manufacturers were also contacted to gather unpublished information and data. Each full text of the original dataset of papers included in the network meta-analysis by Cortese et al. [1] was independently screened by NP and LM, until consensus was reached about their eligibility for the present study. The updated search was conducted with the same search strategy and syntax.

Outcome, data extraction and study quality assessment

The main outcome of the present meta-analysis (which was therefore newly extracted for the present study) was QoL, defined as such by the primary study author, and measured with a validated scale. While for some studies (e.g., those using the Adult ADHD Quality of Life Scale) we analyzed a total QoL score, for others (e.g., those using the Child Health and Illness Profile, CHIP), we used domain/subscale scores relative to QoL. NP and LM identified, for each study, which scale was used to assess QoL, and extracted relevant data (i.e., means and standard deviation of total or domain/subscale QoL scores, before and after the intervention; full statistical results and effect sizes for the comparison between pre- and post-treatment QoL scores in the treatment and placebo arms, if means and standard deviations were not reported in the original paper).

All other relevant study data (i.e., sample characteristics, information about treatment) had already been extracted by Cortese et al. [1] for studies up to 2017, while they were extracted *de novo* for the eligible RCTs retrieved in the updated search. The risk of bias of eligible RCTs for the present meta-analysis was assessed using the Cochrane Risk of Bias tool 2 (ROB-2) [18] which measures bias: 1) arising from the randomization process (selection bias); 2) due to deviations from the intended intervention; 3) due to missing outcome data; 4) in the measurement of outcomes; 5) in the selection of the reported results; and 6) overall risk of bias. A summary of ROB-2 assessment for each study is included in Figure S1, available online. Data not available from the published report(s) of the study were systematically requested from corresponding, first, or senior authors via e-mail.

Data synthesis and analysis

We used the R package *esc*[19] to calculate Hedge's g for each eligible RCT as the standardized mean difference of pre-post intervention changes in QoL between medication and placebo

arms. Random-effects models were used to estimate the pooled effect size via *metafor*[20] in *R 4.3.1*[21], whenever at least two studies reported at least one of the outcomes, for the same type of medication. Effect sizes were nested within studies in multilevel models for those studies that reported multiple effect sizes (e.g., different QoL domains), using the Restricted Maximum-Likelihood estimator. Cross-study heterogeneity was tested with Cochran Q and I^2. Funnel plots and the rank correlation test for funnel plot asymmetry (whenever at least ten studies were included in a meta-analysis) were used to assess publication bias. Meta-regressions were planned – whenever at least ten studies were included in a meta-analysis – to investigate potential moderating effects of the length of the intervention (measured in number of weeks). Subgroup analyses were also conducted to explore whether developmental stage (children and adolescents versus adults) impacted QoL response to medication (whenever at least ten studies were included in a meta-analysis). A narrative synthesis of the findings is presented to describe those studies for which an effect size could not be calculated. A detailed description of reasons for which a study could not be included in the meta-analysis is reported in Table 2.

RESULTS

Seventeen studies could be included in the meta-analysis (5,388 participants in total; 56% of whom randomized to active medication; see Table 1), while ten were summarized in the narrative review only (2,306 participants in total, 31% of whom randomized to active medication; see Table 2). Thirteen studies included data on adults with ADHD, and 14 on children and/or adolescents. Overall, for 22% of trials (18% of studies included in the meta-analysis, 30% of those in the narrative review) risk of bias was rated low, while it was high for 33% of trials (35% of studies included in the meta-analysis, 30% of those in the narrative

review), and there were some concerns for 44% of trials (47% of studies included in the meta-analysis, 40% of those in the narrative review (see Figure S1, available online). Further information about the included studies is available in Table 1 and 2.

[Table 1 approximately here]

[Table 2 approximately here]

A variety of scales were used to measure QoL, and this was mainly dependent on the age of participants being assessed. Specifically, for adults, the following scales were used: Adult ADHD Quality-of-Life Scale (AAQoL) [49]; Adult ADHD Impact Module (AIM-A) [50]; and Quality-of-Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) [51]. For children and adolescents, the following were used: Child Health Questionnaire (CHQ) [52]; the Child Health and Illness Profile – Child Edition (CHIP-CE) [53, 54]; ADHD Impact Module – Child (AIM-C) [55]; the Youth Quality of Life – Research Version (YQOL-R) [56]; and KINDL-R Questionnaire[57]. A higher score in all measures indicates better QoL. Overall, we conducted three meta-analyses, one for each type of medication: amphetamines (lisdexamfetamine and triple-bead mixed amphetamine salts; four studies), atomoxetine (11 studies) and methylphenidate (four studies).

Amphetamines

Four studies on amphetamines (950 participants with ADHD in total; 45% adults) reported relevant data for effect sizes to be computed. The meta-analysis on 14 effect sizes showed that amphetamines led to better QoL than placebo in individuals with ADHD (Hedge's $g = 0.51$, standard error (SE) = 0.20, 95% confidence interval (C.I.) = [0.08, 0.94], $t = 2.57$, $p = 0.0233$; Figure 1). Heterogeneity was significant ($Q = 47.87$; $p < 0.0001$) and the funnel plot did not indicate publication bias (see Figure S2, available online). We could not conduct a meta-

regression to explore whether the length of treatment with amphetamines affected the results of the meta-analysis, or a subgroup analysis to test any differences on the effects of amphetamines on QoL between children/adolescents and adults with ADHD, since less than ten studies were included in the meta-analysis on amphetamines.

One study[41], included in the narrative synthesis, testing the effectiveness of a 3-week treatment with mixed amphetamine salts in children with ADHD, found that this medication improved school functioning (as measured by the PedsQL) but no other QoL domains.

[Figure 1 approximately here]

Methylphenidate

Four studies on methylphenidate (1,094 participants with ADHD; 57% adults) reported relevant data for effect sizes to be computed. The meta-analysis on nine effect sizes found that methylphenidate improved QoL significantly more than placebo in individuals with ADHD (Hedge's g = 0.38, SE = 0.07, 95% C.I. = [0.23, 0.54], t = 5.78, p = 0.0004; Figure 2). Heterogeneity was significant (Q = 23.07; p = 0.0033) and the funnel plot did not indicate publication bias (see Figure S3, available online). We could not conduct a meta-regression to explore whether the length of treatment with methylphenidate affected the results of the meta-analysis, or a subgroup analysis to test any differences on the effects of methylphenidate on QoL between children/adolescents and adults with ADHD, since less than ten studies were included in this meta-analysis.

Among those studies that were only summarized narratively, a 6-week study on adults, conducted by Mick et al. [46], using immediate release methylphenidate and osmotic release methylphenidate (OROS MPH), found that, regardless of whether participants were in intervention or placebo groups, there was an improvement in Q-LES-Q-SF score. Casas et al.

[47] conducted a 13-week study on adults using a variety of doses of methylphenidate and found a statistically significant improvement of QoL from baseline for all medication doses. In the performance and daily functioning scale of the AIM-A, the least-squared means for the group receiving OROS MPH (54 mg) improved by 16.4 (p = 0.0072), and for the group receiving OROS MPH (72 mg) by 19.8 (p = 0.0009). On the daily interference scale, in the 54 mg group QoL score improved by 17.5 (p = 0.0370), and the 72 mg group improved by 17.6 (p = 0.0261). For the relationship and communication subscale score, in the 72 mg group, scores significantly improved by 13.5 (p = 0.0052), while for the living with ADHD subscale, in the 72 mg group scores improved by 5.9 (p = 0.0162). In the general well-being subscale, only the 54 mg OROS MPH presented a significant improvement of QoL scores (by 9.5; p = 0.0356).

Studies that did not find significant effects included the RCT by Rösler et al.[48], assessing the extent to which 5-week methylphenidate treatment improved QoL in adults (Q-LES-Q was used). Similarly, Wigal et al.[42] conducted a brief (1-week) RCT in children and adolescents with ADHD and explored whether methylphenidate improved QoL. They did not find any statistically significant improvement in QoL during the double-blind period, but they reported some improvements in later stages of the study. Lastly, a 5-week RCT, conducted by Spencer et al.[43] on adults, explored the extent to which dexmethylphenidate improved Q-LES-Q scores. Based on their findings, there did not appear to be a significant effect of this medication on QoL.

[Figure 2 approximately here]

Atomoxetine

Eleven studies on atomoxetine (3,344 participants with ADHD; 63% adults) reported relevant data for effect sizes to be computed. The meta-analysis on 15 effect sizes showed that

atomoxetine resulted in significantly better QoL than placebo in individuals with ADHD (Hedge's g = 0.30, SE = 0.05, 95% C.I. = [0.19, 0.40], t = 5.81, $p < 0.0001$; Figure 3). Heterogeneity was significant (Q = 27.20; p = 0.0181) and publication bias was not detected (Kendall's tau = 0.31, p = 0.1128) (see Figure S4, available online).

A meta-regression was conducted to explore whether the length of intervention with atomoxetine affected the meta-analytic findings. There was no significant moderating effect of length of intervention ($F_{1,13}$ = 1.12, p = 0.3097), suggesting that atomoxetine was similarly effective in improving QoL at either 6, 7, 8, 9, 10, 12, 14 or 24 weeks of treatment (based on the included studies). Moreover, we did not find any significant differences in terms of the effects of atomoxetine on QoL between children/adolescents and adults with ADHD ($F_{1,13}$ = 1.63, p = 0.2236).

Among the studies included in the narrative synthesis only, Dell'Agnello et al.[39] conducted an 8-week RCT on children and found that children randomized to the atomoxetine intervention showed improvements in QoL scores (measured via the CHIP-CE), particularly in the satisfaction of self, emotional comfort, individual risk avoidance, threats to achievement, and peer relations subscales. ATX was more efficacious, compared to placebo, in improving individual risk avoidance, risk avoidance and emotional comfort scores. Similar findings emerged from Escobar et al.[40], where parent- and patient-rated reported QoL (measured via CHIP) after a 12-week intervention with atomoxetine improved, although the effect appeared to be smaller when rated by patients, but still higher than the placebo group. There only appeared to be a significant improvement in the risk avoidance subscale (parent- and patient-rated) and achievement subscale (parent-rated). Findings from Wigal et al.[41] 3-week study on atomoxetine efficacy in 101 children with ADHD, showed a statistically significant improvement in QoL, measured using the PedsQL. However, this treatment effect was only statistically significant in the school functioning subscale.

[Figure 3 approximately here]

Other medications (individual studies)

Guanfacine. A 5-week study on adults with ADHD by Iwanami et al.[44] found a statistically significant mean change in total AAQoL score in the intervention group (medium effect size), suggesting that guanfacine was more efficacious at improving QoL in adults with ADHD, compared to placebo.

Modafinil. Arnold[45] explored the effect of modafinil (different doses: 255 mg/day, 340 mg/day, 425 mg/day, 520 mg/day) and placebo on QoL in adults with ADHD over a 9-week period, using the Q-LES-Q-SF to measure QoL. Their findings suggested that this medication, compared to placebo, was not more efficacious in improving QoL, at any dose, from baseline to end-point.

[Figure 4 approximately here]

DISCUSSION

We conducted the first systematic review and meta-analysis investigating the effects of medication for ADHD on quality of life (QoL) in parallel or cross-over RCTs. Overall, we found that methylphenidate, amphetamines, and atomoxetine were significantly more efficacious than placebo in improving QoL in people with ADHD. For atomoxetine, efficacy was significantly detected regardless of length of intervention or participant age. We found a medium effect for amphetamines and methylphenidate (both stimulant medications), and a small effect for atomoxetine (a non-stimulant). Nevertheless, we cannot conclude that any specific medication was significantly better than any other in improving QoL, as 95% C.I. of

the effect size for the three medications overlapped (Figure 4), likely reflecting the heterogeneity in treatment response and outcomes amongst individuals with ADHD. Although it was not possible to meta-analyze data on guanfacine extended release, we found preliminary evidence of positive outcomes of this medication (but not modafinil) on QoL.

Overall, our findings add to those of previous meta-analyses[1, 58] showing the beneficial effects of both stimulant and non-stimulant medications on core ADHD symptoms. Of note, stimulant medications have often been reported to lead to significantly more marked improvements in ADHD core symptoms, compared to non-stimulants, hence why clinical guidelines recommend stimulants as first-choice treatment, followed by non-stimulants[1]. However, in relation to QoL, we found that amphetamines, methylphenidate, and atomoxetine had similar effects. Furthermore, while the effects on ADHD-related symptoms are usually medium-to-high[1], in terms of QoL they were in the medium range. This is in line with previous literature showing that medication-related reductions in ADHD symptoms are often not accompanied by parallel improvements in other domains, e.g., neurocognitive measures, or vice versa[59]. Our study shows that targeting impairing core symptoms of ADHD via medication may not be sufficient to significantly reduce the impact of ADHD on QoL, highlighting the importance of planning multi-modal interventions that combine pharmacological and non-pharmacological interventions. However, due to scarcity of previous literature on the topic, more research is needed to elucidate these interactions and the combined effects of multi-modal interventions on ADHD symptoms, neurocognitive measures and QoL[59].

It could be that, in addition to a reduction in core symptoms, other effects of ADHD medication (such as enhancement of executive functions, including planning, organization, working memory, and impulse control) lead to more efficient task management and more positive academic/professional outcomes. Likewise, the medication-related stabilization of mood and reduced emotional dysregulation may promote emotional well-being, enhanced self-

esteem and self-confidence, and a more positive self-concept, ultimately contributing to greater QoL. However, for some people with ADHD, QoL may not improve significantly, even with medications, or initial improvements may wane on the longer-term[60]. For example, persisting ADHD symptoms or co-occurring psychological distress, emotional dysregulation, "treatment fatigue" (i.e., people who have tried several medications but without success or with intolerable side effects, may become discouraged to continue with any follow-up intervention) or negative side effects (e.g., insomnia, decreased appetite, weight loss, irritability) may all affect health and compromise socio-emotional functioning, with crucial impact on QoL[60, 61]. Moreover, in nine RCTs, researchers recruited participants with ADHD and co-occurring conditions, such as social anxiety, oppositional defiant disorder, and conduct disorder. However, in the other eight RCTs, participants were excluded if that had historical or current mental health conditions, as well as those who had history of substance misuse. Physical health conditions were also a criterion for exclusion, in 12 studies. Given the heterogeneity of inclusion/exclusion criteria across studies, it is however difficult to conclude the extent to which the presence (or absence) of psychiatric and/or medical comorbidities may have influenced the effects of medication on QoL. Therefore, further studies are needed to understand the underlying mechanisms behind the impact of pharmacological, non-pharmacological, and multimodal interventions for ADHD on QoL. Additional research is also needed to clarify if and how much individual factors (e.g., clinical profile, comorbidities, engagement with the intervention) mediate – either positively or negatively – intervention-related changes in ADHD symptomatology and QoL.

Some limitations of our study should be acknowledged. First, although our search was comprehensive across a broad range of dataset, we were only able to identify 17 RCTs reporting QoL outcomes, out of 161 included in the most comprehensive and updated database of existing RCTs examining FDA-approved medications for ADHD (https://med-adhd.org, based on Cortese et al., 2018[1]). This is probably due to the fact that, in the early 2000's (before QoL was

made mandatory to measure in RCTs for ADHD by the European Medicines Agency), QoL was not usually considered an outcome in RCTs, with symptom reduction and side effects receiving more attention and being reported more frequently. Of note, nowadays, QoL is still considered a secondary rather than a primary outcome. Second, we found differences in study methodology and samples, which may have slightly biased the main results of our meta-analyses, leading to significant heterogeneity in the meta-analyses. For example, even though self-report measures were predominantly used, the 17 RCTs included in our meta-analysis used eight different instruments to assess QoL. Third, the instruments used to measure QoL in children and adolescents were more likely to be generic measures of QoL and completed by parents rather than children/young people, whereas those used with adult samples were more likely to be disorder specific, hence much more closely associated to ADHD symptoms and more likely to detect QoL changes in parallel to symptom reductions. Considering that QoL is primarily conceptualized as a self-perception and that parent rated QoL is likely to primarily capture functional outcomes (hence, impairments) and less QoL[62, 63], there may be differences in the outcomes collected in groups of children/adolescents and adults with ADHD. Lastly, especially for the meta-analysis on atomoxetine, there were large differences between RCTs in terms of the length of the intervention (between 6 and 24 weeks). In line with a recent analysis of race/ethnicity in RCTs of medications for ADHD[64], an additional limitation was the suboptimal reporting of race/ethnicity and – when data on race/ethnicity were reported – there was lack of diversity within the samples. For all studies reporting ethnicity/race, aside from Goto et al., [34] the predominant ethnicity was white. Similarly, with gender, men made up the highest proportion of participants in most studies.

Considering these limitations, we recommend that future RCTs of pharmacological, non-pharmacological or multimodal interventions for ADHD, systematically include QoL as a measure of treatment outcome, together with core symptom reduction. For this, it will be

important to increase understanding of the QoL instruments that can be used in clinical practice and research and seek to harmonize their use. It should be noted that different QoL measures could be differently sensitive in detecting improvements in QoL due to a specific intervention or worsening associated to specific symptoms (e.g., ADHD). When deciding what instrument shall be used to measure QoL and changes in this domain, it is important to assess the psychometric properties of such instruments to fully understand their ability to detect changes in QoL overtime. The International Consortium for Health Outcomes Measurement (ICHOM; https://www.ichom.org/) published a consensus on the use of KIDSCREEN-10[65] as a measure of QoL in children and adolescents with anxiety, depression, post-traumatic stress disorder, or obsessive compulsive disorder[66], and neurodevelopmental disorders (including ADHD) (https://www.ichom.org/patient-centered-outcome-measure/neurodevelopmental-disorders)[67]; a similar process could be completed for adults with ADHD.

Besides reaching consensus about what instruments to use to assess QoL, it is also important to consider that there is no agreement, across different scales and instruments, about which QoL domains (e.g., education/work, physical or mental health, social relationships) should be measured or are considered relevant for people with ADHD[63]. Considering that QoL is a complex construct reflecting the subjective satisfaction in different life domains, further research should be conducted to advance our understanding of the processes and mechanisms underlying intervention-related improvements in QoL. For example, it could be that scores on the same QoL scale differ in people from different cultural or ethnic backgrounds, considering the possible role culture/ethnicity may play on self-report QoL, even though this could probably make it more difficult to benchmark across different cross-cultural contexts using the same scales. Similarly, parents of children with ADHD have been found to be more likely to rate their children's QoL worse than the children themselves (who, however, are sometimes over-optimistic when assessing their QoL and global functioning)[68]. Therefore, it would be important

to combine both parent- and self-report measures of QoL, when assessing QoL in children and adolescents. For both children/adolescents and adults with ADHD (but also those with other mental or neurodevelopmental conditions), it is also recommended to measure QoL across different settings, e.g., social, work, and academic; and consider potential confounding factors such as socio-economic status, ethnicity and/or culture[69]. In fact, in the studies included in our review (and more generally, in clinical trials investigating the effects of ADHD medication), the impact of psychosocial factors such as specific characteristics of the familial environment, was not studied. Another relevant point to address in future research is the timeframe by which medication exerts positive effects on QoL. The studies incorporated into our meta-analyses assessed QoL in the short-term, typically within a range of 1 to 6 months. However, we note that there is a notable absence of data examining whether these effects endure over the long-term. Future research should address these gaps, to better understand the effects of ADHD medication on QoL.

Notably, non-pharmacological interventions for ADHD were beyond the scope of our meta-analysis. However, besides Lee et al.[59], who investigated QoL changes associated with cognitive training and found two studies (both reporting non-significant results), we are not aware of any other study systematically investigating the effects of non-pharmacological interventions for ADHD on QoL. This is a gap that future research should address. We recommend including QoL as a primary outcome measure of intervention effectiveness, especially for non-pharmacological interventions that have not yet been tested rigorously via RCTs. Moreover, it should be investigated whether and how much combining pharmacological and non-pharmacological interventions is likely to further improve QoL in people with ADHD, compared to medication alone. For example, medication-related side effects, co-occurring health, or psychological conditions, and/or perceived stigmatization associated to medication use, may – at least in some people with ADHD – indirectly affect QoL, for which non-

pharmacological and psychological interventions may help.

In conclusion, our study demonstrated that, besides being efficacious in reducing ADHD symptomatology, stimulant and non-stimulant medications are effective in improving QoL in children, young people, and adults with ADHD, albeit with smaller effects compared those found for ADHD core symptoms severity. Future research should include QoL as a primary treatment/intervention outcome and explore whether and how much combining or alternating between pharmacological and non-pharmacological interventions is likely to further improve QoL in people with ADHD.

REFERENCES

1. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *The Lancet Psychiatry.* 2018;5(9):727-738. https://doi.org/10.1016/S2215-0366(18)30269-4.

2. American Psychiatric Association. Neurodevelopmental Disorders. *Diagnostic and Statistical Manual of Mental Disorders*: American Psychiatric Association Publishing; 2022.

3. Arrondo G, Solmi, M., Dragioti, E., Eudave, L., Ruiz-Goikoetxea, M., Ciaurriz-Larraz, A. M., Magallon, S., Carvalho, A. F., Cipriani, A., Fusar-Poli, P., Larsson, H., Correll, C. U., & Cortese, S. Associations between mental and physical conditions in children and adolescents: An umbrella review. *Neuroscience and biobehavioral reviews.* 2022;137. https://doi.org/10.1016/j.neubiorev.2022.104662.

4. Hartman CA, Larsson H, Vos M, et al. Anxiety, mood, and substance use disorders in adult men and women with and without attention-deficit/hyperactivity disorder: A substantive and methodological overview. *Neuroscience & Biobehavioral Reviews.* 2023;151:105209. https://doi.org/10.1016/j.neubiorev.2023.105209.

5. Felce D, Perry J. Quality of life: Its definition and measurement. *Research in developmental disabilities.* 1995;16(1):51-74. https://doi.org/10.1016/0891-4222(94)00028-8.

6. Quintero J, Morales I, Vera R, Zuluaga P, Fernández A. The impact of adult ADHD in the quality of life profile. *Journal of attention disorders.* 2019;23(9):1007-1016. https://doi.org/10.1177/1087054717733046.

7. Coghill DR, Banaschewski T, Soutullo C, Cottingham MG, Zuddas A. Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. *European child & adolescent psychiatry.* 2017;26:1283-1307. https://doi.org/10.1007/s00787-017-0986-y.

8. Pawaskar M, Fridman M, Grebla R, Madhoo M. Comparison of quality of life, productivity, functioning and self-esteem in adults diagnosed with ADHD and with symptomatic ADHD. *Journal of attention disorders.* 2020;24(1):136-144. https://doi.org/10.1177/1087054719841129.

9. Barkley RA, Poillion MJ. Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment. *Behavioral disorders.* 1994;19(2):150-152. https://doi.org/10.1177/019874299401900205.

10. Coghill D, Spiel G, Baldursson G, et al. Which factors impact on clinician-rated impairment in children with ADHD? *European child & adolescent psychiatry.* 2006;15:i30-i37. https://doi.org/10.1007/s00787-006-1005-x.

11. Escobar R, Soutullo CA, Hervas A, Gastaminza X, Polavieja P, Gilaberte I. Worse quality of life for children with newly diagnosed attention-deficit/hyperactivity disorder, compared with asthmatic and healthy children. *Pediatrics.* 2005;116(3):e364-e369. https://doi.org/10.1542/peds.2005-0386.

12. Klimkeit E, Graham C, Lee P, Morling M, Russo D, Tonge B. Children should be seen and heard: Self-report of feelings and behaviors in primary-school-age children with ADHD. *Journal of Attention Disorders.* 2006;10(2):181-191. https://doi.org/10.1177/1087054706289926.

13. Strine TW, Lesesne CA, Okoro CA, et al. Emotional and behavioral difficulties and impairments in everyday functioning among children with a history of attention-deficit/hyperactivity disorder. *Preventing chronic disease.* 2006;3(2):A52. https://pubmed.ncbi.nlm.nih.gov/16539793.

14. Cortese S. Pharmacologic Treatment of Attention Deficit–Hyperactivity Disorder. *New England Journal of Medicine.* 2020;383(11):1050-1056. https://doi.org/10.1056/nejmra1917069.

15. Coghill DR, Joseph A, Sikirica V, Kosinski M, Bliss C, Huss M. Correlations Between Clinical Trial Outcomes Based on Symptoms, Functional Impairments, and Quality of

Life in Children and Adolescents With ADHD. *Journal of Attention Disorders.* 2019;23(13):1578-1591. https://doi.org/10.1177/1087054717723984.

16. Tsujii N, Okada T, Usami M, et al. Effect of continuing and discontinuing medications on quality of life after symptomatic remission in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *The Journal of clinical psychiatry.* 2020;81(3):11514. https://doi.org/10.4088/JCP.19r13015.

17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International journal of surgery.* 2021;88:105906. https://doi.org/10.1016/j.ijsu.2021.105906.

18. Higgins J, Altman D, Gøtzsche P, et al. Cochrane bias methods group; cochrane statistical methods group. *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ.* 2011;343(7829):d5928. https://doi.org/10.1136/bmj.d5928.

19. *{esc: Effect Size Computation for Meta Analysis (Version 0.5.1)}* [computer program]2019.

20. Viechtbauer W. Conducting meta-analyses in {R} with the {metafor} package. *Journal of Statistical Software.* 2010;36:1-48. https://doi.org/10.18637/jss.v036.i03.

21. *A Language and Environment for Statistical Computing* [computer program]. Version R version 4.3.1 (2023-06-16): R Foundation for Statistical Computing; 2023.

22. Bangs ME, Hazell P, Danckaerts M, et al. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder and oppositional defiant disorder. . *Pediatrics.* 2008;121:e314–e320. https://doi.org/10.1542/peds.2006-1880.

23. Dittmann RWS, Alexander; Helsberg, Karin; Schneider-Fresenius, Christian; Lehmkuhl, Gerd; Wehmeier, Peter M. Atomoxetine Versus Placebo in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder: A Double-Blind, Randomized, Multicenter Trial in Germany. *Journal of Child and Adolescent Psychopharmacology.* 2011;21(2):97-110. https://doi.org/10.1089/cap.2009.0111.

24. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics.* 2001;108(5):e83-e83. https://doi.org/10.1542/peds.108.5.e83.

25. Svanborg P, Thernlund G, Gustafsson PA, Hägglöf B, Schacht A, Kadesjö B. Atomoxetine improves patient and family coping in attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in Swedish children and adolescents. *European child & adolescent psychiatry.* 2009;18:725-735. https://doi.org/10.1007/s00787-009-0031-x.

26. Brown RT, Perwien A, Faries DE, Kratochvil CJ, Vaughan BS. Atomoxetine in the management of children with ADHD: effects on quality of life and school functioning. *Clinical pediatrics.* 2006;45(9):819-827. https://doi.org/10.1177/0009922806294219.

27. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *American Journal of Psychiatry.* 2008;165(6):721-730. https://doi.org/10.1176/appi.ajp.2007.05091676.

28. Findling RL, Childress AC, Cutler AJ, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2011;50(4):395-405. https://doi.org/10.1016/j.jaac.2011.01.007.

29. Banaschewski T, Soutullo C, Lecendreux M, et al. Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder.

CNS drugs. 2013;27:829-840. https://doi.org/10.1007/s40263-013-0095-5.

30. Adler LA, Spencer TJ, Levine LR, et al. Functional outcomes in the treatment of adults with ADHD. *Journal of Attention Disorders.* 2008;11(6):720-727. https://doi.org/10.1177/1087054707308490.

31. Adler LA, Liebowitz M, Kronenberger W, et al. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. *Depression and Anxiety.* 2009;26(3):212-221. https://doi.org/10.1002/da.20549.

32. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month, double-blind trial. *Journal of Clinical Psychopharmacology.* 2009;29(1):44-50. https://doi.org/10.1097/JCP.0b013e318192e4a0.

33. Durell TM, Adler LA, Williams DW, et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial. *Journal of clinical psychopharmacology.* 2013;33(1):45-54. https://doi.org/10.1097/JCP.0b013e31827d8a23.

34. Goto T, Hirata Y, Takita Y, et al. Efficacy and safety of atomoxetine hydrochloride in Asian adults with ADHD: a multinational 10-week randomized double-blind placebo-controlled Asian study. *Journal of Attention Disorders.* 2017;21(2):100-109. https://doi.org/10.1177/1087054713510352.

35. Adler LA, Dirks B, Deas P, et al. Self-Reported quality of life in adults with attention-deficit/hyperactivity disorder and executive function impairment treated with lisdexamfetamine dimesylate: a randomized, double-blind, multicenter, placebo-controlled, parallel-group study. *BMC Psychiatry.* 2013;13(253). https://doi.org/10.1186/1471-244X-13-253.

36. Spencer T, Landgraf JM, Adler LA, Weisler R, Anderson CS, Youcha S. Attention-deficit/hyperactivity disorder-specific quality of life with triple-bead mixed amphetamine salts (SPD465) in adults: results of a randomized, double-blind, placebo-controlled study. *The Journal of clinical psychiatry.* 2008;69(11):1766–1775. https://doi.org/10.4088/jcp.v69n1112.

37. Goodman DW, Starr HL, Ma Y-W, Rostain AL, Ascher S, Armstrong RB. Randomized, 6-week, placebo-controlled study of treatment for adult attention-deficit/hyperactivity disorder: individualized dosing of osmotic-release oral system (OROS) methylphenidate with a goal of symptom remission. *The Journal of Clinical Psychiatry.* 2017;78(1):9021. https://doi.org/10.4088/JCP.15m10348.

38. Takahashi N, Koh T, Tominaga Y, Saito Y, Kashimoto Y, Matsumura T. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of osmotic-controlled release oral delivery system methylphenidate HCl in adults with attention-deficit/hyperactivity disorder in Japan. *The World Journal of Biological Psychiatry.* 2014;15(6):488-498. https://doi.org/10.3109/15622975.2013.868925.

39. Dell'Agnello G, Maschietto D, Bravaccio C, et al. Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: a placebo-controlled Italian study. *European Neuropsychopharmacology.* 2009;19(11):822-834. https://doi.org/10.1016/j.euroneuro.2009.07.008.

40. Escobar R, Montoya A, Polavieja P, et al. Evaluation of patients' and parents' quality of life in a randomized placebo-controlled atomoxetine study in attention-deficit/hyperactivity disorder. *Journal of child and adolescent psychopharmacology.* 2009;19(3):253-263. https://doi.org/10.1089/cap.2008.0109.

41. Wigal SB, McGough JJ, McCracken JT, et al. A Laboratory School Comparison of

Mixed Amphetamine Salts Extended Release (Adderall XR®) and Atomoxetine (Strattera®) in school-aged children with attention deficit/hyperactivity disorder. *Journal of Attention Disorders.* 2005;9(1):275-289. https://doi.org/10.1177/1087054705281121.

42. Wigal SB, A A, Childress AC, W C, R K. A study of methylphenidate extended-release capsules in a randomized, double-blind, placebo-controlled protocol in children and adolescents with ADHD. *NEI psychopharmacology congress*. United States; 2014. https://doi.org/10.1017/S1092852914000765

43. Spencer TJ, Adler LA, McGough JJ, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry.* 2007;61(12):1380-1387. https://doi.org/10.1016/j.biopsych.2006.07.032.

44. Iwanami A, Saito K, Fujiwara M, Okutsu D, Ichikawa H. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double-blind, placebo-controlled study. *The Journal of clinical psychiatry.* 2020;81(3):7891. https://doi.org/10.4088/JCP.19m12979.

45. Arnold VK, Feifel D, Earl CQ, Yang R, Adler LA. A 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy and safety of modafinil as treatment for adults with ADHD. *Journal of attention disorders.* 2014;18(2):133-144. https://doi.org/10.1177/1087054712441969.

46. Mick E, Faraone SV, Spencer T, Zhang HF, Biederman J. Assessing the validity of the quality of life enjoyment and satisfaction questionnaire—short form in adults with ADHD. *Journal of attention disorders.* 2008;11(4):504-509. https://doi.org/10.1177/1087054707308468.

47. Casas M, Rösler M, Sandra Kooij J, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: a 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. *The World Journal of Biological Psychiatry.* 2013;14(4):268-281. https://doi.org/10.3109/15622975.2011.600333.

48. Rösler M, Ginsberg Y, Arngrim T, et al. Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attention-deficit/hyperactivity disorder treated with OROS methylphenidate. *The World Journal of Biological Psychiatry.* 2013;14(4):282-290. https://doi.org/10.3109/15622975.2011.571283.

49. Brod M, Johnston J, Able S, Swindle R. Validation of the adult attention-deficit/hyperactivity disorder quality-of-life Scale (AAQoL): a disease-specific quality-of-life measure. *Quality of life research.* 2006;15:117-129. https://doi.org/10.1007/s11136-005-8325-z.

50. Landgraf JM. Monitoring quality of life in adults with ADHD: reliability and validity of a new measure. *Journal of attention disorders.* 2007;11(3):351-362. https://doi.org/10.1177/1087054707299400.

51. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacology bulletin.* 1993;29(2):321-326.

52. Landgraf JM, Abetz L, Ware JE. *Child Health Questionnaire (CHQ): A user's manual*: Landgraf & Ware; 1999.

53. Riley AW, Forrest CB, Rebok GW, et al. The child report form of the CHIP-child edition: reliability and validity. *Medical care.* 2004:221-231. https://www.jstor.org/stable/4640731.

54. Riley AW, Forrest CB, Starfield B, Rebok GW, Robertson JA, Green BF. The parent

report form of the CHIP-Child Edition: reliability and validity. *Medical care.* 2004:210-220. https://www.jstor.org/stable/4640730.

55. Landgraf JM, Rich M, Rappaport L. Measuring quality of life in children with attention-deficit/hyperactivity disorder and their families: development and evaluation of a new tool. *Archives of pediatrics & adolescent medicine.* 2002;156(4):384-391. https://doi.org/10.1001/archpedi.156.4.384.

56. Patrick D, Edwards T. Youth Quality of Life Instrument – Short Form (YQOL-SF) Version 2.0. In: Washington Uo, ed. *Seattle Quality of Life Group*; 2013.

57. Bullinger M, Brütt AL, Erhart M, Ravens-Sieberer U, Group BS. Psychometric properties of the KINDL-R questionnaire: results of the BELLA study. *European child & adolescent psychiatry.* 2008;17:125-132. https://doi.org/10.1007/s00787-008-1014-z.

58. Radonjić NV, Bellato A, Khoury NM, Cortese S, Faraone SV. Nonstimulant Medications for Attention-Deficit/Hyperactivity Disorder (ADHD) in Adults: Systematic Review and Meta-analysis. *CNS Drugs.* 2023/05/01 2023;37(5):381-397. https://doi.org/10.1007/s40263-023-01005-8.

59. Lee SH, Thomas; Johnson, Beth; Testa, Renee; Priya, Vishnu; Spencer-Smith, Megan; Coghill, David. Can Neurocognitive Outcomes Assist Measurement-Based Care for Children with Attention-Deficit/Hyperactivity Disorder? A Systematic Review and Meta-Analyses of the Relationships Among the Changes in Neurocognitive Functions and Clinical Outcomes of Attention-Deficit/Hyperactivity Disorder in Pharmacological and Cognitive Training Interventions. *Journal of Child and Adolescent Psychopharmacology.* 2022;32(5):250-277. https://doi.org/10.1089/cap.2022.0028.

60. Adamo N, Seth S, Coghill D. Pharmacological treatment of attention-deficit/hyperactivity disorder: assessing outcomes. *Expert Review of Clinical Pharmacology.* 2015/07/04 2015;8(4):383-397. https://doi.org/10.1586/17512433.2015.1050379.

61. Caye A, Swanson J, Thapar A, et al. Life Span Studies of ADHD—Conceptual Challenges and Predictors of Persistence and Outcome. *Current Psychiatry Reports.* 2016/10/25 2016;18(12):111. https://doi.org/10.1007/s11920-016-0750-x.

62. Jonsson U, Alaie I, Löfgren Wilteus A, et al. Annual Research Review: Quality of life and childhood mental and behavioural disorders – a critical review of the research. *Journal of Child Psychology and Psychiatry.* 2017;58(4):439-469. https://doi.org/10.1111/jcpp.12645.

63. Coghill D, Hodgkins P. Health-related quality of life of children with attention-deficit/hyperactivity disorder versus children with diabetes and healthy controls. *European Child & Adolescent Psychiatry.* 2016/03/01 2016;25(3):261-271. https://doi.org/10.1007/s00787-015-0728-y.

64. Riccioni A, Radua J, Ashaye FO, Solmi M, Cortese S. Systematic Review and Meta-analysis: Reporting and Representation of Race/Ethnicity in 310 Randomized Controlled Trials of Attention-Deficit/Hyperactivity Disorder Medications. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2023/10/25/ 2023. https://doi.org/10.1016/j.jaac.2023.09.544.

65. Ravens-Sieberer U, Herdman M, Devine J, et al. The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. *Quality of Life Research.* 2014/04/01 2014;23(3):791-803. https://doi.org/10.1007/s11136-013-0428-3.

66. Krause KR, Chung S, Adewuya AO, et al. International consensus on a standard set of outcome measures for child and youth anxiety, depression, obsessive-compulsive disorder, and post-traumatic stress disorder. *The Lancet Psychiatry.* 2021;8(1):76-86.

https://doi.org/10.1016/S2215-0366(20)30356-4.

67. Mulraney M, de Silva U, Joseph A, et al. International consensus on a set of standard outcome measures for neurodevelopmental disorders. *JAMA Network Open. (in press, accepted but not yet published)*. https://doi.org/10.1001/jamanetworkopen.2024.16760

68. Danckaerts M, Sonuga-Barke EJS, Banaschewski T, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *European Child & Adolescent Psychiatry.* 2010/02/01 2010;19(2):83-105. https://doi.org/10.1007/s00787-009-0046-3.

69. Coghill D, Danckaerts M, Sonuga-Barke E, Sergeant J, Group tAEG. Practitioner Review: Quality of life in child mental health – conceptual challenges and practical choices. *Journal of Child Psychology and Psychiatry.* 2009;50(5):544-561. https://doi.org/10.1111/j.1469-7610.2009.02008.x.

TABLES

Table 1. Summary of studies included in the meta-analyses.

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
Bangs 2008[22]	151 (67)	Children and adolescents	ATX	8	AIM-C Parent/ caregiver report	Europe and Australia	Intervention: 95.3 White, 91.7 Male. Control: 95.7 White, 97.1 Male.
Dittman 2011[23]	118 (59)	Children and adolescents	ATX	9	KINDL-R Parent/ caregiver report	Germany	Intervention: 86.0 Male. Control: 81.4 Male. Information about race/ethnicity not reported.

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
Michelson 2001[24]	213 (83)	Children and adolescents	ATX	8	CHQ Parent/ caregiver report	US	71.4 Male. Information about race/ethnicity not reported.
Svanborg 2009[25]	49 (50)	Children and adolescents	ATX	10	CHIP-CE Self and Parent/ caregiver report	Sweden	80.8 Male. Information about race/ethnicity not reported.
Brown 2006[26]	92 (49)	Children and adolescents	ATX	7	CHQ Parent/ caregiver report	US	Intervention: 9.9 African American, 24.8 Hispanic, 5.0 Other Race/Ethnicity, 60.4 White, 82.2 Male.

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
							Control: 7.7 African American, 25.0 Hispanic, 7.7 Other Race/Ethnicity, 59.6 White, 76.9 Male.
Newcorn 2008[27]	193, 193 (64)	Children and adolescents	ATX and MPH	6	CHQ Parent/ caregiver report	US	74.3 Male. Information about race/ethnicity not reported.
Findling 2011[28]	232 (79)	Children and adolescents	LDX	4	YQOL-R Self-report	US	14.8 African American, 25.0 Hispanic, 79.0 White, 70.3 Male.
Banaschewski	104, 107 (106)	Children and	LDX and	7	CHIP-CE	Europe (France, Hungary, Spain,	LDX: 0.9 African American, 0.9 Asian, 1.8 Other

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
2012[29]		adolescents	MPH		Parent/ caregiver report	Poland, Belgium, Netherlands, Germany, UK, Italy, Sweden)	race/ethnicity, 96.4 White, 78.4 Male. MPH: 3.6 Other race/ethnicity, 96.4 White, 81.1 Male. Control: 1.8 Other race/ethnicity, 98.2 White, 82.7 Male.
Adler 2008[30]	271 (139)	Adults	ATX	24	AAQoL Self-report	US	Intervention: 5.2 African American, 1.1 Asian, 82.3 Caucasian [a], 7.8 Hispanic, 3.7 Other Race/Ethnicity,

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
							56.1 Male. Control: 7.2 African American, 1.4 Asian, 81.3 Caucasian [a], 9.4 Hispanic, 0.7 Other Race/Ethnicity, 63.3 Male.
Adler 2009[31]	171 (158)	Adults	ATX	14	AAQoL Self-report	US	74.0 Caucasian [a], 53.6 Male.
Adler 2009[32]	250 (251)	Adults	ATX	24	AAQoL Self-report	US	87.9 White. Information about sex/gender not reported.

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
Durell 2013[33]	189 (198)	Adults	ATX	12	AAQoL Self-report	US	Intervention: 5.5 African American, 5.4 Asian, 76.8 Caucasian [a], 12.3 Hispanic, 58.2 Male. Control: 11.6 African American, 3.1 Asian, 73.8 Caucasian [a], 11.1 Hispanic, 0.4 Native American, 56.4 Male.
Goto 2017[34]	178 (190)	Adults	ATX	10	AAQoL Self-report	Japan, Korea and Taiwan	Intervention: 63.7 Japanese, 18.7 Korean, 17.6 Taiwanese, 46.6 Male.

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
							Control: 63.6 Japanese, 19.0 Korean, 17.4 Taiwanese, 48.7 Male.
Adler 2013[35]	80 (81)	Adults	LDX	10	AIM-A Self-report	US	Intervention: 1.3 American Indian or Alaska Native, 11.4 Black or African American, 2.5 Asian, 1.3 Other race/ethnicity, 82.3 White, 50.6 Male. Control: 1.3 American Indian or Alaska Native, 8.8 Black or African American,

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
							1.3 Other race/ethnicity, 88.8 White, 53.8 Male.
Spencer 2008[36]	136 (132)	Adults	MAS	7	AIM-A Self-report	US	Intervention: 4.4 Asian, 6.6 Black, 1.3 Other race/ethnicity, 86.1 White, 50.4 Male. Control: 2.2 Asian, 8.9 Black, 5.2 Other race/ethnicity, 83.7 White, 49.6 Male.
Goodman 2017[37]	169 (172)	Adults	MPH	6	AIM-A	US	Intervention: 4.0 Asian, 12.6 Black or African American,

First author and year	N Intervention (N placebo)	Developmental Stage	Medication	Length of treatment (weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)
					Self-report		2.9 Other race/ethnicity, 80.5 White, 50.6 Male. Control: 0.6 American Indian or Alaska Native, 2.3 Asian, 10.3 Black or African American, 2.3 Other race/ethnicity, 84.6 White, 54.9 Male.
Takahashi 2014[38]	143 (140)	Adults	MPH	8	Q-LES-Q-SF Self-report	Japan	48.9 Male. Information about race/ethnicity not reported.

Note: [a] "Caucasian" was reported in the original paper, with no further information. AAQoL = Adult ADHD Quality-of-Life Scale. AIM-A = The

ADHD Impact Module – Adult. AIM-C = The ADHD Impact Module – Child. ATX = Atomoxetine. CHIP-CE = Child Health and Illness Profile – Child Edition. CHQ = Child Health Questionnaire. KINDL-R = Instrument zur erfassung der gesundheitsbezogenen Lebensqualität von Kindern und jugendlichen. LDX = Lisdexamfetamine. MAS = Mixed Amphetamine Salts. MPH = Methylphenidate. Q-LES-Q-SF = Quality-of-life Enjoyment and Satisfaction Questionnaire Short Form. YQOL-R = Youth Quality of Life – Research Version.

Table 2. Summary of studies included in the narrative review only.

Study	N intervention (N Placebo)	Developmental Stage	Medication	Length of treatment (Weeks)	QoL Scale	Country	Socio-demographic background (% for each RCT arm and group)	Reason of exclusion from meta-analysis
Dell'Agnello 2009[39]	105 (32)	Children and adolescents	ATX	8	CHIP-CE Parent/ caregiver report	Italy, UK	91.9 Male. Information about race/ethnicity not reported.	Relevant data not included in the paper; authors unable to provide raw data.
Escobar 2009[40]	100 (51)	Children and adolescents	ATX	12	CHIP-CE Parent/ caregiv	Spain	Intervention: 98.0 Caucasian [a], 2.0 Hispanic, 79.0 Male. Control: 92.2 Caucasian	Relevant data not included in the paper; unable to contact authors.

					er report		[a], 5.9 Hispanic, 2.0 African, 80.4 Male.	
Wigal 2005[41]	101 (101)	Children and adolescents	ATX and MAS	3	PedsQL Self-report	US	Intervention: 2.9 Asian or Pacific Islander, 17.6 Black or African American, 17.6 Hispanic, 6.9 Other race/ethnicity, 54.9 White, 74.5 Male. Control: 1.0 Asian or Pacific Islander, 14.9 Black or African American, 21.8 Hispanic, 5.9 Other race/ethnicity, 56.4 White, 69.3 Male.	Relevant data not included in the paper; unable to contact authors.
Wigal 2014[42]	183 (47)	Children and	MPH	1	NR	US	Information about	Relevant data not included

		adolescents					race/ethnicity and sex/gender not reported.	in the paper; unable to contact authors.
Spencer 2007[43]	141 (43)	Adults	Dexmethylphenidate	5	Q-LES-Q-SF Self-report	US	57.5 Male. Information about race/ethnicity not reported.	Relevant data not included in the paper; unable to contact authors.
Iwanami 2020[44]	79 (93)	Adults	GXR	5	AAQoL Self-report	Japan	64.5 Male. Information about race/ethnicity not reported.	The only study on guanfacine included, therefore not possible to conduct a meta-analysis.
Arnold 2014[45]	142 (51)	Adults	Modafinil	9	Q-LES-Q-SF Self-report	US	Intervention: 17.6%, Asian, 4.0 Black, 8.0 Other race/ethnicity, 87.0 White, 62.0 Male. Control: 5.0 Asian, 7.0	The only study on modafinil included with data, therefore not possible to conduct a meta-analysis.

							Black, 86.0 White, 53.0 Male. Other 8.0 (1.0)	
Mick 2008[46]	323 (134)	Adults	MPH	6	Q-LES-Q-SF Self-report	US	53.0 Male. Information about race/ethnicity not reported.	Relevant data not included in the paper; unable to contact authors.
Casas 2013[47]	110 (68)	Adults	MPH	13	AIM-A Self-report	Spain, Germany, The Netherlands, Sweden, Belgium	Intervention: 0.5 Asian, 1.0 Black or African, 2.7 Other race/ethnicity, 95.6 White, 51.6 Male. Control: 1.0 Asian, 3.1 Other race/ethnicity, 95.9 White, 53.6 Male.	Relevant data not included in the paper; authors unable to provide raw data.

Rösler 2013[48]	306 (96)	Adults	MPH	5	Q-LES-Q-SF Self-report	Germany, Sweden, Denmark, UK, Finland, Belgium, The Netherlands	Intervention: 2.6 Other race/ethnicity, 97.1 White, 51.9 Male. Intervention: 2.1 Other race/ethnicity, 97.9 White, 61.5 Male.	Relevant data not included in the paper; unable to contact authors.

Note: [a] "Caucasian" was reported in the original paper, with no further information. AIM-A = The ADHD Impact Module – Adult. ATX = Atomoxetine. CHIP-CE = Child Health and Illness Profile – Child Edition. CHQ = Child Health Questionnaire. GXR = Guanfacine Extended Release. MAS = Mixed Amphetamine Salts. MPH = Methylphenidate. NR = Not reported. PedsQL = Pediatric Quality of Life Inventory. Q-LES-Q-SF = Quality-of-life Enjoyment and Satisfaction Questionnaire Short Form.

FIGURE CAPTIONS

Figure 1. Forest Plot of Effect Sizes for Studies Investigating the Effects of Amphetamines vs Placebo on Quality of Life

Note: Each row represents an effect size; for some studies, multiple effect sizes have been extracted (for example, they did not report a single QoL total scores but multiple QoL domain/subscale scores), accounted for in the multi-level meta-analytic model.

Figure 2. Forest Plot of Effect Sizes for Studies Investigating the Effects of Methylphenidate vs Placebo On Quality of Life

Note: Each row represents an effect size; for some studies, multiple effect sizes have been extracted (for example, they did not report a single QoL total scores but multiple QoL domain/subscale scores), accounted for in the multi-level meta-analytic model.

Figure 3. Forest Plot of Effect Sizes for Studies Investigating the Effects of Atomoxetine vs Placebo on Quality of Life

Note: Each row represents an effect size; for some studies, multiple effect sizes have been extracted (for example, they did not report a single QoL total scores but multiple QoL domain/subscale scores), accounted for in the multi-level meta-analytic model.

Figure 4. Summary of Pooled Estimates of Efficacy of Different Medications on Quality of Life

Note: Effect size (Hedge's G) for each medication is represented by a black square, with bars representing the corresponding 95% CIs. Hedge's G was calculated as the difference between the mean change in QoL from baseline to endpoint for medication vs. placebo. Values closer to 1 indicate larger effects for medication than placebo.