Effect of Continuing and Discontinuing Medications on Quality of Life After Symptomatic Remission in Attention-Deficit/Hyperactivity Disorder:

A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This study aimed to compare the effect of continuing and discontinuing medications on quality of life of patients with attention-deficit/hyperactivity disorder (ADHD).

Data Sources: PubMed, Cochrane Library, and Embase databases were searched using generic terms for ADHD, discontinuing, continuing, pharmacotherapy, and randomized controlled trials without date or language restrictions.

Study Selection: Of the 3,672 screened studies, 9 met the predefined inclusion criteria on patients with ADHD; 5 of these 9 studies reporting on 1,463 patients (children and adolescents, n = 894; adults, n = 569) measured quality of life and were included in this meta-analysis. Only randomized, double-blind, placebo-controlled withdrawal trials of ADHD medications were included.

Data Extraction: Data were independently extracted according to the Cochrane Handbook for Systematic Reviews of Interventions. Analyses were based on random-effects models.

Results: Compared with continuing medications, discontinuing them significantly worsened quality of life score in patients with ADHD (standardized mean difference [SMD] = 0.19; 95% CI, 0.08 to 0.30]). Moreover, discontinuing medications worsened this score in children and adolescents with ADHD (SMD = 0.21; 95% CI, 0.06 to 0.36) but not in adults with ADHD (SMD = 0.02; 95% CI, −0.46 to 0.50).

Conclusions: Discontinuing medications was associated with a small but statistically significant decrease in quality of life among children and adolescents with ADHD but not in adults with ADHD. Quality of life can be applied in pharmacologic interventions regarding continuing and discontinuing medication because this concept is related to individuals' appraisal of their situation. Quality of life is an important factor for planning individualized ADHD medication treatment.

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Attention-deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate levels of inattention, hyperactivity, and/or impulsivity.[1] The prevalence rate of this disorder in most cultures is 5%–8% in children and adolescents[1–3] and 2%–5% in adults.[4,5] It causes persistent functional impairments[6] in areas such as interpersonal relationships, educational and occupational attainments,[7] and risk awareness, which is closely associated with mortality risk.[8] Patients with ADHD can present profound functional impairments that reduce their overall quality of life across the lifespan.[9–14]

Current clinical guidelines recommend pharmacologic interventions for patients with severe ADHD.[7,15–18] Recommended medications for patients with ADHD include psychostimulants (eg, methylphenidate and amphetamines) and nonstimulants (eg, atomoxetine and α agonists). Current literature shows that these medications have short-term efficacy and limited safety for improving ADHD symptoms in pediatric, adolescent, and adult individuals.[19–21] Over the past two decades, the prescription rates of ADHD medications have dramatically increased on a global scale.[22–24]

However, the long-term safety and efficacy of ADHD medications remain controversial.[15,19–21,25] Some patients with ADHD receiving medications experience adverse medication effects that have a negative impact on their quality of life,

Clinical Points

- Limited evidence regarding the long-term efficacy and safety of pharmacologic interventions in patients with attention-deficit/hyperactivity disorder (ADHD) raises questions regarding whether, compared with continuing ADHD medications, discontinuing them is more detrimental to quality of life among patients with the disorder.
- Discontinuing medications was found to be associated with a small but significant decrease in quality of life among children and adolescents with ADHD but not in adults with ADHD.
- In patients with ADHD who have responded to medication treatments, quality of life is an important factor for planning medication treatment for the disorder.

especially children and adolescents with ADHD.[14,26] Because of concerns regarding the long-term risks and benefits of ADHD medications, several clinical guidelines recommend at least an annual review of the treatment regimen[7,17] or drug holidays (an agreed cessation of medication for a period of time)[7,16,17] to ascertain the need for continuing these medications. Conversely, some studies[27–29] have shown that discontinuing medications poses an obvious risk of the exacerbation of ADHD symptoms. These inconsistencies among findings raise questions regarding whether clinicians should terminate treatment for patients with ADHD who have responded to their medication treatments and, if so, when termination should be implemented.

Previous systematic reviews and meta-analyses[7,30,31] on withdrawal trials for ADHD medications showed a clinically important exacerbation of ADHD symptoms with withdrawal. Previously published reviews, which included randomized controlled trials as well as open-label or single-blind trials,[7,30] have focused on individual ADHD medications[7] or evaluated the relapse of ADHD symptoms as defined by changes in the severity of those symptoms.[7,30,31] The assessments of symptoms are dependent on responses to medication in the short term. However, once the medication has stabilized, other relevant domains for assessing treatment response are needed, especially for evaluating long-term outcomes.[13,14] Recently, quality of life has been suggested as an important component in the comprehensive assessment for ADHD.[9,14,32]

Quality of life is defined as "the individuals' perception of their position in life, in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns."[33] Available evidence has emphasized that ADHD leads to a reduced quality of life in patients in terms of their subjective sense of well-being and their capacity for everyday functioning.[12,14,34] The concept of quality of life can be applied in clinical practice as well as clinical trials,[32] particularly for an outcome measure of pharmacologic interventions in patients with ADHD.[12] Because improvement in symptoms has been found to correlate moderately, but not perfectly, with improvement in quality of life, quality of life is considered as a construct that relates to, but is distinct from, ADHD symptoms.[14] Furthermore, a comprehensive assessment of the positive and negative effects of ADHD treatments is required when clinicians consider whether ADHD medication should be continued or discontinued.[7] This comprehensive assessment includes a much broader range of outcome measures; ie, quality of life assessment should be incorporated into routine clinical practice rather than simply core ADHD symptoms.[35] Recently, the National Institute for Health and Care Excellence committee[7] has considered that quality of life is one of the critical outcomes for evaluating the potential effects of discontinuing pharmacologic treatment for ADHD. Thus, changes in quality of life could be an important outcome indicator in decisions regarding continuation or discontinuation of medications for individuals with ADHD, beyond changes in ADHD symptoms.

In this systematic review and meta-analysis focusing on randomized, double-blind, placebo-controlled withdrawal trials of ADHD medications, we investigated whether, compared with continuing ADHD medications, discontinuing them was more detrimental to quality of life among patients with ADHD who had responded to their medication treatments. In contrast to previous systematic reviews and meta-analyses, the present study evaluated quality of life and included only enrichment-design studies, wherein participants responded to ADHD medication before entering withdrawal trials. The present study aimed to identify the effect of discontinuing medications after symptomatic remission on quality of life of patients with ADHD. We intended to provide further information regarding whether to discontinue ADHD medications in these patients.

METHODS

We conducted this systematic review and meta-analysis in accordance with the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[36]

Search Strategy and Eligibility Criteria

PubMed, Cochrane Library, and Embase databases were searched within the time frame beginning with the date of database inception to September 21, 2018, with no language restrictions. We used the following search terms: (1) participant terms, eg, *ADHD*; (2) ADHD medication terms, eg, *methylphenidate*; (3) intervention terms, eg, *withdr**, *discontinue**, *stop**, and *withhold**; (4) comparison terms, eg, *continu** and *maintenance**; and (5) study design terms, eg, *randomized*, *double-blind*, and *placebo*. A medical librarian was involved in formulating the search string (details shown in Supplementary Tables 1–3). Several additional eligible studies were identified by examining the reference lists for previously identified systematic reviews and guidelines.[7,30,31] Pharmaceutical companies and experts in the field were also contacted to identify possible reviews for inclusion in the study.

We included only randomized, double-blind, placebo-controlled withdrawal trials of medications for patients with ADHD. We included double-blind, randomized controlled trials with a study duration of at least 1 week that enrolled children and adolescents (aged 5–17 years) or adults (aged ≥ 18 years) with a primary diagnosis of ADHD according to *DSM-III*, *DSM III-R*, *DSM-IV-TR*, *DSM-5*, *ICD-9*, or *ICD-10*. We included studies that examined the discontinuation of the following medications, which comprise drugs approved for ADHD in at least one country, as oral monotherapies: amphetamines (including lisdexamfetamine), atomoxetine, clonidine, guanfacine, and methylphenidate (including dexmethylphenidate).

Studies in which all participants failed to respond to ADHD medications before random assignment to treatment groups (according to the definition provided in the study) were excluded from this meta-analysis.

Two independent authors screened the titles and abstracts of the retrieved references. The full texts of all potentially eligible studies were evaluated. Potentially eligible studies were then retrieved and independently verified for eligibility by the aforementioned authors. Disagreements regarding the eligibility of studies were resolved by discussion between the authors.

Outcomes

The primary outcome was a decrease in quality of life (negative change in the total quality of life score) expressed as standardized mean difference (SMD). If available, we used the intention-to-treat data and adopted the study authors' methods to account for missing data (eg, last observation carried forward). Secondary outcomes included the relapse rate (the proportion of participants who experienced relapse according to study authors' definition).

Data Extraction and Risk of Bias Assessment

Data extraction and study ratings were independently conducted by the authors using a standardized form (Excel, Microsoft; Redmond, Washington). Any discrepancy between the authors was resolved by reaching a consensus. The following variables were extracted from each study: first author, publication year, participant details (number of participants, mean age, age range, and sex distribution [% male]), type of ADHD medication, duration of initial phase, duration of trial, the quality of life scores (mean and SD), relapse rate, and study key findings.

We assessed the methodological quality of the trials using the risk of bias criteria from the Cochrane Handbook for Systematic Reviews of Interventions.[37]

Statistical Analysis

Owing to an anticipated heterogeneity, a random-effects meta-analysis model was applied using the Review Manager software (2014; Copenhagen, Denmark; RevMan. Review Manager Version 5.3). For continuous data, SMDs and 95% CIs were calculated as the effect sizes (ESs). ESs were presented as a mean ES obtained by combining ESs related to different quality of life measures mentioned in Table 1 (Adult Attention-Deficit/Hyperactivity Disorder Quality of Life [AAQoL], Child Health Questionnaire [CHQ], Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form [Q-LES-Q], and Weiss Functional Impairment Rating Scale-Parent report [WFIRS-P]). Because quality of life measures related to different quality of life domains (ie, global domain score for WFIRS-P, overall score for Q-LES-Q, psychosocial summary score for CHQ, and total score for AAQoL), mean ESs were calculated for each study as an overall quality of life outcome.

For binary data, risk ratio (RR) and 95% CIs and number needed to harm (NNH) were calculated. Definitions of relapse varied among the studies included in this study (Table 1); we calculated RRs, 95% CIs, and NNHs as the proportion of participants who experienced relapse according to study authors' definition. The heterogeneity of effects was examined using the I^2 statistic.[37]

To investigate the potential sources of heterogeneity and confounding effects, we conducted subgroup meta-analyses. Specifically, we classified the enrolled studies according to age distribution (children and adolescents aged 5–17 years or adults aged ≥ 18 years) and the type of ADHD medications (stimulants and nonstimulants).

Potential publication bias was examined using funnel plots for each outcome including more than 10 studies, which is the minimum number required to use the funnel plot.[37] A P value of ≤ .05 was considered statistically significant.

RESULTS

The literature search yielded 4,571 articles; after eliminating duplicates, 3,672 articles were retrieved. Of them, 3,642 articles were excluded on the basis of title or abstract because they focused on constructs not related to the aims of the present study. Of the 30 articles that were inspected for their full texts, 9 met our predefined inclusion criteria on patients with ADHD[38–46] (Figure 1): 5 studies measured quality of life,[39,41,42,45,46] and all 9 studies measured relapse.[38–46] Of the 9 studies, 5 focused on children and adolescents,[38–42] whereas 4 focused on adults.[43–46] Five studies included in this meta-analysis used stimulants (ie, dexmethylphenidate, lisdexamfetamine, and osmotic release oral system methylphenidate),[38,40,43–45] whereas the other 4 studies used nonstimulants (atomoxetine and guanfacine).[39,41,42,46] In total, 1,126 children and adolescents aged 6–17 years (boys, n = 937; girls, n = 189) and 708 adults aged 18–65 years (men, n = 374; women, n = 311; data were not available for 23 adults) were included (Table 1). The duration of initial phase ranged from 3 to 52 weeks, and the duration of randomized withdrawal phase ranged from 2 to 36 weeks. The results of the risk of bias assessment for each study are provided in Supplementary Figure 1.

Primary Outcome

Of the 9 studies that met our predefined inclusion criteria, 5 studies reporting on 1,463 patients with ADHD (boys/

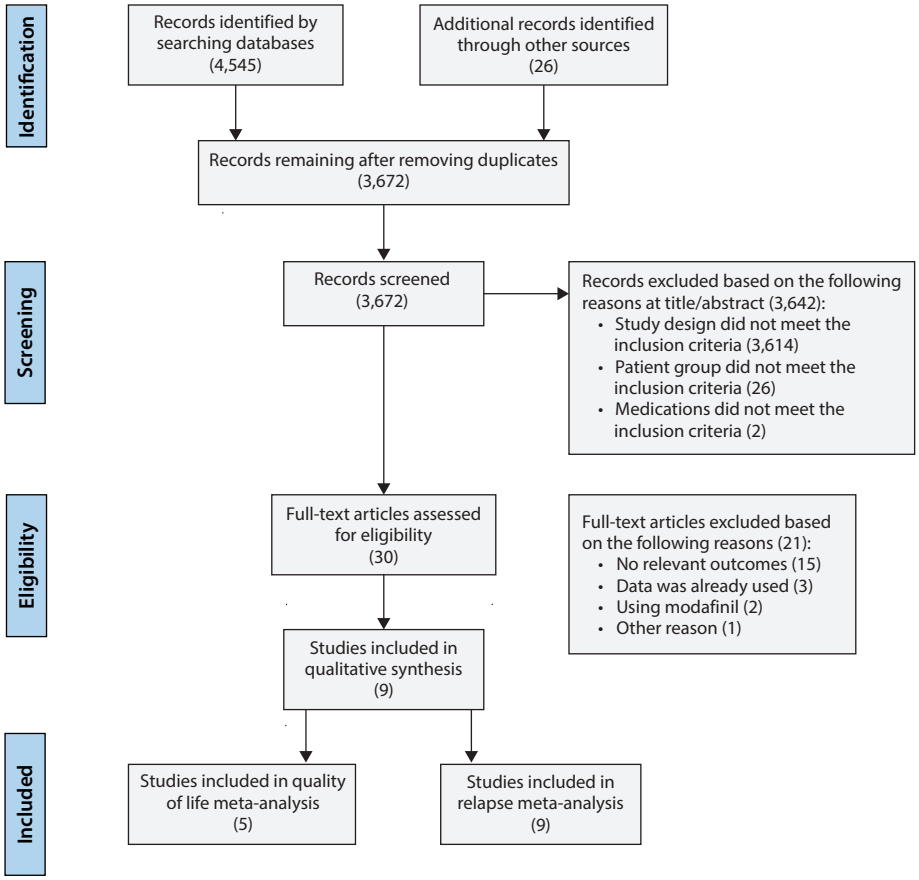
Table 1. Study Characteristics of Randomized, Double-Blind, Placebo-Controlled Withdrawal Trials[a]

Study	N (age range, y)	Duration of Lead-In Phase	Inclusion Criteria or RWP	RWP							
				Comparison/ Intervention	Duration	n	Age, mean ± SD, y	Male, %	Discontinuation of RWP, n (%)	Relapse Definition	Outcome Measures
Children and Adolescents											
Arnold et al 2004[38]	75 (6–16)	6 wk	CGI-I score of ≤2 at the end of lead-in phase	Dexmethylphenidate Placebo	2 wk	35 40	10.1 ± 2.9 9.9 ± 2.7	85.7 77.5	0 (0) 0 (0)	Treatment failure, defined as CGI-I score ≥6 relative to that at visit of 8	CGI, Math tests, SNAP-ADHD
Buitelaar et al 2007[39]	163 (6–15)	52 wk	≤25% Decrease in ADHD-RS-IV total score from lead-in baseline and a CGI-S score of ≤2 after 10 wk	Atomoxetine Placebo	24 wk	81 82	10.7 ± 2.4 11.0 ± 2.0	88.9 90.2	1 (1.2) 1 (1.2)	Increase in ADHD-RS-IV total score by ≥90% to that at study entry and in CGI-S score by ≥2 points at the end of the initial 10-wk treatment period	ADHD-RS, CGI-S, **CHQ**, CDRS-R, CPRS-R, MASC
Coghill et al 2014[40]	157 (6–17)	26 wk	≤30% Decrease in ADHD-RS-IV total score from lead-in baseline and a CGI-S score of ≤2, with tolerable side effects	Lisdexamfetamine Placebo	6 wk	78 79	11.0 ± 2.63 11.3 ± 2.58	78.2 78.5	0 (0) 1 (1.3)	Increase in ADHD-RS-IV total score by ≥50% and CGI-S score by ≥2 points, compared with that at RWP start point	ADHD-RS-IV, CGI-I, CGI-S
Michelson et al 2004[41]	416 (6–15)	12 wk	≤25% Decrease in ADHD-RS-IV total score from lead-in baseline and a CGI-S score of ≤2 during wk 9–10	Atomoxetine Placebo	36 wk	292 124	10.6 ± 2.3 10.1 ± 2.3	89.4 90.3	9 (3.1) 1 (0.8)	Increase in ADHD-RS-IV total score by ≥90% and in CGI-S score by ≥2 points compared with that at study baseline point	ADHD-RS, CGI-S, **CHQ**, CDRS-R, CPRS-R, MASC
Newcorn et al 2016[42]	315 (6–17)	13 wk	≤30% Decrease in ADHD-RS-IV total score from lead-in baseline and a CGI-S score of ≤2 during wk 12–13	Guanfacine Placebo	26 wk	157 158	10.7 ± 2.64 11.0 ± 2.69	75.2 73.4	3 (1.9) 2 (1.3)	Increase in ADHD-RS-IV total score by ≥50% and in CGI-I score by ≥2 points compared with that at RWP baseline and at 2 consecutive visits	ADHD-RS-IV, CGI-I, CGI-S, **WFIRS-P**, HUI2/3
Adults											
Biederman et al 2010[43]	23 (19–60)	24 wk	≤30% Decrease in AISRS total score from lead-in baseline and a CGI-S score of ≤2 during wk 12–13	OROS-MPH Placebo	4 wk	12 11	NA NA	NA NA	NA NA	Increase in CGI-I score by ≥2 points compared with that at the end of phase 1 or improvement in AISRS score by ≤15% for 2 consecutive visits	CGI-I, AISRS, HDRS, HARS, GAF
Brams et al 2012[44]	116 (18–55)	3 wk	ADHD-RS-IV total score at lead-in baseline <22 and a CGI-S score of ≤3	Lisdexamfetamine Placebo	6 wk	56 60	36.3 ± 10.95 35.1 ± 11.39	43.3 43.1	0 (0) 1 (1.7)	Increase in ADHD-RS-IV total score by ≥50% and in CGI-I score by ≥2 points compared with that at RWP baseline	CGI-I, ADHD-RS
Buitelaar et al 2012[45]	45 (18–65)	52 wk	Patients who completed initial 7-wk open-label phase trial and those with a stable dose for at least 4 wk at the end of open-label trial	OROS-MPH Placebo	4 wk	23 22	37.5 ± 12.0 35.1 ± 9.8	47.8 31.8	2 (8.7) 5 (22.7)	Worsening of CAARS-O:SV total score by >50% from that at baseline	CAARS, CGI-S, CGI-C, SDS, **Q-LES-Q**
Upadhyaya et al 2013[46]	524 (18–50)	24 wk	≤30% Decrease in CAARS-Inv:SV total score and a CGI-S score of ≤3 maintained through the lead-in phase	Atomoxetine Placebo	25 wk	266 258	33.7 ± 9.5 32.4 ± 9.4	56.8 60.1	82 (30.8) 93 (36.0)	CGI-S score of ≥4 points at 2 consecutive visits and CAARS-Inv:SV score at week 24 of ≥80% compared with that at baseline	CAARS-Inv:SV, CAARS- O:SV, CGI ADHD-S, **AAQoL**, CAARS-S:SV, EQ-5D

[a]Boldface represents scales used in primary analysis.

Abbreviations: AAQoL = Adult ADHD Quality of Life Questionnaire; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; AISRS = Adult ADHD Investigator Symptom Report Scale; CAARS-O:SV = CAARS (Conners' Adult ADHD Rating Scale)–Observer Screening Version; CAARS-Inv:SV = CAARS–Investigator Screening Version; CAARS-S:SV = CAARS–Self Report: Screening Version; CDRS-R = Children's Depression Rating Scale–Revised; CGI-ADHD-S = Clinical Global Impressions (CGI) ADHD-Severity scale; CGI-C = CGI-Change scale; CGI-I = CGI-Improvement scale; CGI-S = CGI-Severity of Illness scale; CHQ = Child Health Questionnaire; CPRS-R = Revised Conners' Parent and Teacher Rating Scales, Short Form; d-MPH = dexmethylphenidate; EQ-5D = EuroQol-5 Dimensions Questionnaire; GAD = generalized anxiety disorder; GAF = Global Assessment of Functioning; GXR = guanfacine; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HUI2/3 = Health Utility Index-Mark 2 and Mark 3; MASC = Multidimensional Anxiety Scale for Children; NA = not available; OROS-MPH = Osmotic release oral system methylphenidate; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; RWP = randomized withdrawal phase; SAD = separation anxiety disorder; SDS = Sheehan Disability Scale; SNAP-ADHD = Swanson, Nolan, and Pelham ADHD Rating Scale; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent report.

Figure 1. PRISMA 2009 Flow Diagram



men, n = 1,077; girls/women, n = 386) measured quality of life and were included in our primary outcome meta-analysis.[39,41,42,45,46] Of these 5 studies measuring quality of life, 2 used the CHQ,[39,41] 1 used the WFIRS-P,[42] 1 used the AAQoL,[46] and 1 used the Q-LES-Q.[45] Quality of life measures used in this meta-analysis were only observer-rated measures (CHQ and WFIRS-P) in children and adolescents with ADHD and only self-reported measures (AAQoL and Q-LES-Q) in adults with ADHD. Four studies reporting on 371 patients with ADHD (boys/men, n = 260; girls/women, n = 88; data were not available for 23 adults) did not measure quality of life and were not included in our primary outcome meta-analysis.[38,40,43,44] Two of these 4 studies focused on children and adolescents,[38,40] and 2 studies focused on adults.[43,44] All of these 4 studies that did not measure quality of life used stimulants (ie, dexmethylphenidate, lisdexamfetamine, and osmotic release oral system methylphenidate).[38,40,43,44]

We divided these 5 studies, measuring quality of life, into the following subgroups: studies including children and adolescents (3 studies; N = 894; boys, n = 753 and girls, n = 141)[39,41,42]; studies including adults (2 studies; N = 569; men, n = 324 and women, n = 245)[45,46]; studies using stimulants (1 study; N = 45; men, n = 18 and women, n = 27)[45]; and studies using nonstimulants (4 studies; N = 1,418; boys/men, n = 1,059 and girls/women, n = 359).[39,41,42,46] Two of the 3 studies in the children and adolescents subgroup used the CHQ,[39,41] and the remaining study used the WFIRS-P.[42] The 2 studies in the adults subgroup used the AAQoL[46] and the Q-LES-Q.[45] The one study in the stimulants subgroup used the Q-LES-Q[45]; of the 4 studies in the nonstimulants subgroup, 2 used the CHQ[39,41] and 1 each used the WFIRS-P[42] and AAQoL.[46]

Decreases in quality of life were higher among individuals discontinuing ADHD medications compared with those continuing ADHD medications (SMD = 0.19; 95% CI, 0.08 to 0.30) (Figure 2A).[39,41,42,45,46] In the subgroup analysis restricted to children and adolescents with ADHD,[39,41,42] decreases in quality of life were higher among patients discontinuing ADHD medications compared with those maintaining these medications (SMD = 0.21; 95% CI, 0.06 to 0.36) (Figure 2B). In the subgroup analysis restricted to adults with ADHD,[45,46] no significant difference was observed (SMD = 0.02; 95% CI, −0.46 to 0.50) (Figure 2C).

In the subgroup analysis restricted to nonstimulants,[39,41,42,46] decreases in quality of life were higher among patients discontinuing medications compared with those continuing them (SMD = 0.21; 95% CI, 0.10 to 0.32) (Figure 2D). A subgroup analysis restricted to stimulants was not conducted because only 1 study investigated changes in quality of life using stimulants.[45]

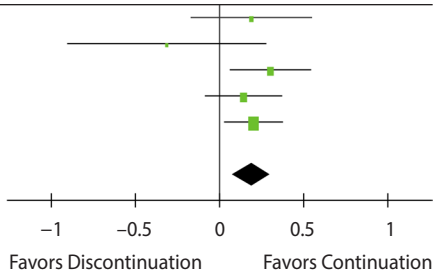
Figure 2. Forest Plots of the Comparison Between the Effect of Discontinuing and Continuing ADHD Medications on Quality of Life After Symptomatic Remission in (A) Patients With ADHD, (B) Children and Adolescents With ADHD Subgroup, (C) Adults With ADHD, and (D) Patients Receiving Nonstimulant Medications

A. All Patients

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight, %	Standardized Mean Difference IV, Random (95% CI)
Buitelaar et al 2007[39]	2.9	10.9	62	0.9	10.1	59	9.6	0.19 (−0.17 to 0.55)
Buitelaar et al 2012[45]	2.7	12.4	22	6.5	11.4	23	3.5	−0.31 (−0.90 to 0.27)
Michelson et al 2004[41]	9.5	12	96	5.6	13.2	235	21.5	0.30 (0.06 to 0.54)
Newcorn et al 2016[42]	0.23	0.49	151	0.16	0.49	150	23.9	0.14 (−0.08 to 0.37)
Upadhyaya et al 2013[46]	4	17.67	258	0.4	17.94	266	41.5	0.20 (0.03 to 0.37)
Total (95% CI)			**589**			**733**	**100.0**	**0.19 (0.08, 0.30)**

Heterogeneity: $\tau^2 = 0.00$, $\chi^2_4 = 3.86$ ($P = .43$); $I^2 = 0\%$

Test for overall effect: $z = 3.36$ ($P = .0008$)

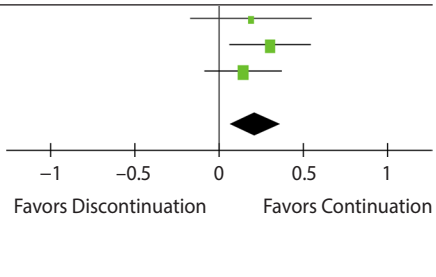


B. Children and Adolescents

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight, %	Standardized Mean Difference IV, Random (95% CI)
Buitelaar et al 2007[39]	2.9	10.9	62	0.9	10.1	59	17.4	0.19 (−0.17 to 0.55)
Michelson et al 2004[41]	9.5	12	96	5.6	13.2	235	39.1	0.30 (0.06 to 0.54)
Newcorn et al 2016[42]	0.23	0.49	151	0.16	0.49	150	43.5	0.14 (−0.08 to 0.37)
Total (95% CI)			**309**			**444**	**100.0**	**0.21 (0.06 to 0.36)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.93$ ($P = .63$); $I^2 = 0\%$

Test for overall effect: $z = 2.80$ ($P = .005$)

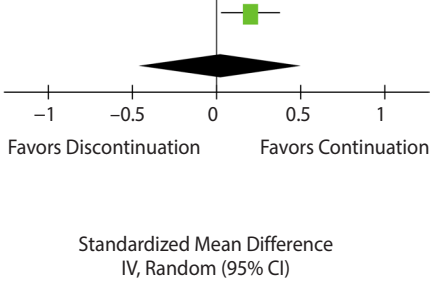


C. Adults

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight, %	Standardized Mean Difference IV, Random (95% CI)
Buitelaar et al 2012[45]	2.7	12.4	22	6.5	11.4	23	34.5	−0.31 (−0.90 to 0.27)
Upadhyaya et al 2013[46]	4	17.67	258	0.4	17.94	266	65.5	0.20 (0.03 to 0.37)
Total (95% CI)			**280**			**289**	**100.0**	**0.02 (−0.46 to 0.50)**

Heterogeneity: $\tau^2 = 0\ 08$, $\chi^2_1 = 2.72$ ($P = .10$); $I^2 = 63\%$

Test for overall effect: $z = 0.10$ ($P = .92$)

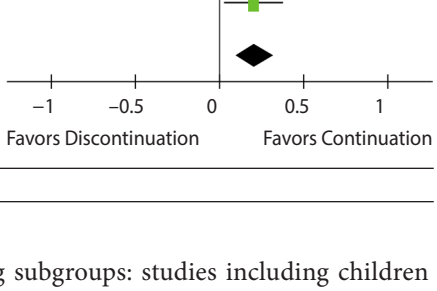


D. Patients Receiving Nonstimulant Medications

Study or Subgroup	Discontinuation Mean	SD	Total	Continuation Mean	SD	Total	Weight, %	Standardized Mean Difference IV, Random (95% CI)
Buitelaar et al 2007[39]	2.9	10.9	62	0.9	10.1	59	9.9	0.19 (−0.17 to 0.55)
Michelson et al 2004[41]	9.5	12	96	5.6	13.2	235	22.3	0.30 (0.06 to 0.54)
Newcorn et al 2016[42]	0.23	0.49	151	0.16	0.49	150	24.8	0.14 (−0.08 to 0.37)
Upadhyaya et al 2013[46]	4	17.67	258	0.4	17.94	266	43.0	0.20 (0.03 to 0.37)
Total (95% CI)			**567**			**710**	**100.0**	**0.21 (0.10 to 0.32)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 0.94$ ($P = .82$); $I^2 = 0\%$

Test for Overall Effect: $z = 3.63$ ($P = .0003$)



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, IV = inverse variance.

I^2 values were low (0%) throughout the analyses, except for the analysis focusing on adults with ADHD (63%).

Secondary Outcome

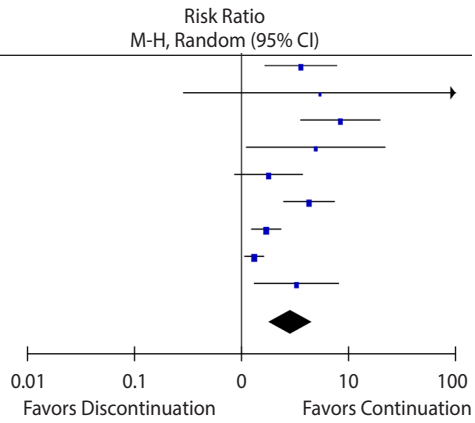
Nine studies reported relapse rates (N = 1,834; boys/men, n = 1,311; girls/women, n = 500; data were not available for 23 adults).[38–46] We divided these 9 studies into the following subgroups: studies including children and adolescents (5 studies, N = 1,126; boys, n = 937; girls, n = 189)[38–42]; studies including adults (4 studies, N = 708; men, n = 374; women, n = 311; data were not available for 23 adults)[43–46]; studies using stimulants (5 studies, N = 416; boys/men, n = 252; girls/women, n = 141; data were not available for 23 adults)[38,40,43–45]; and studies using

Figure 3. Forest Plots of the Comparison Between the Effect of Discontinuing and Continuing ADHD Medications on Relapse in (A) Patients With ADHD, (B) Children and Adolescents With ADHD, (C) Adults With ADHD, (D) Patients Receiving Stimulant Medications, and (E) Patients Receiving Nonstimulant Medications

A. All Patients

Study or Subgroup	Discontinuation Events	Discontinuation Total	Continuation Events	Continuation Total	Weight, %	Risk Ratio M-H, Random (95% CI)
Arnold et al 2004[38]	24	39	6	35	11.7	3.59 (1.66 to 7.75)
Biederman et al 2010[43]	2	11	0	12	2.2	5.42 (0.29 to 101.77)
Brams et al 2012[44]	45	60	5	56	10.9	8.40 (3.59 to 19.64)
Buitelaar et al 2007[39]	10	82	2	81	6.3	4.94 (1.12 to 21.85)
Buitelaar et al 2012[45]	12	22	7	23	12.1	1.79 (0.87 to 3.70)
Coghill et al 2014[40]	52	77	12	76	13.9	4.28 (2.49 to 7.35)
Michelson et al 2004[41]	47	124	65	292	15.8	1.70 (1.25 to 2.32)
Newcorn et al 2016[42]	98	151	74	150	16.5	1.32 (1.08 to 1.61)
Upadhyaya et al 2013[46]	19	258	6	266	10.5	3.26 (1.33 to 8.04)
Total (95% CI)		**824**		**991**	**100.0**	**2.85 (1.78 to 4.56)**
Total events	309		177			

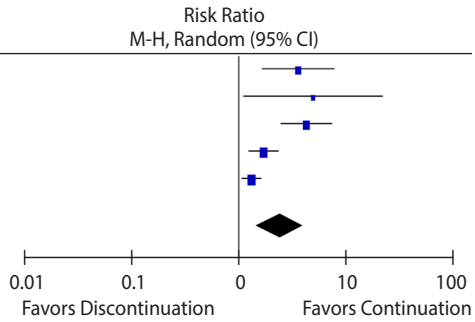
Heterogeneity: $\tau^2 = 0.34$; $\chi^2_8 = 45.56$ ($P < .00001$); $I^2 = 82\%$
Test for overall effect: $z = 4.36$ ($P < .0001$)



B. Children and Adolescents

Study or Subgroup	Discontinuation Events	Discontinuation Total	Continuation Events	Continuation Total	Weight, %	Risk Ratio M-H, Random (95% CI)
Arnold et al 2004[38]	24	39	6	35	17.3	3.59 (1.66 to 7.75)
Buitelaar et al 2007[39]	10	82	2	81	8.4	4.94 (1.12 to 21.85)
Coghill et al 2014[40]	52	77	12	76	21.5	4.28 (2.49 to 7.35)
Michelson et al 2004[41]	47	124	65	292	25.6	1.70 (1.25 to 2.32)
Newcorn et al 2016[42]	98	151	74	150	27.1	1.32 (1.08 to 1.61)
Total (95% CI)		**473**		**634**	**100.0**	**2.41 (1.44 to 4.04)**
Total events	231		159			

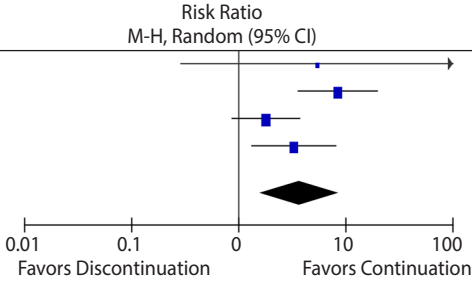
Heterogeneity: $\tau^2 = 0.25$; $\chi^2_4 = 25.32$ ($P < .0001$); $I^2 = 84\%$
Test for overall effect: $z = 3.34$ ($P = .0008$)



C. Adults

Study or Subgroup	Discontinuation Events	Discontinuation Total	Continuation Events	Continuation Total	Weight, %	Risk Ratio M-H, Random (95% CI)
Biederman et al 2010[43]	2	11	0	12	7.1	5.42 (0.29 to 101.77)
Brams et al 2012[44]	45	60	5	56	30.5	8.40 (3.59 to 19.64)
Buitelaar et al 2012[45]	12	22	7	23	33.1	1.79 (0.87 to 3.70)
Upadhyaya et al 2013[46]	19	258	6	266	29.3	3.26 (1.33 to 8.04)
Total (95% CI)		**351**		**357**	**100.0**	**3.70 (1.58 to 8.69)**
Total events	78		18			

Heterogeneity: $\tau^2 = 0.44$; $\chi^2_3 = 8.20$ ($P = .04$); $I^2 = 63\%$
Test for overall effect: $z = 3.00$ ($P = .003$)



(continued)

nonstimulants (4 studies, N = 1,418; boys/men, n = 1,059; girls/women, n = 359).[39,41,42,46]

In our analyses of the secondary outcome relapse, a statistically significant RR of 2.85 was observed (95% CI, 1.78 to 4.56) among patients with ADHD (Figure 3A).[38–46] NNH for the relapse of ADHD symptoms was 4 among all patients. I^2 value was high at 82%.

A subgroup analysis confirmed the results of the secondary outcome analyses regarding relapse, with statistically significant RRs of 2.41 (95% CI, 1.44 to 4.04) for children and adolescents (5 studies, Figure 3B),[38–42] 3.70 (95% CI, 1.28 to 8.69) for adults (4 studies, Figure 3C),[43–46] 3.87 (95% CI, 2.26 to 6.62) for stimulants (5 studies, Figure 3D),[38,40,43–45] and 1.77 (95% CI, 1.20 to 2.62) for nonstimulants (4 studies, Figure 3E).[39,41,42,46]

For these subgroup analyses, I^2 values were consistently high at 51%–84%.

DISCUSSION

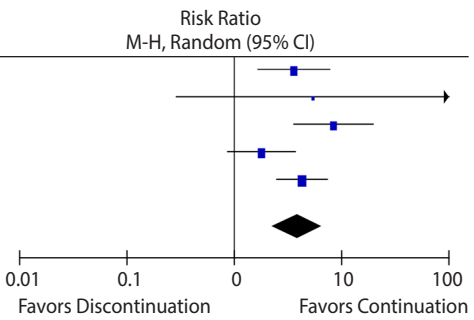
In this systematic review, we investigated and performed meta-analyses of randomized, double-blind, placebo-controlled withdrawal trials for ADHD medications. We also explored whether discontinuing any ADHD medication was associated with decreased quality of life compared with continuing this medication in patients with ADHD who had responded to medication treatments. Because previous systematic reviews and meta-analyses typically evaluated the relapse of ADHD symptoms, this meta-analysis is the first focusing on the effect of discontinuing medication on

Figure 3 (continued).

D. Patients Receiving Stimulant Medications

Study or Subgroup	Discontinuation Events	Discontinuation Total	Continuation Events	Continuation Total	Weight, %	Risk Ratio M-H, Random (95% CI)
Arnold et al 2004[38]	24	39	6	35	22.7	3.59 (1.66 to 7.75)
Biederman et al 2010[43]	2	11	0	12	3.1	5.42 (0.29 to 101.77)
Brams et al 2012[44]	45	60	5	56	20.6	8.40 (3.59 to 19.64)
Buitelaar et al 2012[45]	12	22	7	23	23.9	1.79 (0.87 to 3.70)
Coghill et al 2014[40]	52	77	12	76	29.6	4.28 (2.49 to 7.35)
Total (95% CI)		**209**		**202**	**100.0**	**3.87 (2.26 to 6.62)**
Total events	135		30			

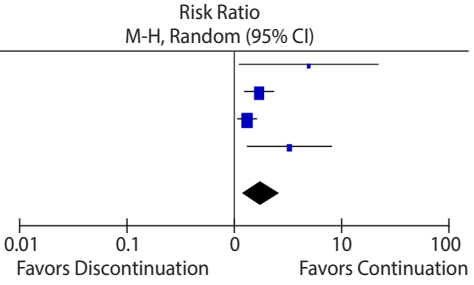
Heterogeneity: $\tau^2 = 0.18$; $\chi^2_4 = 8.19$ ($P = .08$); $I^2 = 51\%$
Test for overall effect: $z = 4.93$ ($P < .00001$)



E. Patients Receiving Nonstimulant Medications

Study or Subgroup	Discontinuation Events	Discontinuation Total	Continuation Events	Continuation Total	Weight, %	Risk Ratio M-H, Random (95% CI)
Buitelaar et al 2007[39]	10	82	2	81	6.0	4.94 (1.12 to 21.85)
Michelson et al 2004[41]	47	124	65	292	37.2	1.70 (1.25 to 2.32)
Newcorn et al 2016[42]	98	151	74	150	43.2	1.32 (1.08 to 1.61)
Upadhyaya et al 2013[46]	19	258	6	266	13.5	3.26 (1.33 to 8.04)
Total (95% CI)		**615**		**789**	**100.0**	**1.77 (1.20 to 2.62)**
Total events	174		147			

Heterogeneity: $\tau^2 = 0.08$; $\chi^2_3 = 8.37$ ($P = .04$); $I^2 = 64\%$
Test for overall effect: $z = 2.88$ ($P = .004$)



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, M-H = Mantel-Haenszel.

quality of life after symptomatic remission in patients with ADHD.

We reported that discontinuing any ADHD medication was associated with a small but statistically significant risk of reduced quality of life in patients with ADHD. Our main finding was partly supported by previous findings that showed little advantage of discontinuing medications in patients with ADHD.[7,30,31] The results of subgroup analyses also favored our preliminary finding. Despite small ESs, our results are clinically significant for patients with ADHD who experience a considerable decrease in quality of life after discontinuing medications. After discontinuing medications, regularly assessing quality of life may support decisions regarding whether treatment should be resumed for patients with ADHD.

However, with small ESs, the impact of such discontinuation on quality of life may be not considered clinically relevant for most patients with ADHD. One possible explanation for changes in quality of life observed after discontinuing medications is that medications help patients with ADHD develop better coping abilities against stressful situations. Once their symptoms have stabilized, patients could partly maintain these coping skills even after discontinuing medications. These improved and maintained coping skills might impact the quality of life in some individuals with ADHD because coping helps in maintaining stability in quality of life.[47] Our hypothesis is supported by a study[48] that demonstrated continued effects of medication after its discontinuation on quality of life even when ADHD symptoms worsened. Banaschewski et al[48] hypothesized that residual benefits associated with medications extend beyond the point of discontinuing treatment or that underlying deficits in quality of life attenuate over the course of treatment. Although quality of life is related to individuals' appraisal of their situation, it can allow clinicians to better integrate the patients' perspective into their clinical management, including adherence to pharmacologic treatments.[32] Thus, quality of life can be considered in pharmacologic interventions to direct continuing and discontinuing medication.

In adults with ADHD, the effect of discontinuing medications on quality of life was nonsignificant. Differences in environmental demands or stress between children/adolescents and adults as well as better coping abilities in response to environmental demands among adults with ADHD[7] may explain this result. Another explanation for the null effect found for adults is that adults are more likely to compensate for symptom return after discontinuing ADHD medications by increasing substance use (eg, cigarettes/nicotine, marijuana) to self-treat ADHD symptoms.[49,50] Because no studies included in our meta-analysis investigated the occurrences of substance use after discontinuing ADHD medications, we cannot exclude this possibility. Further studies are needed to investigate the relationship between discontinuing medication and increased substance use. However, substantial statistical heterogeneity within our analysis restricted to adults with ADHD was considerable ($I^2 = 63\%$). This heterogeneity may be explained by the methodological differences across the studies included in our analysis. Further studies that control for confounding

factors such as ADHD subtype or psychiatric comorbidities (eg, substance abuse) are needed to determine the association between discontinuing medication and quality of life in adults with ADHD.

Conversely, the duration of randomized withdrawal trials was relatively short in some studies, varying between 3 and 52 weeks for pre-randomization phase and between 2 and 36 weeks for randomized withdrawal phase. Although there is limited and inconsistent evidence regarding the long-term effects of medications on improving functional impairments or quality of life,[30,51] it is possible that responses related to quality of life in patients with ADHD are affected by the duration of dose increase in pre-randomization phase or duration of randomized withdrawal phase. Furthermore, patients who clearly noticed a decrease in quality of life after discontinuing medications may have dropped out during study periods. These effects may have confounded our results. Of note, a number of patients with ADHD in the studies included in this meta-analysis continued to participate in the trials after discontinuing medications, while taking placebos (Table 1).

Finally, our analysis of the secondary outcome relapse showed a statistically significant RR of 2.85 in patients with ADHD. NNH for the relapse of ADHD symptoms was 4. All subgroup analyses supported the results of the secondary outcome analysis, with moderate RR ranging from 1.77 to 3.87. However, there were substantial heterogeneities among all the analyses. One possible explanation for these heterogeneities may be the numerous methodological differences in the definition of relapse among studies covered in this meta-analysis. Another possibility is that the assessments of symptoms are sensitive to medication responses in the short term rather than responses associated with discontinuing medications.[13,14]

Several limitations of our meta-analysis need to be considered. First, as data were meta-analyzed when outcomes were reported in at least 2 studies, we were unable to conduct a meta-analysis regarding quality of life among subgroups restricted to stimulants. Second, the present meta-analysis included only published studies while excluding unpublished studies or studies without adequate statistical information. If unpublished studies were more likely to contain null findings, their inclusion would have potentially reduced the effects seen here even further. In addition, we could not explore potential publication bias because our analysis included fewer than 10 studies, which is the minimum number required to use the funnel plot (funnel plots were shown in Supplementary Figure 2). This limitation warrants future research that includes unpublished data. Third, quality of life measures used in this meta-analysis were only observer-rated measures in children and adolescents with ADHD. This limits our findings for child-age samples because of the well-recognized positive illusory bias in children with ADHD, ie, they might have an overoptimistic view of their situation.[12] Finally, the tools used to assess quality of life and symptom severity differed among the studies. This variation might relate to conflicting findings across studies included in this meta-analysis, especially with regard to our results on quality of life. Further research involving randomized withdrawal trials using ADHD-specific quality of life measures (eg, the AAQoL) or using measures of both quality of life and functional impairments are needed to further explore and confirm the utility of quality of life as an outcome of pharmacologic interventions for patients with ADHD. Moreover, research is needed to investigate the interactions and relationships among symptoms, functional impairments, and quality of life in patients with ADHD. If confirmed, these relationships and interactions may lead to an improved understanding of factors affecting quality of life in ADHD.

In summary, discontinuing ADHD medication was associated with a small but statistically significant risk of decreased quality of life in children and adolescents with ADHD. Although discontinuing ADHD medications may be dependent on patient responses,[7] our results highlight the potential clinical utility of quality of life as a tool for determining this discontinuation compared with symptom rating scales. Regular assessments regarding the overall quality of life after discontinuing medication may assist in making decisions regarding continuing the withdrawal or resumption of medications for patients with ADHD. We believe that our results will help clinicians in considering the potential risks and benefits of discontinuing medications and optimizing individualized treatments for patients with ADHD.

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Potential conflicts of interest: During the past 3 years, **Dr Tsujii** reports procuring personal fees from Janssen, Sumitomo Dainippon, Mitsubishi Tanabe, Yoshitomi, GlaxoSmithKline, Otsuka, Shionogi, and Takeda. **Dr Okada** reports procuring personal fees from Eli Lilly Japan, Teijin, Shionogi, Meiji Seika, Sawai, Janssen, Takeda, Yoshitomiyakuhin, Pfizer, Shire Japan, Mochida, Sumitomo Dainippon, and Astellas and also has received research grants from the Japan Society for the Promotion of Science; Japan Agency for Medical Research and Development; Japan Society for the Promotion of Science; Ministry of Health, Labour and Welfare; Ministry of Education, Culture, Sports, Science and Technology; and Otsuka. **Dr Usami** reports procuring personal fees from Janssen, Takeda, Shionogi, Otsuka, Takata, and Pfizer Japan not pertaining to the present study. **Dr Kuwabara** reports procuring personal fees from Meiji Seika and Otsuka. **Dr Fujita** reports procuring personal fees from Shionogi. **Dr Negoro** reports procuring personal fees from Janssen, Eli Lilly Japan, Shionogi, Shire, Otsuka, and Takeda. **Dr Iida** reports procuring personal fees from Janssen, Eli Lilly Japan, Shionogi, Shire Japan, Otsuka, Mochida, MSD KK, and Sumitomo Dainippon and has received grants from the Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; and Agency for Medical Research and Development. **Dr Saito** reports procuring personal fees from Eli Lilly Japan, Janssen, Otsuka, Sumitomo Dainippon, Shionogi, and Takeda and has received grants from the Ministry of Health, Labour and Welfare; Japan Society for the Promotion of Science; and Health Economics and Policy. **Ms Kawamura** reports no conflicts of interest to declare.

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Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
2. Willcutt EG. The prevalence of *DSM-IV* attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. 2012;9(3):490–499.
3. Thomas R, Sanders S, Doust J, et al. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics*. 2015;135(4):e994–e1001.
4. Simon V, Czobor P, Bálint S, et al. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry*. 2009;194(3):204–211.
5. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry*. 2010;10(1):67.
6. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med*. 2006;36(2):159–165.
7. National Guideline Centre (UK). Attention deficit hyperactivity disorder: diagnosis and management. National Institute for Health and Care Excellence website. https://www.nice.org.uk/guidance/ng87. Published March 2018. Accessed November 23, 2019.
8. Dalsgaard S, Østergaard SD, Leckman JF, et al. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015;385(9983):2190–2196.
9. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1(1):15020.
10. Able SL, Johnston JA, Adler LA, et al. Functional and psychosocial impairment in adults with undiagnosed ADHD. *Psychol Med*. 2007;37(1):97–107.
11. Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. *J Adolesc Health*. 2010;46(3):209–217.
12. Danckaerts M, Sonuga-Barke EJ, Banaschewski T, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *Eur Child Adolesc Psychiatry*. 2010;19(2):83–105.
13. Epstein JN, Weiss MD. Assessing treatment outcomes in attention-deficit/hyperactivity disorder: a narrative review. *Prim Care Companion CNS Disord*. 2012;14(6):11r01336.
14. Coghill DR, Banaschewski T, Soutullo C, et al. Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. *Eur Child Adolesc Psychiatry*. 2017;26(11):1283–1307.
15. Kooij JJS, Bijlenga D, Salerno L, et al. Updated European Consensus Statement on diagnosis and treatment of adult ADHD. *Eur Psychiatry*. 2019;56(1):14–34.
16. Bolea-Alamañac B, Nutt DJ, Adamou M, et al; British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(3):179–203.
17. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.
18. Wolraich M, Brown L, Brown RT, et al; Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007–1022.
19. Joseph A, Ayyagari R, Xie M, et al. Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. *Eur Child Adolesc Psychiatry*. 2017;26(8):875–897.
20. Padilha SCOS, Virtuoso S, Tonin FS, et al. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27(10):1335–1345.
21. 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. *Lancet Psychiatry*. 2018;5(9):727–738.
22. Yoshida M, Obara T, Kikuchi S, et al. Drug prescriptions for children with ADHD in Japan: a study based on health insurance claims data between 2005 and 2015. *J Atten Disord*. 2020;24(2):175–191.
23. Hales CM, Kit BK, Gu Q, et al. Trends in prescription medication use among children and adolescents—United States, 1999–2014. *JAMA*. 2018;319(19):2009–2020.
24. Renoux C, Shin JY, Dell'Aniello S, et al. Prescribing trends of attention-deficit hyperactivity disorder (ADHD) medications in UK primary care, 1995–2015. *Br J Clin Pharmacol*. 2016;82(3):858–868.
25. McCarthy S, Asherson P, Coghill D, et al. Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. *Br J Psychiatry*. 2009;194(3):273–277.
26. Wehmeier PM, Schacht A, Dittmann RW, et al. Effect of atomoxetine on quality of life and family burden: results from a randomized, placebo-controlled, double-blind study in children and adolescents with ADHD and comorbid oppositional defiant or conduct disorder. *Qual Life Res*. 2011;20(5):691–702.
27. Ingram S, Hechtman L, Morgenstern G. Outcome issues in ADHD: adolescent and adult long-term outcome. *Ment Retard Dev Disabil Res Rev*. 1999;5(3):243–250.
28. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*. 2004;113(4):762–769.
29. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics*. 2004;113(4):754–761.
30. van de Loo-Neus GH, Rommelse N, Buitelaar JK. To stop or not to stop? how long should medication treatment of attention-deficit hyperactivity disorder be extended? *Eur Neuropsychopharmacol*. 2011;21(8):584–599.
31. Buitelaar J, Asherson P, Soutullo C, et al. Differences in maintenance of response upon discontinuation across medication treatments in attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol*. 2015;25(10):1611–1621.
32. Coghill D, Danckaerts M, Sonuga-Barke E, et al; ADHD European Guidelines Group. Practitioner review: quality of life in child mental health—conceptual challenges and practical choices. *J Child Psychol Psychiatry*. 2009;50(5):544–561.
33. WHOQOL. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1995;41(10):1403–1409.
34. Ahnemark E, Di Schiena M, Fredman AC, et al. Health-related quality of life and burden of illness in adults with newly diagnosed attention-deficit/hyperactivity disorder in Sweden. *BMC Psychiatry*. 2018;18(1):223.
35. Wong ICK, Banaschewski T, Buitelaar J, et al; European ADHD Guidelines Group. Emerging challenges in pharmacotherapy research on attention-deficit hyperactivity disorder-outcome measures beyond symptom control and clinical trials. *Lancet Psychiatry*. 2019;6(6):528–537.
36. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
37. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Cochrane Training website. http://handbook.cochrane.org. 2011. Accessed November 23, 2019.
38. Arnold LE, Lindsay RL, Conners CK, et al. A double-blind, placebo-controlled withdrawal trial of dexmethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2004;14(4):542–554.
39. Buitelaar JK, Michelson D, Danckaerts M, et al. A randomized, double-blind study of continuation treatment for attention-deficit/hyperactivity disorder after 1 year. *Biol Psychiatry*. 2007;61(5):694–699.
40. Coghill DR, Banaschewski T, Lecendreux M, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder: randomized-withdrawal study design. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):647–657.e1.
41. Michelson D, Buitelaar JK, Danckaerts M, et al. Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):896–904.
42. Newcorn JH, Harpin V, Huss M, et al. Extended-release guanfacine hydrochloride in 6–17-year olds with ADHD: a randomised-withdrawal maintenance of efficacy study. *J Child Psychol Psychiatry*. 2016;57(6):717–728.
43. Biederman J, Mick E, Surman C, et al. A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol*. 2010;30(5):549–553.
44. Brams M, Weisler R, Findling RL, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomized withdrawal design. *J Clin Psychiatry*. 2012;73(7):977–983.

45. Buitelaar JK, Trott GE, Hofecker M, et al. Long-term efficacy and safety outcomes with OROS-MPH in adults with ADHD. *Int J Neuropsychopharmacol*. 2012;15(1):1–13.
46. Upadhyaya H, Ramos-Quiroga JA, Adler LA, et al. Maintenance of response after open-label treatment with atomoxetine hydrochloride in international European and non-European adult outpatients with attention-deficit/hyperactivity disorder: a placebo-controlled, randomised withdrawal study. *Eur J Psychiatry*. 2013;27(3):185–205.
47. Schwartz CE, Rapkin BD. Reconsidering the psychometrics of quality of life assessment in light of response shift and appraisal. *Health Qual Life Outcomes*. 2004;2(1):16.
48. Banaschewski T, Johnson M, Lecendreux M, et al. Health-related quality of life and functional outcomes from a randomized-withdrawal study of long-term lisdexamfetamine dimesylate treatment in children and adolescents with attention-deficit/hyperactivity disorder. *CNS Drugs*. 2014;28(12):1191–1203.
49. Osland S, Hirsch L, Pringsheim T. Smoking, alcohol and drug use in youth and adults with attention-deficit hyperactivity disorder. *BJPsych Open*. 2017;3(3):141–146.
50. McCabe SE, Dickinson K, West BT, et al. Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: a multi-cohort national study. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):479–486.
51. Fredriksen M, Halmøy A, Faraone SV, et al. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. *Eur Neuropsychopharmacol*. 2013;23(6):508–527.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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Supplementary Material

Article Title: Effect of Continuing and Discontinuing Medications on Quality of Life After Symptomatic Remission in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis

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Supplementary Table 1: Search syntax for PubMed

#	Search terms	Number of references
#1	(Attention Deficit Disorder with Hyperactivity/drug therapy[MH] OR ADHD[TIAB] OR AD/HD[TIAB] OR AD-HD[TIAB] OR ADDH[TIAB] OR attention def* [TIAB] OR "brain dysfunction"[TIAB])	34810
#2	Withholding Treatment[MH:NoExp] OR Placebo Effect[MH]	14982
#3	(drug*[TIAB] OR Pharmacotherap*[TIAB] OR medication*[TIAB] OR "Central Nervous System Stimulants"[MH] OR stimulant[TIAB] OR "non-stimulant"[TIAB] OR "Adrenergic alpha-Agonists"[MH] OR "alpha adrenergic agonist"[TIAB] OR "alpha adrenergic receptor"[TIAB] OR ”Dopamine Uptake Inhibitors”[MH] OR “dopamine reuptake inhibitor” [TIAB] OR “norepinephrine reuptake inhibitor”[TIAB] OR “dopamine releaser”[TIAB] OR "Amphetamine"[MH] OR Amphetamine*[TIAB] OR "Atomoxetine Hydrochloride"[MH] OR atomoxetine[TIAB] OR Clonidine[TW] OR Methylphenidate[MH] OR Methylphenidate[TIAB] OR Dexmethylphenidate[TIAB] OR lisdexamfetamine[TW] OR guanfacine[TW])	1758504
#4	(withdr*[TIAB] OR discontinu*[TIAB] OR abstinence[TIAB] OR avoid*[TIAB] OR ceas*[TIAB] OR cessation*[TIAB] OR remov*[TIAB] OR stop*[TIAB] OR Withhold*[TIAB] OR continu*[TIAB] OR maintenance*[TIAB])	2306248
#5	#3 AND #4	266642
#6	#2 OR #5	280599
#7	#1 AND #6	2084
#8	#7 AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[TIAB] OR placebo[TIAB] OR drug therapy[sh] OR randomly[TIAB] OR trial[TIAB] OR groups[TIAB])	
#9	#7 AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [TIAB] OR placebo [TIAB] OR clinical trials as topic [MH: noexp] OR randomly [TIAB] OR trial [ti]) NOT (animals [mh] NOT humans [mh])	621
#10	#7 AND (Meta-Analysis[ptyp] OR systematic[sb])	

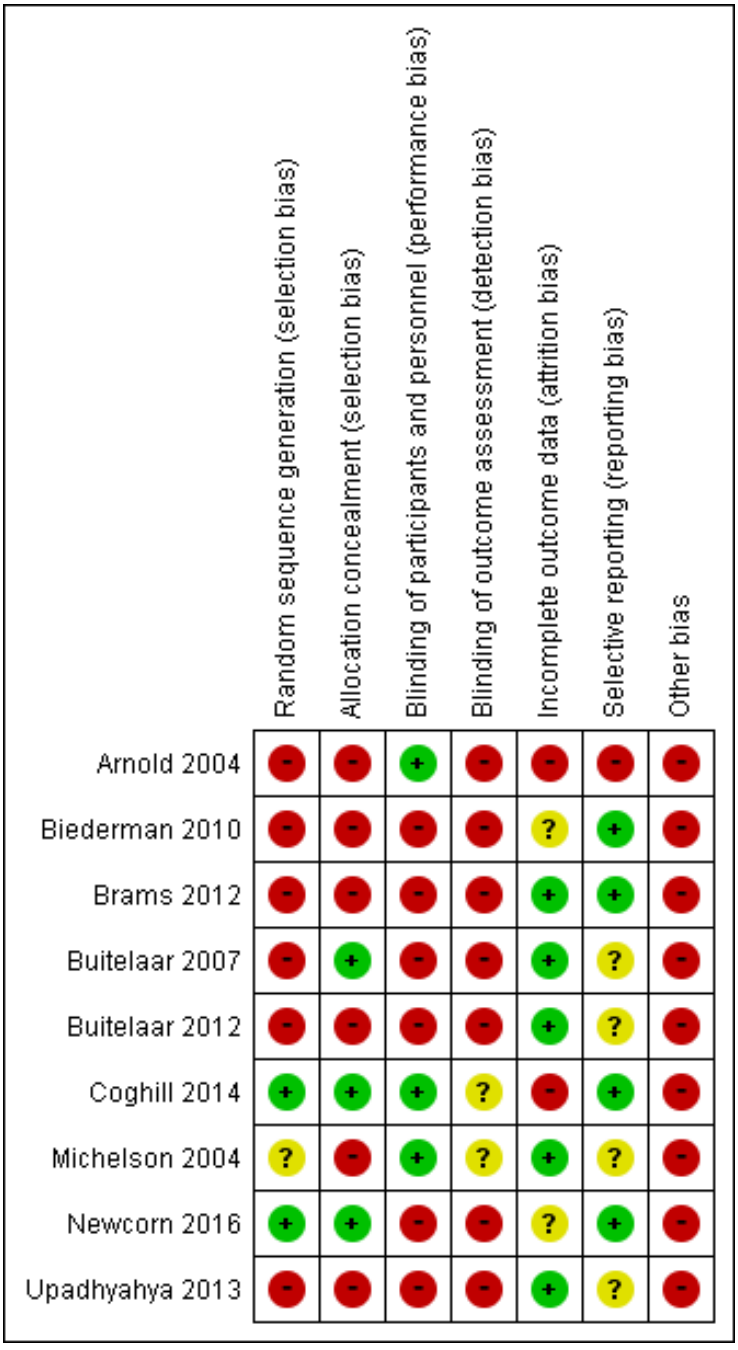
Supplementary Table 2: Search syntax for Cochrane Library

#	Search terms	Number of references
#1	[mh "Attention Deficit Disorder with Hyperactivity"/DT]	1327
#2	ADHD:ti,ab,kw	3292
#3	AD-HD:ti,ab,kw	39
#4	ADDH:ti,ab,kw	24
#5	attention def*:ti,ab,kw	8470
#6	brain dysfunction:ti,ab,kw	215
#7	#1 or #2 or #3 or #4 or #5 or #6	8942
#8	[mh ^"Withholding Treatment"]	334
#9	[mh "Placebo Effect"]	1418
#10	#8 or #9	1751
#11	drug*:ti,ab,kw	375119
#12	Pharmacotherap*:ti,ab,kw	6971
#13	medication*:ti,ab,kw	66035
#14	[mh "Central Nervous System Stimulants"]	2249
#15	stimulant:ti,ab,kw	2199
#16	non-stimulant:ti,ab,kw	52
#17	[mh "Adrenergic alpha-Agonists"]	1095
#18	alpha adrenergic agonist:ti,ab,kw	46
#19	alpha adrenergic receptor:ti,ab,kw	590
#20	[mh "Dopamine Uptake Inhibitors"]	309
#21	dopamine reuptake inhibitor:ti,ab,kw	31
#22	norepinephrine reuptake inhibitor:ti,ab,kw	329
#23	dopamine releaser:ti,ab,kw	2
#24	[mh Amphetamine]	897
#25	Amphetamine*:ti,ab,kw	1625
#26	[mh "Atomoxetine Hydrochloride"]	306
#27	[mh Clonidine]	1845
#28	Clonidine:ti,ab,kw	3539
#29	[mh Methylphenidate]	1481
#30	Methylphenidate:ti,ab,kw	2385
#31	Dexmethylphenidate:ti,ab,kw	61
#32	[mh lisdexamfetamine]	142
#33	lisdexamfetamine:ti,ab,kw	277
#34	[mh guanfacine]	153
#35	guanfacine:ti,ab,kw	280
#36	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35	409830
#37	withdr*:ti,ab,kw	35050
#38	discontinu*:ti,ab,kw	26722
#39	abstinence:ti,ab,kw	6059
#40	avoid*:ti,ab,kw	18614
#41	ceas*:ti,ab,kw	1317
#42	cessation*:ti,ab,kw	13290
#43	reduc*:ti,ab,kw	317809
#44	remov*:ti,ab,kw	24280
#45	stop*:ti,ab,kw	16446
#46	Withhold*:ti,ab,kw	876
#47	placebo:ti,ab,kw	227716
#48	continu*:ti,ab,kw	94124
#49	maintenance*:ti,ab,kw	32274
#50	#37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49	577590
#51	#36 and #50	248242
#52	#10 or #51	249121
#53	#7 and #52	3537
#54	Review	484
#55	Trials	3040

Supplementary Table 3: Search syntax for Embase databases

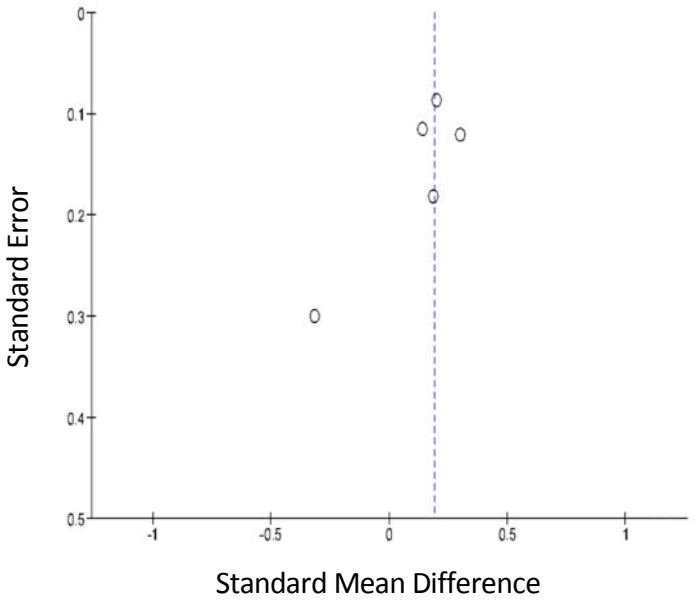
#	Search terms	Number of references
#1	attention deficit disorder'/exp/dm_dt	11,077
#2	adhd:ti,ab,kw	30,930
#3	ad hd':ti,ab,kw	470
#4	addh:ti,ab,kw	145
#5	attention* def*':ti,ab,kw	35,311
#6	brain dysfunction*':ti,ab,kw	4,509
#7	#1 or #2 or #3 or #4 or #5 or #6	51,651
#8	drug withdrawal'/de	164,504
#9	placebo effect'/de	5,088
#10	#8 or #9	169,506
#11	drug therapy'/de	574,939
#12	drug*':ti,ab,kw	2,057,126
#13	pharmacotherap*':ti,ab,kw	50,027
#14	medication*':ti,ab,kw	444,369
#15	amphetamine'/de	33,926
#16	amphetamine*':ti,ab,kw	29,994
#17	atomoxetine'/de	4,849
#18	atomoxetin*':ti,ab,kw	2,254
#19	clonidine'/de	40,405
#20	clonidine':ti,ab,kw	17,880
#21	methylphenidate'/de	20,545
#22	methylphenidate':ti,ab,kw	9,160
#23	dexmethylphenidate'/de	667
#24	dexmethylphenidate':ti,ab,kw	126
#25	lisdexamfetamine'/de	1,111
#26	lisdexamfetamine':ti,ab,kw	543
#27	guanfacine'/de	3,034
#28	guanfacine':ti,ab,kw	1,173
#29	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28	2,810,937
#30	withdr*':ti,ab,kw	168,127
#31	discontinu*':ti,ab,kw	176,476
#32	abstinence':ti,ab,kw	26,846
#33	avoid*':ti,ab,kw	459,593
#34	ceas*':ti,ab,kw	28,175
#35	cessation*':ti,ab,kw	88,143
#36	reduc*':ti,ab,kw	3,810,259
#37	remov*':ti,ab,kw	721,561
#38	stop*':ti,ab,kw	174,091
#39	withhold*':ti,ab,kw	9,203
#40	placebo':ti,ab,kw	275,346
#41	continu*':ti,ab,kw	1,221,297
#42	maintenance*':ti,ab,kw	328,184
#43	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	6,369,130
#44	#29 and #43	927,809
#45	#10 or #44	1,050,842
#46	#7 and #45	7,594
#47	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,286,136
#48	#46 and #47	3,085
#49	cohort analysis'/de OR 'longitudinal study'/de OR 'prospective study'/de OR 'follow up'/de OR cohort*:ti,ab,kw	2,343,573
#50	#46 and #49	1,061
#51	#46 AND #47 AND [embase]/lim	2,831
#52	#46 AND #49 AND [embase]/lim	1,012
#53	#51 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	984
#54	#52 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	526

Supplementary Figure 1: Risk of bias summary



Supplementary Figure 2: Funnel plot of publication bias for the comparison between discontinuing and continuing ADHD medications on the quality of life after symptomatic remission

A. Studies measured quality of life



B. Studies reported relapse