META-ANALYSIS

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

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Objective: We conducted a systematic review and meta-analysis to quantify the effect of attention-deficit/hyperactivity disorder (ADHD) medication on quality of life (QoL), and to understand whether 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 years or more with a diagnosis of ADHD based on the *DSM* (from third to fifth editions) or the *International Classification of Diseases* (*ICD;* ninth or tenth revision), 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, and did not differ between children/adolescents and adults.

Conclusion: In addition to being efficacious in reducing ADHD core symptom 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.

Key words: ADHD; stimulants; non-stimulants; quality of life; RCT

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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] Instruments aimed at assessing QoL are usually self-reported (mostly used with adults), whereas 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 observed, with individuals 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 (atomoxetine, clonidine, guanfacine, viloxazine).[14] As QoL is related to ADHD symptom 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 *et al.*[7] conducted a systematic review to assess such effects. Most of the eligible studies (ie, 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 2 randomized controlled trials (RCTs) of lisdexamfetamine and guanfacine extended release[15] found associations among medication-related changes in ADHD symptomatology, QoL, and functional outcomes. Although all of 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 the 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 crossover) RCTs, is available. Moreover, it is not clear whether stimulant (eg, methylphenidate, amphetamine) and non-stimulant (eg, 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 crossover RCTs to estimate the effects of ADHD medication on QoL, and secondary analyses to investigate whether these effects differed in children/young people vs adults, as well as by class of medications, and whether they were moderated by the length of treatment.

METHOD

Data Sources, Searches, and Study Selection

We followed the most recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] (Table S1, available online, provides 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[1] (https://med-adhd.org/) which we updated on February 27, 2023, to identify RCTs including people of any age with a diagnosis of ADHD based on the *DSM* (from third to fifth editions) or the *International Classification of Diseases* (*ICD*) (ninth or tenth revision), and reporting data on QoL (measured with a validated scale). For crossover RCTs, we included only data at pre-crossover or, if pre-crossover data were not available, at endpoint after wash-out (when conducted), to avoid a carry-over effect.

The original search in Cortese *et al.*[1] was conducted in PubMed, BIOSIS Previews, CINAHL, 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), 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 its 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. Although for some studies (eg, those using the Adult ADHD Quality of Life Scale) we analyzed a total QoL score, for others (eg, those using the Child Health and Illness Profile [CHIP]) we used domain/subscale scores relative to QoL. Authors NP and LM identified, for each study, which scale was used to assess QoL, and extracted relevant data (ie, means and SDs 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 SDs were not reported in the original paper).

All other relevant study data (ie, sample characteristics, information about treatment) had already been extracted by Cortese *et al.*[1] for studies up to 2017, whereas 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 as follows: (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 author via e-mail.

Data synthesis and analysis

We used the R package *esc*[19] to calculate the 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 2 studies reported at least 1 of the outcomes, for the same type of medication. Effect sizes were nested within studies in multi-level models for those studies that reported multiple effect sizes (eg, different QoL domains), using the Restricted Maximum-Likelihood estimator. Cross-study heterogeneity was tested with Cochran's Q and I^2. Funnel plots and the rank correlation test for funnel plot asymmetry (whenever at least 10 studies were included in a meta-analysis) were used to assess publication bias. Meta-regressions were planned (whenever at least 10 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 vs adults) affected QoL response to medication (whenever at least 10 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

A total of 17 studies were included in the meta-analysis (5,388 participants in total; 56% of whom randomized to active medication) (Table 1[22-38]), whereas 10 were summarized in the narrative review only (2,306 participants in total, 31% of whom randomized to active medication) (Table 2[39-48]). A total of 13 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 (Figure S1, available online). Further information about the included studies is available in Table 1 and 2.

A variety of scales were used to measure QoL, and this was dependent mainly 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]; Child Health and Illness Profile–Child Edition (CHIP-CE)[53,54]; ADHD Impact Module–Child (AIM-C)[55]; 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 3 meta-analyses, one for each type of medication: amphetamines (lisdexamfetamine and triple-bead mixed amphetamine salts; 4 studies), methylphenidate (4 studies), and atomoxetine (11 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% CI = 0.08, 0.94, $t = 2.57$, $p = 0.0233$) (Figure 1). Heterogeneity was significant ($Q = 47.87$; $p < .0001$), and the funnel plot did not indicate publication bias (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, as fewer than 10 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

TABLE 1 Summary of Studies Included in the Meta-Analyses

First author, year, reference	Intervention, n (placebo, n)	Developmental stage	Medication	Length of treatment (wk)	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
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 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 2012[29]	104, 107 (106)	Children and adolescents	LDX and MPH	7	CHIP-CE Parent/caregiver report	Europe (France, Hungary, Spain, Poland, Belgium, Netherlands, Germany, UK, Italy, Sweden)	LDX: 0.9 African American, 0.9 Asian, 1.8 other 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

(*continued*)

TABLE 1 Continued

First author, year, reference	Intervention, n (placebo, n)	Developmental stage	Medication	Length of treatment (wk)	QoL scale	Country	Socio-demographic background (% for each RCT arm and group)
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, 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
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 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, 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

(*continued*)

TABLE 1 Continued

First author, year, reference	Intervention, n (placebo, n)	Developmental stage	Medication	Length of treatment (wk)	QoL scale	Country	Socio-demographic background (% for each RCT arm and group)
Goodman 2017[37]	169 (172)	Adults	MPH	6	AIM-A Self-report	US	Intervention: 4.0 Asian, 12.6 Black or African American, 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: *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.*

[a]*"Caucasian" was reported in the original paper, with no further information.*

amphetamine salts in children with ADHD, found that this medication improved school functioning (as measured by the PedsQL) but no other QoL domains.

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 9 effect sizes found that methylphenidate improved QoL significantly more than placebo in individuals with ADHD (Hedge's $g = 0.38$, SE = 0.07, 95% CI = 0.23, 0.54, $t = 5.78$, $p = .0004$) (Figure 2). Heterogeneity was significant ($Q = 23.07$; $p = .0033$), and the funnel plot did not indicate publication bias (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, as fewer than 10 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 in 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 ($p = .0072$), and for the group receiving OROS MPH (72 mg) by 19.8 ($p = .0009$). On the daily interference scale, in the 54-mg group the QoL score improved by 17.5 ($p = .0370$), and in the 72-mg group it improved by 17.6 ($p = .0261$). For the relationship and communication subscale score, in the 72-mg group, scores significantly improved by 13.5 ($p = .0052$), whereas for the living with ADHD subscale, in the 72-mg group scores improved by 5.9 ($p = .0162$). In the general well-being subscale, only the 54-mg OROS MPH demonstrated a significant improvement in QoL scores (by 9.5; $p = .0356$).

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

TABLE 2 Summary of Studies Included in the Narrative Review Only

First author, year, reference	Intervention, n (placebo, n)	Developmental stage	Medication	Length of treatment (wk)	QoL scale	Country	Socio-demographic background (% for each RCT arm and group)	Reason for 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/ caregiver report	Spain	Intervention: 98.0 Caucasian,[a] 2.0 Hispanic, 79.0 male Control: 92.2 Caucasian,[a] 5.9 Hispanic, 2.0 African, 80.4 male	Relevant data not included in the paper; unable to contact authors
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 adolescents	MPH	1	NR	US	Information about race/ ethnicity and sex/ gender not reported	Relevant data not included in the paper; unable to contact authors
Spencer 2007[43]	141 (43)	Adults	Dexmethyl-phenidate	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

(*continued*)

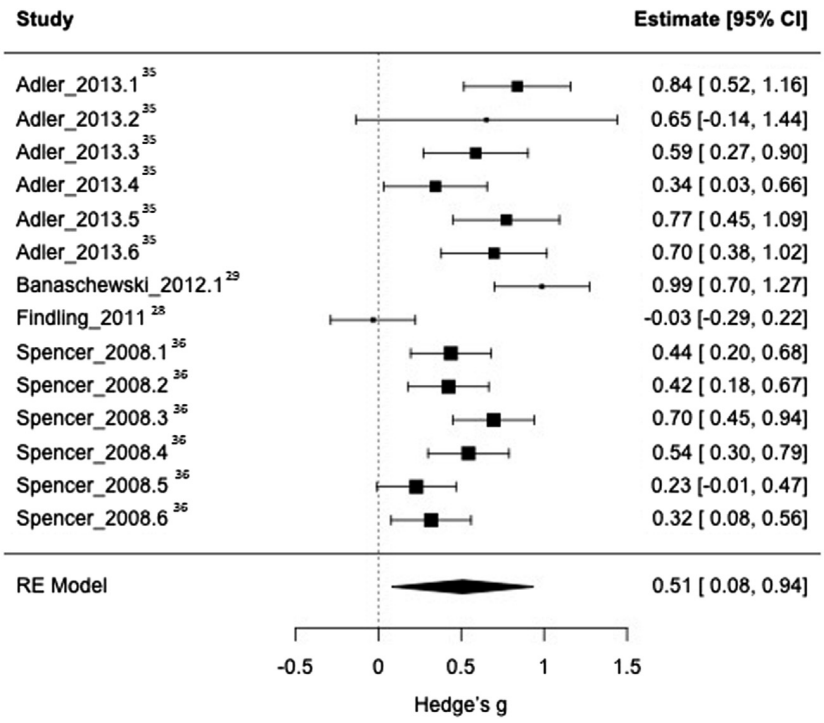
TABLE 2 Continued

First author, year, reference	Intervention, n (placebo, n)	Developmental stage	Medication	Length of treatment (wk)	QoL scale	Country	Socio-demographic background (% for each RCT arm and group)	Reason for exclusion from meta-analysis
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 Black, 1.0 other race/ethnicity, 86.0 White, 53.0 male	The only study on modafinil included with data, therefore not possible to conduct a meta-analysis
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, 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, 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: 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.

[a] *"Caucasian" was reported in the original paper, with no further information.*

FIGURE 1 Forest Plot of Effect Sizes for Studies Investigating the Effects of Amphetamines (ATX) vs Placebo on Quality of Life (QoL)



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.*

some improvements in later stages of the study. Finally, a 5-week RCT conducted by Spencer *et al.*[43] in 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.

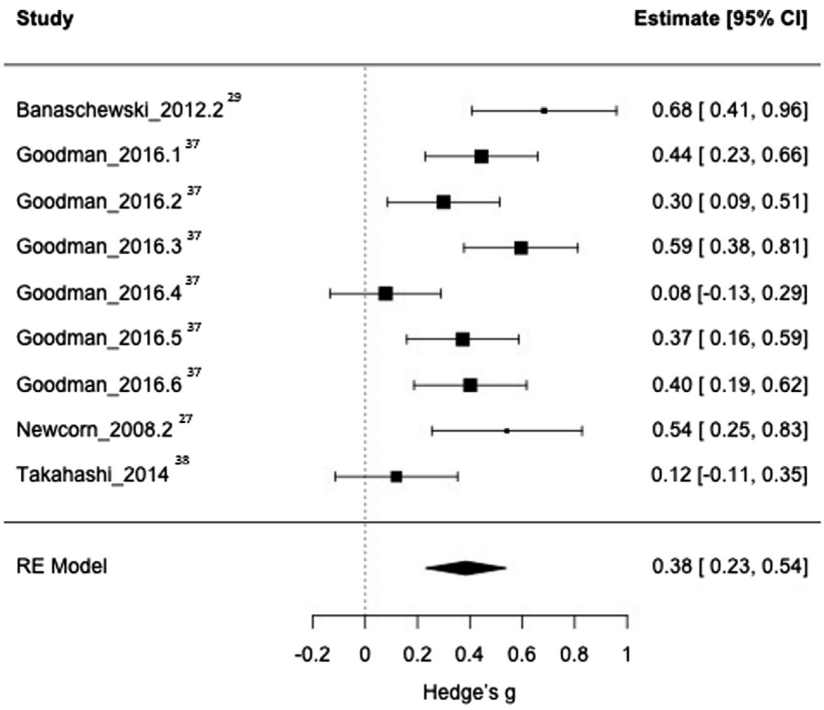
Atomoxetine

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% CI = 0.19, 0.40, $t = 5.81$, $p < .0001$) (Figure 3). Heterogeneity was significant ($Q = 27.20$; $p = .0181$), and publication bias was not detected (Kendall tau = 0.31, $p = .1128$) (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 ($F_{1,13} = 1.12$, $p = .3097$), suggesting that atomoxetine was similarly effective in improving QoL at 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 ($F_{1,13} = 1.63$, $p = .2236$).

Among the studies included in the narrative synthesis only, Dell'Agnello *et al.*[39] conducted an 8-week RCT in 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. Atomoxetine was more efficacious, compared to placebo, in improving risk avoidance and emotional comfort. Similar findings emerged from a study by Escobar *et al.*,[40] in which 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 in the placebo group. There appeared to be a significant improvement only in the risk avoidance subscale (parent- and patient-rated) and achievement subscale (parent-rated). Findings from Wigal *et al.*[41] in a 3-week study on atomoxetine efficacy in 101 children with ADHD showed a statistically significant improvement in QoL, measured using the PedsQL.

FIGURE 2 Forest Plot of Effect Sizes for Studies Investigating the Effects of Methylphenidate (MPH) vs Placebo on Quality of Life (QoL)



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.*

However, this treatment effect was statistically significant only in the school functioning subscale.

Other Medications (Individual Studies)

Guanfacine. A 5-week study in 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.

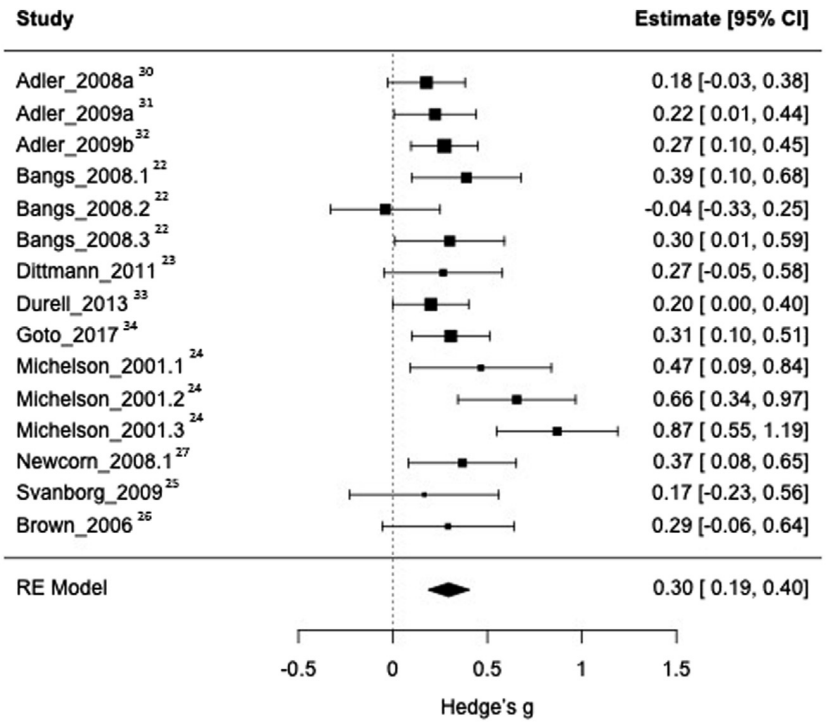
Modafinil. Arnold *et al.*[45] explored the effect of modafinil (different doses: 255 mg/d, 340 mg/d, 425 mg/d, 520 mg/d) and placebo on QoL in adults with ADHD over a 9-week period, using the Q-LES-Q-SF to measure QoL. Their findings suggested that this medication, compared to placebo, was not more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

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 crossover 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 the 95% CI of the effect size for the 3 medications overlapped (Figure 4), likely reflecting the heterogeneity in treatment response and outcomes among 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, which is why

FIGURE 3 Forest Plot of Effect Sizes for Studies Investigating the Effects of Atomoxetine (ATX) vs Placebo on Quality of Life (QoL)

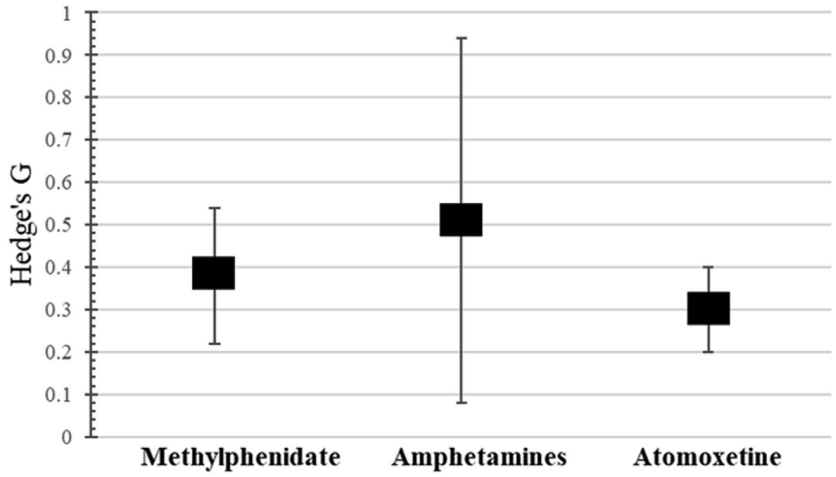


Note: Each row represents an effect size. For some studies, multiple effect sizes have been extracted (for example, they did not report a single QoL total scores but multiple QoL domain/subscale scores), accounted for in the multi-level meta-analytic model.

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, although 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, for example, 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, because of the 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 emotion 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 in the longer term.[60] For example, persisting ADHD symptoms or co-occurring psychological distress, emotion dysregulation, "treatment fatigue" (ie, 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 (eg, insomnia, decreased appetite, weight loss, irritability) may all affect health and compromise socio-emotional functioning, with a crucial impact on QoL.[60,61] Moreover, in 9 RCTs, researchers recruited participants with ADHD and co-occurring conditions, such as social anxiety, oppositional defiant disorder, and conduct disorder. However, in the other 8 RCTs, participants were excluded if they had a history of or current mental health

FIGURE 4 Summary of Pooled Estimates of Efficacy of Different Medications on Quality of Life (QoL)



Note: *Effect size (Hedge's g) for each medication is represented by a black square, with bars representing the corresponding 95% CIs. The 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 for placebo.*

condition, as well as those who had a 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, however, it is 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 multi-modal interventions for ADHD on QoL. Additional research is also needed to clarify whether and to what extent individual factors (eg, 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 able to identify only 17 RCTs reporting QoL outcomes, 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 2000s (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 8 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 or young people, whereas those used with adult samples were more likely to be disorder specific, and hence much more closely associated with ADHD symptoms and more likely to detect QoL changes in parallel with 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. Finally, 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 the study by Goto *et al.*,[34] the predominant ethnicity was White. Similarly, with sex/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 our 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 (eg, ADHD). When deciding which instrument should 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 over time. 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 which 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 (eg, 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 that culture/ethnicity may play in 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 overly 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 (eg, social, work, and academic), and to 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 within 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 2 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 with 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 with those found for ADHD core symptoms severity. Future research should include QoL as a primary treatment/intervention outcome, and should explore whether and how much combining or alternating between pharmacological and non-pharmacological interventions is likely to further improve QoL in people with ADHD.

CRediT authorship contribution statement

Alessio Bellato: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Data curation. **Nadia J. Perrott:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Lucia Marzulli:** Writing – review &

editing, Data curation. **Valeria Parlatini:** Writing – review & editing, Investigation, Data curation. **David Coghill:** Writing – review & editing. **Samuele Cortese:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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