National Institute for Health and Care Excellence

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Attention deficit hyperactivity disorder (update)

[I]Withdrawal from pharmacological treatment and drug holidays

NICE guideline NG87

Intervention evidence review

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This evidence review was developed by the National Guideline Centre

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1 Withdrawal from pharmacological treatment and drug holidays

Introduction

A common question often asked to healthcare professionals about ADHD medication, particularly about stimulants, is the impact of a stopping medication or taking a 'drug holiday'. A drug holiday is an agreed cessation of medication for a period of time. Questions can be directly related to the impact of cessation on ADHD symptoms both in the short and long term but also on the safety issues around stopping and then restarting medication. There is a lot of confusing information in the media and on the internet about whether it is a good thing to have a break from medication in holidays or at times (for example, weekends) when there is perhaps a reduced importance placed on the benefits that medication can provide in supporting concentration and focus at school or at work. For parents or carers of children with ADHD they may see this is an opportunity for children to catch up on growth or to simply be themselves.

This chapter includes two reviews that evaluate the clinical effects of withdrawing pharmacological treatment for ADHD to inform decisions between people with ADHD, their families and carers, and their clinicians about taking a break or stopping pharmacological treatment. The first review (section 1.1) evaluates the effect of withdrawing pharmacological treatment in people with ADHD who have experienced a positive response to an adequate trial of pharmacological treatment. The second review (section 1.2) evaluates the effect of a structured drug holiday.

This review should be read alongside the review on managing medication (for more information, see evidence report H on managing treatment). This is a qualitative review that explored the issues that are important to people with ADHD when considering whether to start, adjust, or discontinue treatment for ADHD to inform discussions between clinicians and people with ADHD and supported the committee's decision making here.

1.1 Review question: What are the clinical effects of withdrawing from pharmacological treatment for ADHD?

1.1.1 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Children and adults young people with ADHD who have received an adequate course of treatment
Intervention	Discontinuing any ADHD medication
Comparison	Continuing any ADHD medication
Outcomes	**Critical** • Quality of life [continuous] • ADHD symptoms [continuous] • Clinical Global Impressions (CGI) scale (worse or much worse) [dichotomous] **Important**

	• Serious adverse events (all) [dichotomous] • Behavioural (children)/Functional (adults) measures [continuous] • Emotional dysregulation [continuous] • Academic outcomes (children) [continuous] • Substance use (alcohol and drug use) [dichotomous] • Self-harm [dichotomous]
Study design	RCTs, systematic reviews of RCTs. Blinded and open label trials to be included.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[29] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.1.3 Clinical evidence

1.1.3.1 Included studies

(a) Eleven studies (based on 17 publication) were included in the review; [1,3,5,7,9-11,13,19,22,27,30,35-37,43,45] these are summarised in Table 2 and Table 3 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 4, Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

(b) Outcome varies from protocol; rather than number of people who were rated as being 'much worse' or 'very much worse', this outcome is the number of people who improved following continuation or withdrawal from treatment.

Table 5, Table 6, Table 7, Table 8, Table 9, Table 10 and Table 11).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

In one study (Wolraich 2001) it was not clear whether prior to randomisation participants had received an adequate course of methylphenidate and how many participants had experienced a positive response to methylphenidate. The paper stated that 67% of participants had previously been receiving methylphenidate for 1 month or longer as prescribed by their personal physician. The remaining participants were titrated to 'optimal dose' of methylphenidate, however it was not stated if all of these participants experienced a positive response to treatment, and no participants were excluded for non-response. As the majority of participants were receiving methylphenidate prior to the trial, and had opted to enter a further trial of methylphenidate, it was assumed that the majority of participants had experienced a positive response to methylphenidate prior to randomisation, therefore this trial was included but downgraded for indirectness and analysed separately.

1.1.3.2 Excluded studies

See the excluded studies list in appendix I.

1.1.3.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review for children and young people

Study	Intervention and comparison	Population	Outcomes	Comments
Coghill 2014[13]; Banachews	Stopping Lisdexamphetamine dimesylate (placebo)	Age stratum 5 to 18	Quality of life at 6 weeks	All participants had at least moderate severity

Study	Intervention and comparison	Population	Outcomes	Comments
ki 2014[3]	vs continuing Lisdexamphetamine dimesylate	Children (6-17 years; mean = 11 years, SD = 2.6) who had received Lisdexamphetamine dimesylate. Non-responders to amphetamines were excluded from the outset (N = 157). Original trial was 4 weeks of dose optimisation followed by 20-52 weeks of dose maintenance and a 2 week fixed dose period.	ADHD symptoms at 6 weeks Behaviour at 6 weeks	ADHD, defined as an ADHD-RS-IV score >/=28 at baseline of the original study. (moderate severity)
Michelson 2004[27], Buitelaar 2007[9], Hazell 2006[19]	Stopping Atomoxetine (placebo) vs. continuing Atomoxetine	Age stratum 5 to 18 Children (6-15 years; mean = 10.3, SD = 2.3) who were responders to atomoxetine during an earlier phase of the trial. Data reported separately for participants who received treatment for 3-months and those who received treatment for 12-months (overlap between groups) (N = 416)	ADHD symptoms at 6- and 9-months Relapse at 6- and 9-months (≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S) Adverse events at 9-months (only for children treated for 3-months)	Majority of population combined subtype (73%); baseline ADHD-RS score = 15.8)
Prince 2000[30]	Stopping Nortriptyline (placebo) vs. Continuing Nortriptyline	Age stratum 5 to 18 Children (6-17 years; mean = 9.8, SD = 9.2) who were responders to nortriptyline over 6 weeks during an earlier phase of the trial (N = 23)	CGI-I at 3 weeks	59% with comorbid oppositional disorder, 13% with conduct disorder. No baseline symptom severity reported
Wilens 2006[43]	Stopping OROS methylphenidate (placebo) vs. continuing OROS methylphenidate	Age stratum 5 to 18 Children (13-18 years; mean = 14.6, SD = 1.5) who were responders to OROS methylphenidate over 4-weeks during an earlier phase of the trial (N = 177)	ADHD symptoms at 2 weeks CGI-I at 2 weeks	All with a CGAS score of 41 – 70, ADHD-RS (Inv) score prior to treatment = 31.26 (all participants, including those excluded from the withdrawal phase)
Wolraich 2001[45]	Stopping OROS methylphenidate	Age stratum 5 to 18	ADHD symptoms at 2	Unclear if participants

Study	Intervention and comparison	Population	Outcomes	Comments
	(placebo) vs. continuing OROS methylphenidate	Children (6-12 years; mean = 9, SD = 1.8) who had either previously been prescribed MPH (67%; either immediate or modified release MPH) or OROS-MPH was titrated to 'optimal dose' prior to the trial (N=197)	weeks CGI-I (mean) at 2 weeks	received an adequate trial of OROS MPH prior to the study; unclear how many participants experienced a positive response to MPH prior to withdrawal

Table 3: Summary of included studies for adults

Study	Intervention and comparison	Population	Outcomes	Comments
Biederman 2010[5]	Stopping OROS methylphenidate (placebo) vs. continuing OROS methylphenidate	Adults (19-60 years; mean = 35, SD = 8.8) who had previously responded to OROS methylphenidate over >6 months in two earlier phases of the trial (N = 23)	Relapse at 4 weeks (defined as CGI-I score of 6 or 7, or a worsening in the AISRS score so that improvement was <15% from baseline for 2 consecutive visits)	All participants were on a stable medication regimen for at least 3 months and had a CGI-Severity score of 3 or lower
Brams 2012[7]	Stopping Lisdexamphetamine dimesylate (placebo) vs continuing Lisdexamphetamine dimesylate	Adults (18-55 years; mean = 35.8, SD = 11.15) who had received Lisdexamphetamine dimesylate for ≥6 months with an acceptable safety profile (N = 116)	Symptoms of ADHD at 6 weeks	Baseline ADHD-RS-IV scores <22 and CGI-S ratings or 1-3
Buitelaar 2012[10]	Stopping OROS methylphenidate (placebo) vs. continuing OROS methylphenidate	Adults (18-65 years; mean = 36 years, SD = 10) who had received OROS methylphenidate for ≥1 year, including during an earlier phase of the trial (N = 45)	Quality of life at 4 weeks ADHD symptoms at 4 weeks Relapse at 4 weeks (≥50% increase in symptoms from baseline on the CAARS:O-SV) Function at 4 weeks	53% of sample were combined subtype, baseline CAARS: O-SV = 12.1 in stopping group and 16.5 in continuing group
Huss 2014[22]	Stopping ER-methylphenidate (placebo) vs. continuing ER-	Adults (18-60 years; mean = 35.4 years, SD = 11.38) who had	ADHD symptoms at 6-months Relapse at 6-months (≥30%	No severity information; all population mean ADHD-RS at

Study	Intervention and comparison	Population	Outcomes	Comments
	methylphenidate	experienced a positive response to ER methylphenidate over 5-14 weeks (depending on group membership in earlier phases of the trial) (N = 489)	increase in symptoms AND who score was <30% improvement since the beginning of receiving treatment) Adverse events at 6-months	baseline (including those excluded from the withdrawal phase = 39.2; no SD reported) (unclear severity)
Upadhyaya 2013[35], Adler 2014[1], Camporeale 2013[11], Upadhyaya 2015[36]	Stopping atomoxetine (placebo) vs. continuing Atomoxetine	Adults (18-50 years; mean = 33.1 years, SD = 9.4) who responded to atomoxetine over up to 6-months during an earlier phase of the trial (N = 524)	Quality of life at 25 weeks ADHD symptoms at 25 weeks Adverse outcomes at 25 weeks Self-harm (suicide-related events, including suicidal ideation and suicidal behaviour) at 25 weeks	a score of >/=20 on CAARS-Inv-SV 18-item total score; a CGI-S rating of >/=4 (moderately ill) at the first two visits (moderate severity)
Waxmonsky 2014[37]	Stopping Lisdexamphetamine dimesylate (placebo) vs. continuing Lisdexamphetamine dimesylate	Adults (mean age = 40.7 years, SD = 5.5) who were responders to Lisdexamphetamine dimesylate over 4-5 weeks in an earlier phase of the trial (N = 19)	CGI-I at 30 days	Participants were required to have a score of ≥28 on the ADHD-RS along with at least moderate severity on the CGI-S (moderate severity) *note: half of all participants experienced a 1-week break from treatment prior to randomisation into the withdrawal phase. Length of withdrawal phase is unclear (states 30 days, but diagram implies may be longer)

See appendix D for full evidence tables.

1.1.3.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Stopping methylphenidate vs. continuing methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing MPH	Risk difference with withdrawal from MPH (95% CI)
ADHD symptoms - Total symptoms; self-report Conners Wells Adolescent Self-Report of Symptoms Scale: 0-261. High is poor outcome	177 (1 study) 2 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms - total symptoms; self-report in the control groups was 57.57	The mean ADHD symptoms - total symptoms; self-report in the intervention groups was 17.75 higher (3.94 to 31.56 higher)
ADHD symptoms - Total symptoms; parent rated ADHD-RS: Parent rated; 0-54. High is poor outcome	177 (1 study) 2 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms - total symptoms; parent rated in the control groups was 16.65	The mean ADHD symptoms - total symptoms; parent rated in the intervention groups was 4.19 higher (0.55 to 7.83 higher)
CGI-I (number of people who are much improved or very much improved (score 1 or 2)	177 (1 study) 2 weeks	MODERATE[b] due to indirectness	RR 0.6 (0.42 to 0.87)	517 per 1000	207 fewer per 1000 (from 67 fewer to 300 fewer)

(c) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
(d) Outcome varies from protocol; rather than number of people who were rated as being 'much worse' or 'very much worse', this outcome is the number of people who improved following continuation or withdrawal from treatment.

Table 5: Clinical evidence summary: Stopping methylphenidate vs. continuing methylphenidate in participants who may not have all experienced a positive response to methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing MPH	Risk difference with withdrawal from MPH (95% CI)

ADHD symptoms - Inattention/overactivity; parent rated IOWA conners: 0-15. High is poor outcome	192 (1 study) 4 weeks	LOW[a,b] due to risk of bias, indirectness		The mean ADHD symptoms - inattention/overactivity; parent rated in the control groups was 6.17	The mean ADHD symptoms - inattention/overactivity; parent rated in the intervention groups was 3.94 higher (2.93 to 4.95 higher)
ADHD symptoms - Inattention/overactivity; teacher rated IOWA conners: 0-15. High is poor outcome	192 (1 study) 4 weeks	LOW[a,b] due to risk of bias, indirectness		The mean ADHD symptoms - inattention/overactivity; teacher rated in the control groups was 6.35	The mean ADHD symptoms - inattention/overactivity; teacher rated in the intervention groups was 3.42 higher (2.24 to 4.60 higher)
ADHD symptoms - Oppositional/defiant; parent rated IOWA conners: 0-15. High is poor outcome	192 (1 study) 4 weeks	LOW[a,b] due to risk of bias, indirectness		The mean ADHD symptoms - oppositional/defiant; parent rated in the control groups was 4.98	The mean ADHD symptoms - oppositional/defiant; parent rated in the intervention groups was 3.62 higher (2.39 to 4.85 higher)
ADHD symptoms - Oppositional/defiant; teacher rated IOWA conners: 0-15. High is poor outcome	192 (1 study) 4 weeks	LOW[a,b] due to risk of bias, indirectness		The mean ADHD symptoms (1-2 weeks) - oppositional/defiant; teacher rated in the control groups was 2.5	The mean ADHD symptoms (1-2 weeks) - oppositional/defiant; teacher rated in the intervention groups was 2.88 higher (1.61 to 4.15 higher)
CGI-I Mean score on the CGI-I. Scale from: 1 to 7. High is good outcome	192 (1 study) 4 weeks	LOW[a,b] due to risk of bias, indirectness			The mean CGI-I in the intervention groups was 1.71 lower (2.15 to 1.27 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.

1.1.3.5 Evidence for withdrawing Atomoxetine

Table 6: Clinical evidence summary: Stopping atomoxetine vs. continuing atomoxetine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing ATX	Risk difference with withdrawal from ATX (95% CI)

ADHD symptoms (Treatment for 3m) Change in ADHD-RS-IV. Scale from: 0 to 54	413 (1 study) 9 months	MODERATE[a] due to imprecision		The mean ADHD symptoms (treatment for 3m) in the control groups was 6.8	The mean ADHD symptoms (treatment for 3m) in the intervention groups was 5.5 higher (2.53 to 8.47 higher)
ADHD symptoms - Treatment for 12m change in ADHD-RS-IV. Scale from: 0 to 54	158 (1 study) 6 months	MODERATE[a] due to imprecision		The mean ADHD symptoms (treatment for 12m) in the control groups was 1.7	The mean ADHD symptoms (treatment for 12m) in the intervention groups was 6.1 higher (2.72 to 9.48 higher)
ADHD symptoms (relapse; treatment for 3m) Number of people who 'relapsed'; defined by ≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S	415 (1 study) 9 months	MODERATE[b] due to indirectness	RR 1.69 (1.3 to 2.19)	284 per 1000	196 more per 1000 (from 85 more to 338 more)
ADHD symptoms (relapse; treatment for 12m) Number of people who 'relapsed'; defined by ≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S	163 (1 study) 6 months	LOW[a,b] due to indirectness, imprecision	RR 2.63 (1.09 to 6.39)	74 per 1000	121 more per 1000 (from 7 more to 399 more)
Adverse outcomes Number of participants with at least 1 new or worsened adverse event	415 (1 study) 9 months	LOW[a,c] due to risk of bias, imprecision	RR 0.82 (0.68 to 0.99)	654 per 1000	118 fewer per 1000 (from 7 fewer to 209 fewer)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.1.3.6 Evidence for withdrawing Lisdexamphetamine

Table 7: Clinical evidence summary: Stopping lisdexamphetamine vs. continuing lisdexamphetamine

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with continuing Lisdex	Risk difference with withdrawal from Lisdex (95% CI)
ADHD symptoms change in ADHD-RS-IV. Scale from: 0 to 54. High is poor outcome	146 (1 study) 6 weeks	VERY LOW[a,b] due to risk of bias, indirectness		The mean ADHD symptoms in the control groups was 1.9	The mean ADHD symptoms in the intervention groups was 12.6 higher (9.81 to 15.39 higher)
Behaviour at <3 months Weiss functional impairment rating scale (Parent report) (WFIRS-P) [assesses function in previous 4 weeks. Scale from: 0 to 3. High is poor outcome	128 (1 study) 6 weeks	LOW[a,b] due to risk of bias, imprecision		The mean behaviour score in the control groups was 0.58	The mean behaviour score in the intervention groups was 0.13 higher (0.01 to 0.25 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1.1.3.7 Evidence for withdrawing Nortriptyline

Table 8: Clinical evidence summary: Stopping Nortriptyline vs. continuing Nortriptyline

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing nortriptyline	Risk difference with withdrawal from nortriptyline (95% CI)
CGI-I The number of people who are much improved or very much improved; score of 1-2	23 (1 study) 3 weeks	LOW[a,b] due to risk of bias, imprecision	RR 0.34 (0.12 to 0.98)	727 per 1000	480 fewer per 1000 (from 15 fewer to 640 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1.1.4 Evidence in adults

1.1.4.1 Evidence for withdrawing methylphenidate

Table 9: Clinical evidence summary: Stopping methylphenidate vs. continuing methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing MPH	Risk difference with withdrawal from MPH (95% CI)
Health related quality of life Change in Q-LES-Q (short form). Scale from: ? to ?. Assume that high is good outcome, but unclear	45 (1 study) 4 weeks	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision		The mean health related quality of life in the control groups was -6.5 1	The mean health related quality of life in the intervention groups was 3.8 higher (3.17 lower to 10.77 higher)
ADHD symptoms Change in CAARS:S-SV total (self-reported) . Scale from: 0 to 84. High is poor outcome	45 (1 study) 4 weeks	LOW[b,c] due to risk of bias, indirectness		The mean ADHD symptoms in the control groups was 4.4	The mean ADHD symptoms in the intervention groups was 0.4 lower (7.39 lower to 6.59 higher)
ADHD symptoms (relapse) the number of patients who relapse (defined as ≥50% increase in symptoms from baseline on the CAARS:O-SV in one study; and CGI-I score of 'much worse' or 'very much worse' or a worsening in the AISRS score so that relative improvement relative to baseline severity was <15% improvement for 2 consecutive visits by the second study)	68 (2 studies) 4 weeks	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RR 1.7 (0.73 to 3.93)	171 per 1000	120 more per 1000 (from 46 fewer to 502 more)
ADHD symptoms (relapse) Number of patients who experienced a ≥30% increase in ADHD-RS and whose score was <30% improvement	467 (1 study) 6 months	MODERATE[c] due to indirectness	RR 2.33 (1.77 to 3.06)	213 per 1000	283 more per 1000 (from 164 more to 439 more)

since the beginning of all of the trial phases					
Behaviour Change in function (Sheehan disability scale). Scale from: 0 to 30. High is poor outcome	45 (1 study) 4 weeks	VERY LOW[c,d] due to indirectness, imprecision		The mean behaviour in the control groups was 2.2	The mean behaviour in the intervention groups was 0.6 lower (4.87 lower to 3.67 higher)
Adverse outcomes Number of patients who experienced any adverse event	482 (1 study) 6 months	LOW[b,c] due to risk of bias, indirectness	RR 0.67 (0.52 to 0.86)	546 per 1000	180 fewer per 1000 (from 76 fewer to 262 fewer)

(a) Unclear if participants' score were transformed into a percentage, or if raw scores were used (range of raw scores is 14-70).
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(c) Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes.
(d) Downgraded by 1 increment if the confidence interval crossed 1MID or by 2 increments if the confidence interval crossed both MIDs.

1.1.4.2 Evidence for withdrawing Atomoxetine

Table 10: Clinical evidence summary: Stopping Atomoxetine vs. continuing Atomoxetine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing ATX	Risk difference with withdrawal from ATX (95% CI)
Health related quality of life EQ-5D. Scale from: 0 to 1. High is good outcome	524 (1 study) 25 weeks	HIGH		The mean health related quality of life in the control groups was 0.9	The mean health related quality of life in the intervention groups was 0 higher (0.03 lower to 0.03 higher)
ADHD symptoms CAARS (self-report). Scale from: 0 to 18. High is poor outcome	524 (1 study) 25 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms in the control groups was	The mean ADHD symptoms in the intervention groups was 2.6 higher

				14.1	(0.98 to 4.22 higher)
ADHD symptoms CAARS (carer-report). Scale from: 0 to 18. High is poor outcome	524 (1 study) 25 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms in the control groups was 16.2	The mean ADHD symptoms in the intervention groups was 1.7 higher (0.06 lower to 3.46 higher)
Adverse outcomes Number of patients experiencing a treatment-related adverse event	524 (1 study) 25 weeks	LOW[a,b] due to indirectness, imprecision	RR 0.8 (0.65 to 0.98)	470 per 1000	94 fewer per 1000 (from 9 fewer to 164 fewer)
Self-harm Number of participants experiencing Suicide-related events (including suicidal ideation and suicidal behaviour)	524 (1 study) 25 weeks	LOW[b,c] due to risk of bias, indirectness	RR 0.52 (0.13 to 2.04)	23 per 1000	11 fewer per 1000 (from 20 fewer to 23 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.1.4.3 Evidence for withdrawing Lisdexamphetamine

Table 11: Stopping lisdexamphetamine vs continuing lisdexamphetamine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing Lisdex	Risk difference with withdrawal from Lisdex (95% CI)
ADHD symptoms Change in ADHD-RS-IV. Scale from: 0 to 54. High is poor outcome	116 (1 study) 4 weeks	MODERATE[a] due to indirectness		The mean ADHD symptoms in the control groups was 1.6	The mean ADHD symptoms in the intervention groups was 15.2 higher (14.7 to 15.7 higher)
CGI-I	19	VERY LOW[b,c]	RR 0.39	778 per 1000	474 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuing Lisdex	Risk difference with withdrawal from Lisdex (95% CI)
number of people who are 'much improved' or 'very much improved' (i.e. score of 1 or 2)	(1 study) 4 weeks	due to risk of bias, imprecision	(0.14 to 1.06)		(from 669 fewer to 47 more)

(a) Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

1.1.5 Economic evidence

1.1.5.1 Included studies

No relevant health economic studies were identified.

1.1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.1.6 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.1.7 Evidence statements

1.1.7.1 Clinical evidence statements

Children and young people under the age of 18

1.1.7.1.1 Evidence for stopping methylphenidate vs. continuing methylphenidate

- No evidence was identified for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, behaviour outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important harm of withdrawal for ADHD symptoms total (PT self-rated; 1 study moderate quality) (PT parent rated; 1 study moderate quality) CGI scale (PT; 1 study moderate quality) at two weeks.

1.1.7.1.2 Evidence for stopping methylphenidate vs. continuing methylphenidate in participants who may not have all experienced a positive response to methylphenidate

- No evidence was identified for quality of life, ADHD hyperactivity symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important harm of withdrawal for ADHD inattention/over activity symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality), behavioural outcomes (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality) and CGI scale (PT; 1 study low quality) at four weeks.

1.1.7.1.3 Evidence for stopping atomoxetine vs. continuing atomoxetine

- No evidence was identified for quality of life, clinical global impression scale, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, emotional dysregulation, behaviour outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit of withdrawal for adverse events (PT; 1 study low quality).
- There was a clinically important harm of withdrawal for ADHD symptoms total with children who had been receiving treatment for 3-months (PT investigator rated; 1 study moderate quality), ADHD symptoms total children who had been receiving treatment for

12-months (PT investigator rated; 1 study moderate quality) and the number of people who relapsed at 9 months (for children receiving treatment for 3-months) (PT; 1 study moderate quality) and 6 months (for children receiving treatment for 12-months) (PT; 1 study low quality).

1.1.7.1.4 Evidence for stopping lisdexamphetamine vs continuing lisdexamphetamine

- No evidence was identified for quality of life, CGI scale, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits of withdrawal for behaviour outcomes (PT parent rated; 1 study low quality) at 6 weeks.
- There was a clinically important harm of withdrawal for ADHD symptoms (PT investigator-rated; 1 study very low quality) at 6 weeks.

1.1.7.1.5 Evidence for stopping Nortriptyline vs. continuing Nortriptyline

- No evidence was identified for quality of life, ADHD symptoms total, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, behaviour outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important harm of withdrawal for CGI scale (PT; 1 study low quality) at 3 weeks.

Adults over the age of 18

1.1.7.1.6 Evidence for stopping methylphenidate vs. continuing methylphenidate

- No evidence was identified for CGI scale, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit of withdrawal for adverse outcomes (PT; 1 study low quality).
- There were no clinically important benefits of withdrawal for quality of life (PT; 1 study very low quality), ADHD symptoms total (PT self-rated; 1 study low quality) and behaviour outcomes (PT; 1 study very low quality) at 4 weeks.
- There was a clinically important harm of withdrawal for ADHD symptoms total on those who relapse at 4 weeks (PT; 2 studies very low quality) and 6 months (PT; 1 study moderate quality).

1.1.7.1.7 Evidence for stopping Atomoxetine vs. continuing Atomoxetine

- No evidence was identified for CGI scale, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, emotional dysregulation, behaviour outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit of withdrawal for adverse events (PT; 1 study low quality) after 25 weeks.
- There were no clinically important benefits of withdrawal for quality of life (PT; 1 study high quality), ADHD symptoms total (PT self-rated; 1 study moderate quality) (PT carer-rated; 1 study moderate quality) and self-harm (PT; 1 study low quality) after 25 weeks.

1.1.7.1.8 Evidence for stopping lisdexamphetamine vs continuing lisdexamphetamine

- No evidence was identified for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, behaviour outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important harm of withdrawal for ADHD symptoms total (PT; 1 study moderate quality) and CGI scale (PT; 1 study very low quality) after 4 weeks.

1.1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.2 Review question: What are the clinical effects of 'drug holidays' from pharmacological treatment for ADHD?

1.2.1 PICO table

For full details see the review protocol in appendix A.

Table 12: PICO characteristics of review question

Population	Children, young people and adults with ADHD
Intervention	Holiday from pharmacological treatment (stopping and restarting treatment at least once prior to follow-up)
Comparison	Continuing pharmacological treatment
Outcomes	Outcomes to be assessed at a short duration (up to 3 months) and a long duration (>3 months) **Critical** • Quality of life [continuous] • ADHD symptoms [continuous] • CGI scale (much worse or very much worse) [dichotomous] **Important** • Reduction in adverse outcomes [dichotomous] • Serious adverse events (all) [dichotomous] • Behavioural (children)/Functional (adults) measures [continuous] • Emotional dysregulation [continuous] • Academic outcomes (children) [continuous] • Substance use (alcohol and drug use) [dichotomous] • Self-harm [dichotomous]
Study design	RCTs, systematic reviews of RCTs. Blinded and open label trials to be included.

The committee were interested in evaluating the clinical effects of 'drug holidays' from pharmacological treatment for ADHD. The committee were aware that children, young people and adults with ADHD may frequently choose to take breaks from pharmacological treatment, which may vary from very short breaks (for example, not taking medication at weekends) to longer breaks (for example not taking medication during school holidays. In this review the committee were interested in knowing whether taking a break from treatment was associated with any clinical harms or benefits after restarting treatment (the effects of

stopping treatment as experienced prior to restarting are covered elsewhere: see section 1.1). The committee were interested in studies that evaluated the impact of drug holidays in the short term (for example, after a single break) as well as in the long-term (after multiple breaks).

1.2.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[29] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.2.3 Clinical evidence

1.2.3.1 Included studies

One study was included in the review;[25] this is summarised in Table 13 below. This blinded RCT conducted with children compared the clinical effects of stopping pharmacological treatment at weekends over a 4 week period. Evidence from this study is summarised in the clinical evidence summary below (Table 14).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.2.3.2 Excluded studies

See the excluded studies list in appendix I.

1.2.3.3 Summary of clinical studies included in the evidence review

Table 13: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Martins 2004[25]	Methylphenidate with placebo taken at weekend (2 days) vs. methylphenidate for 7 days a week. Intervention continued for 4 weeks.	Boys (6-14 years) N = 40 Brazil ADHD severity not stated	ADHD symptoms during the final weekend of the trial (parent-rated) or during the first day back at school after the final weekend (after 4 weeks, teacher-rated); Number of adverse events during the final weekend of the trial (after 4 weeks, parent-rated)	All effect estimates have been calculated from alternative data provided in the report (F or t value and sample size)

See appendix D for full evidence tables.

1.2.3.4 Quality assessment of clinical studies included in the evidence review

Table 14: Clinical evidence summary: Weekend breaks from treatment vs 7-day treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 7 day treatment	Risk difference with Weekend breaks (95% CI)
ADHD symptoms - Parent rated (symptoms over the final weekend) Conners Abbreviated Rating Scale. Scale from: 0 to 30; higher is worse outcome	40 (1 study) 4 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean ADHD symptoms in the control groups was not reported[a]	The mean ADHD symptoms over the final weekend (parent rated) in the intervention groups was 0.26 standard deviations lower (0.87 lower to 0.34 higher)
ADHD symptoms - Teacher rated (symptoms on the first day back at school after the final weekend) Conners Abbreviated Rating Scale. Scale from: 0 to 30; higher is worse outcome	40 (1 study) 4 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean ADHD symptoms in the control groups was not reported[a]	The mean ADHD symptoms on the first day back at school after the final weekend (teacher rated) in the intervention groups was 0 standard deviations higher (0.6 lower to 0.61 higher)
Number of minor adverse events on the final weekend of the trial Barkley's side effect rating scale. Scale from: 0 to 9; higher is worse outcome	40 (1 study) 4 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean number of adverse events on in the control groups was not reported[a]	The mean number of adverse events on the final weekend of the trial in the intervention groups was 0.45 standard deviations lower (1.06 lower to 0.16 higher)

(a) Raw mean scores for each group are not reported.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(c) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

1.2.4 Economic evidence

1.2.4.1 Included studies

No relevant health economic studies were identified.

1.2.4.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.2.5 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.2.6 Evidence statements

1.2.6.1 Clinical evidence statements

1.2.6.1.1 Children aged 5-18

Weekend breaks from treatment vs 7-day treatment

No evidence for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, clinical global impression scale, discontinuation due to side effects, serious adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.

There was a clinical benefit of drug holidays for parent rated ADHD symptoms total recorded over the final weekend after 4 weeks of intervention (1 study very low quality) and minor adverse events on the final weekend of the trial after 4 weeks of intervention (1 study, very low quality).

There was no clinical difference for teacher rated ADHD symptoms total on the first day back at school after the final weekend after 4 weeks of intervention (1 study very low quality).

1.2.6.2 Health economic evidence statements

No relevant health economic studies were identified.

1.3 The committee's discussion of the evidence

1.3.1 Withdrawal from pharmacological treatment

1.3.1.1 Interpreting the evidence

1.3.1.1.1 The outcomes that matter most

The guideline committee identified health-related quality of life, symptoms of ADHD (as rated by the person with ADHD, parents and carers, teachers, and investigators) and the CGI-I, as critical outcomes for evaluating the potential effects of withdrawing pharmacological treatment for ADHD. The committee also considered reduction in adverse outcomes, serious

adverse events, behaviour/function, emotional dysregulation, academic outcomes, substance use, and self-harm to be important outcomes.

The committee were interested in whether withdrawing treatment would result in any clinical harm or clinical benefit across the population of people with ADHD, as well as whether withdrawal would demonstrate no clinical difference compared to continuing (equivalence). Furthermore, the committee were interested in considering the size of the effect, as well as absolute numbers of people with ADHD who experienced the outcome. The committee believed that this information would help to guide clinicians to discuss the potential risks and benefits of withdrawing from pharmacological treatment.

1.3.1.1.2 The quality of the evidence

In children and young people, the evidence for the effects of withdrawing from methylphenidate was of moderate quality, and low quality in an indirect population; the evidence for withdrawing from atomoxetine was of moderate to low quality; the evidence for withdrawing from lisdexamphetamine was of very low quality; and the evidence for withdrawing from nortriptyline was of very low quality.

In adults, the evidence for withdrawing from methylphenidate was of moderate to very low quality; the evidence for withdrawing from Atomoxetine was of high to low quality; and the evidence for withdrawing from lisdexamphetamine was of moderate to very low quality. The committee noted that, within each comparison, most outcomes were taken from only one study. Furthermore, no data was reported in the studies for many of the outcomes on the protocol, and there was no evidence for withdrawing from many of the pharmacological treatments on the protocol. The committee also raised concerns that people with ADHD who volunteer to enter withdrawal trials may not be representative of the wider population of people with ADHD. The trial populations are likely to reflect the group of people who are already considering withdrawal as an option.

No evidence was found for children under the age of 5.

In general the quality of the evidence was downgraded due to concerns over risk of bias, imprecision and indirectness. Overall the quality of the evidence meant that the committee agreed it was not appropriate to make strong recommendations about stopping ADHD medication and instead focused on regular reviewing the concept with the person with ADHD.

1.3.1.1.3 Benefits and harms

Withdrawal from methylphenidate

In children and young people, the evidence demonstrated that withdrawal from methylphenidate was associated with a clinical harm for symptoms of ADHD and in the number of people who demonstrate an improvement in symptoms (CGI-I).

In adults, the evidence demonstrated no clinical difference between withdrawal from methylphenidate and continuing for health-related quality of life, self-reported symptoms of ADHD, and behaviour at 4 weeks, and clinical benefit of withdrawal for the number of adverse events at 6-months, but a clinical harm of withdrawal for the number of people who relapsed at both 4-weeks and 6-months.

Withdrawal from atomoxetine

In children and young people, the evidence demonstrated that withdrawal from Atomoxetine was associated with a clinical harm for ADHD symptoms (investigator-rated) and for relapse at 6 months (for children receiving treatment for 3-months) and 9 months (for children receiving treatment for 12-months), but a clinical benefit for adverse effects after 9-months in children who had been receiving treatment for 12-months.

In adults, the evidence demonstrated no clinical difference between withdrawal from Atomoxetine and continuing for health-related quality of life (EQ-5D), ADHD symptoms (self- and carer-rated), and the number of people who reported a 'suicide related event' at 25 weeks, and a clinical benefit of withdrawal for adverse outcomes at 25 weeks.

Withdrawal from lisdexamphetamine

In children and young people the evidence demonstrated no clinical difference between withdrawal from lisdexamphetamine for behaviour (parent-rated) but a clinical harm of withdrawal for ADHD symptoms (investigator-rated) at 6 weeks.

In adults, the evidence demonstrated a clinical harm of withdrawal for ADHD symptoms at 4 weeks and the number of people who demonstrated an improvement in symptoms (CGI-I) and 4 weeks.

Withdrawal from nortriptyline

In children and young people, the evidence demonstrated a clinical harm of withdrawal for the number of children and young people who demonstrated improvement by CGI at 3 weeks.

Summary

The committee considered that the evidence indicated that withdrawal from pharmacological treatment was associated with a risk in the exacerbation of symptoms of ADHD. However, the committee noted that a number of children, young people and adults in the studies continued to experience an improvement in symptoms following withdrawal, usually while taking a placebo. In children and young people, the committee noted, based on their experience, that withdrawal may also be associated with an increased risk of deterioration in behaviour; however there was little evidence that withdrawal had a significant impact on quality of life and behaviour in adults. The committee considered that this may reflect a greater need for pharmacological treatment in children and young people compared to adults, who may have developed improved coping strategies over time. The GC noted that withdrawal from pharmacological treatment was associated with consistent reductions in adverse effects of treatment.

1.3.1.2 Cost effectiveness and resource use

No economic studies were identified for this review.

The trade-offs involved in this question around withdrawal involve looking at whether withdrawing treatment, which would mean the cost of the treatment would no longer accrue a cost - does not have any detrimental impact on health, versus whether the cost of continuing treatment is outweighed by the health benefit the treatment provides.

It is assumed that if withdrawing treatment is found to be safe and effective compared to continuing treatment, this will also be cost effective as we would be reducing drug costs. However, if continuing treatment is found to be more effective, then assuming the initial treatment prescribed was cost effective, its continuation has to be considered cost effective. The economic considerations in this review are mostly driven by the clinical evidence.

Withdrawing was found to be more harmful for children than for adults. This may be because adults have become better at coping without medication.

Because of the nature of the question, staying on a drug was compared to stopping the drug, so indirect comparisons have to be made between different treatments as to whether one treatment has more of a long term impact on the condition than another. Stopping the drug in the trials also usually meant a placebo was given as they were RCTs, so it is possible a

placebo effect may also be present, in which case the impact of withdrawal may be being underestimated.

Something to note is that EQ-5D data was available for adults, which reported a utility of 0.9 in both groups, for stopping versus withdrawing atomoxetine. If it's the same in both groups, and also there was no clinical difference for ADHD symptoms and behaviour, then we could infer from this evidence that the EQ-5D is sensitive to the condition because it correctly detected that there was no change.

The committee made a consensus recommendation that discontinuation can be discussed and considered with patients, and offer trials of discontinuation if this is appropriate.

1.3.1.3 Other factors the committee took into account

The committee made a recommendation to review medication at least once a year, this is good clinical practice and there are drugs safety alerts for ADHD medicines that require regular review. The areas for review were agreed by consensus and are extrapolated from the evidence in the pharmacological reviews on effectiveness, safety, withdrawal and drug holidays and the qualitative reviews in this guideline. The committee agreed that it was important to understand the preferences of the person taking the medication as well as understanding the impact of medication on the symptoms. The committee noted the importance of establishing if drug optimisation had been achieved and if so, if troublesome symptoms still persisted. At this point it is important to establish if the symptoms are related to other conditions and if they are related to ADHD what other support can be offered.

The committee concluded that the evidence supported the possibility of a worsening of ADHD symptoms on withdrawal of medication, however the evidence also supported a reduction in adverse events after withdrawal. The committee agreed therefore that overall it would be appropriate for healthcare professionals to discuss the option of discontinuation or dose reduction with people with ADHD. The committee noted that the appropriateness of discontinuation or dose reduction will vary from person to person and that this could only be decided on an individual level. For example, if people with ADHD are struggling to manage adverse effects of treatment, or if people with ADHD or their clinicians are unsure if treatment is continuing to be of benefit, discontinuation may be more appropriate. Discontinuation of treatment could be short or long term depending on the response of the person with ADHD.

1.3.2 Drug holidays

1.3.2.1 Interpreting the evidence

1.3.2.1.1 The outcomes that matter most

The committee considered quality of life, ADHD symptoms and CGI assessment of response to be critical outcomes. ADHD symptoms were separately considered as total, hyperactivity and inattention subscales. The committee did not prioritise any one subscale. ADHD symptoms were separately considered when reported by self, parent, teacher and investigator. The committee considered that all had their merit but that symptoms reported by teacher or investigator were likely to be the most objective assessment of effects.

The committee considered intervention related discontinuations, serious adverse events, behavioural/functional measures, emotional dysregulation and academic outcomes to be important outcomes.

1.3.2.1.2 The quality of the evidence

The quality of the evidence was very low for all outcomes included in this review. There was only evidence available for total ADHD symptoms as rated by teachers and parents and

adverse events, only from one small study with the outcomes downgraded for risk of bias and imprecision.

The committee noted that the only evidence found was for weekend breaks from medication use and not for any longer periods of drug holiday and only for methylphenidate.

1.3.2.1.3 Benefits and harms

In the evidence identified in this review, there was a clinically important benefit of drug holidays in terms of parent rated ADHD symptoms and adverse events.. The committee discussed other benefits and harms of drug holidays. Although the trial showed drug holidays causing an improvement in ADHD symptoms, the committee agreed that was unlikely to be a specific effect and more a marker of the low quality of evidence, However the committee agreed that drug holidays they may well reduce adverse events. One of the harms of drug holidays are that encouraging people to take breaks from their medication may lead to worse adherence overall, even during non “holiday” periods.

1.3.2.2 Cost effectiveness and resource use

Similarly to the review on withdrawal, if drug holidays are found to be safe and effective compared to continuing treatment all the time, this will also be cost effective as we would be reducing drug costs. But if continuing treatment full time is found to be more effective, then assuming the initial treatment prescribed was cost effective, its continuation has to be considered cost effective. The economic considerations for this review will be mainly based on the clinical outcomes.

Holidays may have other benefits such as a break in adverse events, which could also impact quality of life.

Only one clinical study was identified in this review and this was in children and compared taking methylphenidate on weekdays with placebo on weekends versus taking methylphenidate all week. It found that drug holidays had benefit on ADHD symptoms and in reducing adverse events. It’s possible that a placebo effect was present in which case there may not in fact be any benefit of taking a break if the drug is not effective at weekends. The type of drug may also have an impact because some wear off more quickly.

The committee came to a consensus decision that it is likely to be very patient specific as to whether a patient may benefit from a break from treatment. Tying in with the discontinuations review, it was recommended that it should be a clinician’s decision whether a patient may benefit from a short trial of discontinuation.

1.3.2.3 Other factors the committee took into account

See section 1.3.1.3.

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Appendices

Appendix A: Review protocols

A.1 Withdrawal from pharmacological treatment

Table 15: Review protocol: Withdrawal from pharmacological treatment

Field	Content
Review question	What are the clinical effects of withdrawing from pharmacological treatment for ADHD?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	Inform recommendations about withdrawal of pharmacological treatment
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with ADHD Stratified by age –under 5, aged 5 to 18, over 18 intervention (drug withdrawing from)
Eligibility criteria – interventions	Methylphenidate; Stopping Methylphenidate; Continuing CNS stimulants; Stopping CNS stimulants; Continuing Methylphenidate modified release; Stopping Methylphenidate modified release; Continuing Dexamfetamine; Stopping Dexamfetamine; Continuing Lisdexamphetamine dimesylate; Stopping Lisdexamphetamine dimesylate; Continuing Atomoxetine; Stopping Atomoxetine; Continuing Guanfacine; Stopping Guanfacine; Continuing Clonidine; Stopping Clonidine; Continuing Tricyclics; Stopping Tricyclics; Continuing SSRIs; Stopping SSRIs; Continuing SNRIs; Stopping SNRIs; Continuing MAOIs; Stopping MAOIs; Continuing Risperidone; Stopping Risperidone; Continuing Olanzapine; Stopping

Field	Content
	Olanzapine; Continuing Clozapine; Stopping Clozapine; Continuing Haloperidol; Stopping Haloperidol; Continuing Quetiapine; Stopping Quetiapine; Continuing Aripiprazole; Stopping Aripiprazole; Continuing Carbamazepine; Stopping Carbamazepine; Continuing Valproate; Stopping Valproate; Continuing Lamotrigine; Stopping Lamotrigine; Continuing Lithium; Stopping Lithium; Continuing Asenapine; Stopping Asenapine; Continuing Buspirone; Stopping Buspirone; Continuing Bupropion; Stopping Bupropion; Continuing Nicotine; Stopping Nicotine; Continuing Modafinil; Stopping Modafinil; Continuing Melatonin; Stopping Melatonin; Continuing Sativex; Stopping Sativex; Continuing ACeI; Stopping ACeI; Continuing
Eligibility criteria – comparator(s) / control or reference (gold) standard	Stopping any specific medication vs continuing any specific medication.
Outcomes and prioritisation	Critical Quality of life [continuous] ADHD symptoms (total; parent) [continuous] [children and young people] ADHD symptoms (total; teacher) [continuous] [children and young people] ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (total; carer/partner) [continuous] [adults] ADHD symptoms (total; investigator) [continuous] ADHD symptoms (inattention; parent) [continuous] [children and young people] ADHD symptoms (inattention; teacher) [continuous] [children and young people]

Field	Content
	ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (inattention; carer/partner) [continuous] [adults] ADHD symptoms (inattention; investigator) [continuous] ADHD symptoms (hyperactivity; parent) [continuous] [children and young people] ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people] ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults] ADHD symptoms (hyperactivity; investigator) [continuous] CGI scale (worse or much worse) [dichotomous] Important Reduction in adverse events [dichotomous] Serious adverse events (all) [dichotomous] Behavioural (children)/Functional (adults) measures [continuous] Emotional dysregulation [continuous] Academic outcomes (children) [continuous] Substance use (alcohol and drug use) [dichotomous] Self-harm [dichotomous]
Eligibility criteria – study design	RCT Systematic Review
Other inclusion exclusion criteria	Unit of randomisation: Patient Crossover study: Not permitted Minimum duration of study: Not defined Other exclusions: Adherence study, inappropriate method of diagnosis - ADHD diagnosis made not using DSM-III or ICD-10 or later versions. Studies evaluating treatments for ADHD in a population of people with autistic spectrum disorder will be included if no formal diagnosis of ADHD is made but there is evidence of moderate to severe symptoms of hyperactivity, impulsivity and/or inattention through validated symptom questionnaires.
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroup analyses if heterogeneity: Secure estate (Secure estate; Looked after children; General population); Population may be at higher risk and may experience differential impact of withdrawal ADHD severity (Majority mild; Majority moderate; Majority severe; Mixed population); Impact of withdrawal may vary depending on baseline symptom severity Study design (Blinded; Open label); The effect of withdrawing may alter depending on whether people are unblinded Duration of withdrawal (One dose; 1-2 days (including weekend); 2 days - 1 month; 1-3 months; >3 months); Longer breaks may be associated with a greater impact of withdrawal Prior length of treatment (< 2 weeks; 2-4 weeks; 3-6 months; 6-12 months; >12 months); Cumulative effects of treatment may impact on the effect of withdrawal, although direction of impact is unclear
Selection process – duplicate screening / selection / analysis	No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline.

Field	Content
Data management (software)	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library,PsycINFO Date: From October 2007 Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – from 2008 Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/cg72
Highlight if amendment to previous protocol	Not an amendment
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual and the separate Methods report for this guideline.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Gillian Baird in line with section 3 of Developing NICE guidelines: the manual and the methods section of this guideline. Staff from NGC undertook systematic literature searches, critically appraised the evidence, conducted meta-analysis and cost-

Field	Content
	effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual and the methods section of this guideline.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 16: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B. For questions being updated, the search will be run from December 2007, which was the cut-off date for the searches conducted for NICE guideline CG72
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2001 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[29] Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Review question	All questions – health economic evidence
	Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix I. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. Economic evaluations that are based on studies excluded from the clinical review will be excluded.

A.2 Drug holidays

Table 17: Review protocol: Drug holidays

Field	Content
Review question	What are the clinical effects of 'drug holidays' from pharmacological treatment for ADHD?
Type of review question	Intervention

Field	Content
	A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	Assess the impact of drug holidays on children, young people and adults with ADHD
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with ADHD. Stratified by age: Children (<5 years) Children and young people (5 to 18 years) Adults (>18 years) Line of therapy is not an inclusion criteria
Eligibility criteria – interventions	Holiday from pharmacological treatment (stopping and restarting treatment at least once prior to follow-up) Continuing pharmacological treatment
Eligibility criteria – comparator(s) / control or reference (gold) standard	All interventions will be compared with each other unless otherwise stated
Outcomes and prioritisation	Critical Quality of life [continuous] ADHD symptoms (total; parent) [continuous] [children and young people] ADHD symptoms (total; teacher) [continuous] [children and young people] ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (total; carer/partner) [continuous] [adults] ADHD symptoms (total; investigator) [continuous] ADHD symptoms (inattention; parent) [continuous] [children and young people] ADHD symptoms (inattention; teacher) [continuous] [children and young people] ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (inattention; carer/partner) [continuous] [adults] ADHD symptoms (inattention; investigator) [continuous] ADHD symptoms (hyperactivity; parent) [continuous] [children and young people] ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people] ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults] ADHD symptoms (hyperactivity; investigator) [continuous] CGI scale (improved or much improved) [dichotomous] Important Reduction in adverse outcomes [dichotomous] Serious adverse events (all) [dichotomous]

Field	Content
	Behavioural (children)/Functional (adults) measures [continuous] Emotional dysregulation [continuous] Academic outcomes (children) [continuous] Substance use (alcohol and drug use) [dichotomous] Self-harm [dichotomous]
Eligibility criteria – study design	RCTs Systematic Review of RCTs
Other inclusion exclusion criteria	Unit of randomisation: Patient Crossover study: Not permitted Minimum duration of study: 2 weeks Other exclusions: Adherence study Inappropriate method of diagnosis - ADHD diagnosis made not using DSM-III or ICD-10 or later versions. Studies evaluating treatments for ADHD in a population of people with autistic spectrum disorder will be included if no formal diagnosis of ADHD is made but there is evidence of moderate to severe symptoms of hyperactivity, impulsivity and/or inattention through validated symptom questionnaires.
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroup analyses if there is heterogeneity: Secure estate (Secure estate; Looked after children; General population); Population may be at higher risk and may experience differential impact of withdrawal ADHD severity (Majority mild; Majority moderate; Majority severe; Mixed population); Impact of withdrawal may vary depending on baseline symptom severity Study design (Blinded; Open label); The effect of withdrawing may alter depending on whether people are unblinded Duration of withdrawal (One dose; 1-2 days (including weekend); 2 days - 1 month; 1-3 months; >3 months); Longer breaks may be associated with a greater impact of withdrawal Prior length of treatment (< 2 weeks; 2-4 weeks; 3-6 months; 6-12 months; >12 months); Cumulative effects of treatment may impact on the effect of withdrawal, although direction of impact is unclear
Selection process – duplicate screening / selection / analysis	No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline.
Data management (software)	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library,PsycINFO Date: From October 2007 Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – from 2008 Language: Restrict to English only Supplementary search techniques: backward citation searching

Field	Content
	Key papers: Not known
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/cg72
Highlight if amendment to previous protocol	Not an amendment
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual and the separate Methods report for this guideline.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Gillian Baird in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, critically appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual and the methods section of this guideline.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 18: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B. For questions being updated, the search will be run from December 2007, which was the cut-off date for the searches conducted for NICE guideline CG72
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2001 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[29] Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix I. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable).

Review question	All questions – health economic evidence
	OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. Economic evaluations that are based on studies excluded from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for the following review questions are detailed below:

- Withdrawal from pharmacological treatment
- Drug holidays

The search strategies complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches for were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 19: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews 2007 to 2017 Issue 4 of 12 CENTRAL 2007 to 2017 Issue 3 of 12 DARE and NHSEED 2007 to 2015 Issue 1 of 4 HTA 2007 to 2017 Issue 1 of 4	None
PsycINFO (ProQuest)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7

9.	exp Child Development Disorders, Pervasive/
10.	(autistic or autism or asperger*).ti,ab.
11.	pervasive developmental disorder*.ti,ab.
12.	(asd or pdd or pdd-nos).ti,ab.
13.	or/9-12
14.	hyperkinesis/
15.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*).ti,ab.
16.	14 or 15
17.	13 and 16
18.	8 or 17
19.	limit 18 to English language
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	Animals, Laboratory/
33.	exp animal experiment/
34.	exp animal model/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ab.
42.	placebo.ab.
43.	drug therapy.fs.
44.	randomly.ab.
45.	trial.ab.
46.	groups.ab.
47.	or/39-46
48.	Clinical Trials as topic.sh.
49.	trial.ti.
50.	or/39-42,44,48-49
51.	Meta-Analysis/
52.	Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.

54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	38 and (50 or 61)

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	exp autism/
10.	(autistic or autism or asperger*).ti,ab.
11.	pervasive developmental disorder*.ti,ab.
12.	(asd or pdd or pdd-nos).ti,ab.
13.	or/9-12
14.	hyperactivity/
15.	hyperkinesia/
16.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*).ti,ab.
17.	or/14-16
18.	13 and 17
19.	8 or 18
20.	limit 19 to English language
21.	letter.pt. or letter/
22.	note.pt.
23.	editorial.pt.
24.	case report/ or case study/
25.	(letter or comment*).ti.
26.	or/21-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animal/ not human/
30.	nonhuman/

31.	exp Animal Experiment/
32.	exp Experimental Animal/
33.	animal model/
34.	exp Rodent/
35.	(rat or rats or mouse or mice).ti.
36.	or/28-35
37.	20 not 36
38.	random*.ti,ab.
39.	factorial*.ti,ab.
40.	(crossover* or cross over*).ti,ab.
41.	((doubl* or singl*) adj blind*).ti,ab.
42.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
43.	crossover procedure/
44.	single blind procedure/
45.	randomized controlled trial/
46.	double blind procedure/
47.	or/38-46
48.	systematic review/
49.	meta-analysis/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	37 and (47 or 58)

Cochrane Library (Wiley) search terms

#1.	[mh ^"attention deficit and disruptive behavior disorders"]
#2.	[mh ^"attention deficit disorder with hyperactivity"]
#3.	((attenti* or disrupt*) near/3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)):ti
#4.	((attenti* or disrupt*) near/3 disorder*):ab
#5.	(adhd or addh or ad next hd or ad-hd):ti,ab
#6.	(attenti* near/3 deficit*):ti,ab
#7.	(((hyperkin* or (hyper near/1 kin*)) near/1 (syndrome* or disorder*)) or hkd):ti,ab
#8.	(minimal near/1 brain near/2 (dysfunct* or disorder*)):ti,ab
#9.	(or #1-#8)
#10.	[mh "Child Development Disorders, Pervasive"]

#11.	(autistic or autism or asperger*):ti,ab
#12.	(pervasive next developmental next disorder*):ti,ab
#13.	(asd or pdd or pdd-nos):ti,ab
#14.	(or #10-#13)
#15.	[mh ^hyperkinesis]
#16.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*):ti,ab
#17.	#15 or #16
#18.	#14 and #17
#19.	#9 and #17

PsycINFO (ProQuest) search terms

1.	(SU.EXACT.EXPLODE("Attention Deficit Disorder") OR TI((attenti* OR disrupt*) NEAR/3 (adolescent* OR adult* OR behav* OR child* OR class OR classes OR classroom* OR condition* OR difficult* OR disorder* OR learn* OR people OR person* OR poor OR problem* OR process* OR youngster*)) OR AB((attenti* OR disrupt*) NEAR/3 disorder*) OR TI,AB(adhd OR addh OR ad-hd OR ad??hd) OR TI,AB(attenti* NEAR/3 deficit*) OR TI,AB(((hyperkin* OR (hyper-kin*)) NEAR/1 (syndrome* OR disorder*)) OR hkd) OR TI,AB(minimal NEAR/1 brain NEAR/2 (dysfunct* OR disorder*))) OR ((SU.EXACT.EXPLODE("Autism Spectrum Disorders") or TI,AB(autistic or autism or asperger*) or TI,AB(pervasive-developmental-disorder*) or TI,AB(asd or pdd or pdd-nos)) AND (SU.EXACT("Hyperkinesis") or TI,AB(hyperactiv* or inattent* or hyperkin* or hyper-kin*)))
2.	(su.exact.explode("clinical trials") OR ti,ab((clinical OR control*) NEAR/3 trial*) OR ti,ab((single* OR double* OR treble* OR triple*) NEAR/5 (blind* OR mask*)) OR ti,ab(volunteer* OR control-group OR controls) OR su.exact("placebo") OR ti,ab(placebo*))
3.	((SU.EXACT("Literature Review") or RTYPE(review) or ti(review) or me(literature review)) AND (ti,ab(systematic or evidence or methodol* or quantitative*))) or (SU.EXACT("Meta Analysis") or ti,ab(meta-analys* or metanalys* or metaanalys* or meta analys*) or ti,ab((systematic or evidence* or methodol* or quantitative*) near/3 (review* or overview*)) or ti,ab((pool* or combined or combining) near/2 (data or trials or studies or results)) or RTYPE(systematic or meta*) or ME(meta analysis or systematic review))
4.	1 AND (2 OR 3)
5.	Limit to English
6.	NOT (Dissertations & Theses AND Books)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ADHD population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 28 April 2017	Exclusions Health economics
Embase	2014 – 28 April 2017	Exclusions Health economics

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - 2008 – 28 April 2017 NHSEED - 2008 to March 2015	None

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/

38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/

21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

NHS EED and HTA (CRD) search terms

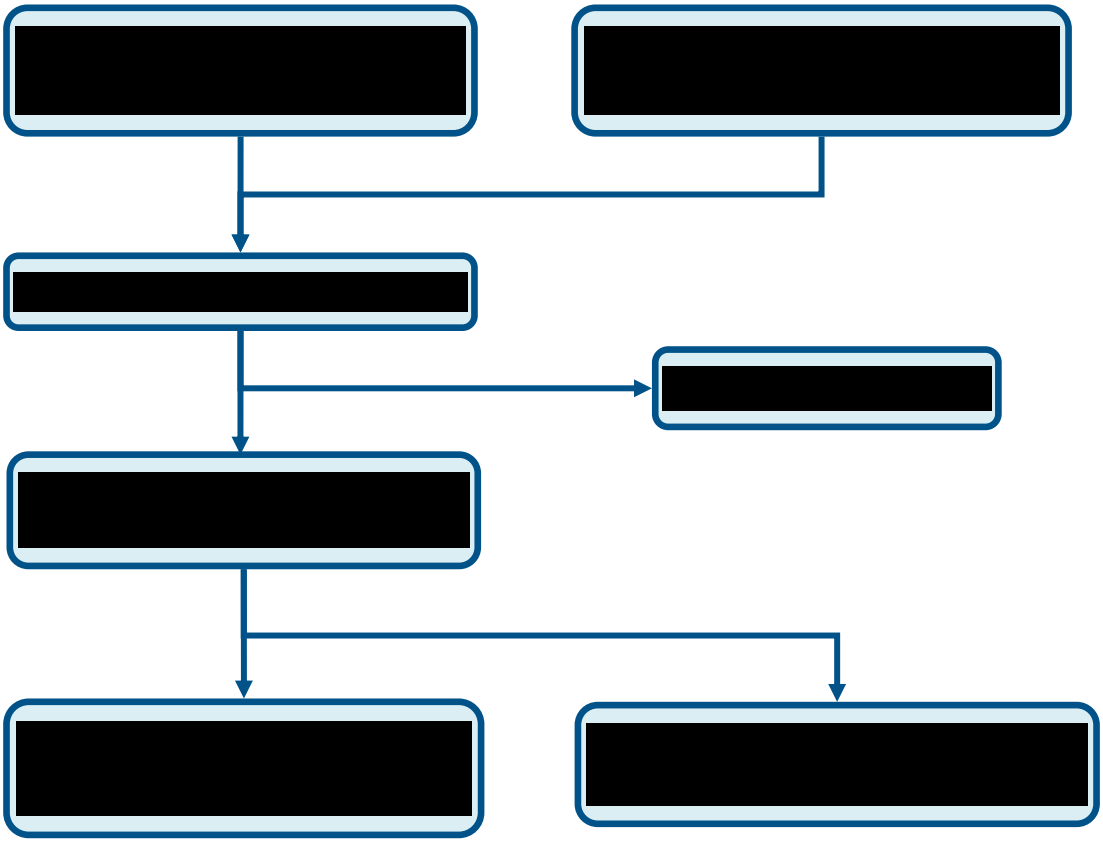
#1.	MeSH DESCRIPTOR Attention Deficit and Disruptive Behavior Disorders
#2.	MeSH DESCRIPTOR Attention Deficit Disorder with Hyperactivity
#3.	(((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))):TI
#4.	(((attenti* or disrupt*) adj3 disorder*))
#5.	((adhd or addh or ad hd or ad??hd))
#6.	((attenti* adj3 deficit*))

#7.	((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd))
#8.	((minimal brain adj2 (dysfunct* or disorder*)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(#9) IN NHSEED, HTA

Appendix C: Clinical evidence selection

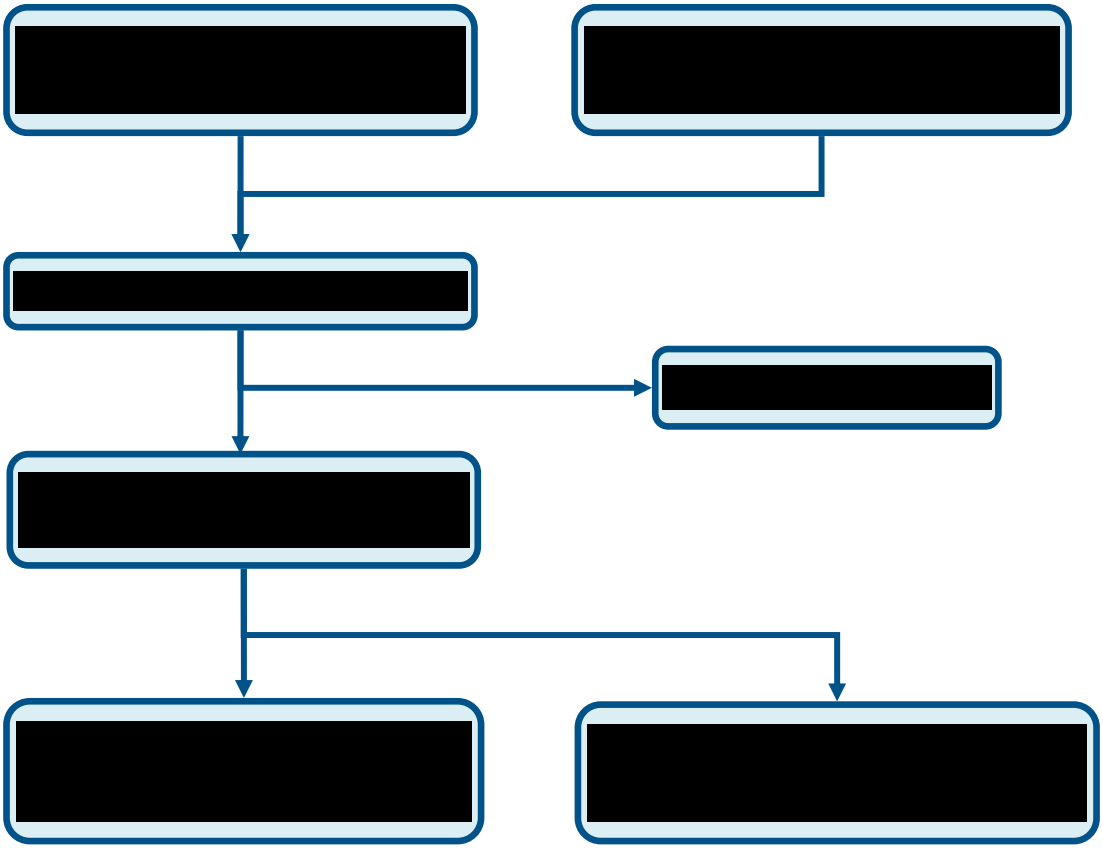
C.1 Withdrawal from pharmacological treatment

Figure 1: Flow chart of clinical study selection for the review of withdrawal



C.2 Drug holidays

Figure 2: Flow chart of clinical article study selection for the review of drug holidays



Appendix D: Clinical evidence tables

D.1 Withdrawal from pharmacological treatment

Study	Biederman 2010[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adults (>18 years): Adults 19-60 years
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD diagnosis using DSM-IV; AISRS score >/=24; subjects treated for anxiety disorders and depression who were on a stable medication regimen for at least 3 months and who had a disorder-specific Clinical Global Impression (CGI)-Severity score of 3 or lower (mildly ill) were included. All participants included in the withdrawal phase of the trial also were required to have responded to treatment with methylphenidate in the previous 2 phases on the study (phase 1 = a RCT of OROS-MPH vs placebo over 6 weeks and phase 2 = a maintenance of response phase of OROS-MPH vs placebo over 24 weeks. Note that phase 2 also includes those who responded to placebo).
Exclusion criteria	Participants with clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ of less than 80, delirium, dementia, or amnestic disorders, other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidality), drug or alcohol abuse or dependence within the 6 months preceding the study, or a previous adequate trial of MPH; pregnant or breast-feeding females.
Age, gender and ethnicity	Age - Mean (SD): 35 years (8.8) in original study; demographics for withdrawal study not reported. Gender (M:F): 59:66 (original study; demographics for withdrawal study not reported). Ethnicity:
Further population details	1. ADHD severity: Majority mild (CGI-Severity score of 3 or lower, and those who responded to either OROS-MPH or placebo). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Methylphenidate modified release - Stopping. Stopping OROS-Methylphenidate

	(placebo). Previous medication was titrated to optimal response (a maximum daily dosage of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dosage was increased by 36 mg/d but only for subjects who failed to attain an a priori definition of improvement (CGI-I of 1 or 2 or a reduction in the AISRS score of larger than 30%) and who did not experience adverse effects. Duration 4 weeks. Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2 days - 1 month (4 weeks). 2. Prior length of treatment: 6-12 months (At least 6-months. An additional 6 weeks for those who were randomised to OROS-MPH during the first phase of the trial). 3. Study design: Blinded (Blinded). (n=12) Intervention 2: Methylphenidate modified release - Continuing. Continuing OROS-MPH. Previous medication was titrated to optimal response (a maximum daily dosage of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dosage was increased by 36 mg/d but only for subjects who failed to attain an a priori definition of improvement (CGI-I of 1 or 2 or a reduction in the AISRS score of larger than 30%) and who did not experience adverse effects. Duration 4 weeks. Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2 days - 1 month (4 weeks). 2. Prior length of treatment: 6-12 months (At least 6-months. An additional 6-weeks for those randomised to OROS-MPH during the first phase of the trial). 3. Study design: Blinded (Blinded).
Funding	Study funded by industry (Ortho-McNeil Janssen Scientific Affairs)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING OROS-MPH versus CONTINUING OROS-MPH Protocol outcome 1: ADHD symptoms total at 1-2 weeks - Actual outcome for Adults (>18 years): Relapse (defined as CGI score of 1 or 2 or a worsening in the AISRS score so that relative improvement relative to baseline severity was <15% improvement for 2 consecutive visits) at 4 weeks; Group 1: 2/11, Group 2: 0/12; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Brams 2012[7]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=116)
Countries and setting	Conducted in Unknown multicentre, USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Adults (>18 years): Adults 18-55 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged 18-55 years with baseline ADHD-RS-IV scores <22 and CGI-S ratings or 1-3. Participants were required to have received commercially available lisdexamphetamine dimesylate (30, 50, or 70 mg/d) for >/= 6months with an acceptable safety profile. All to have a BMI of between 18.5 and 40.
Exclusion criteria	Participants were excluded if they had a current Axis I or II comorbid psychiatric disorder that was uncontrolled with significant symptoms or controlled with a prohibited medication; current risk or history of suicide attempts; concurrent chronic or acute illness or disability; history of seizures; current diagnosis or Tourette disorder; current abnormal thyroid function or glaucoma; family history of sudden cardiac death or ventricular arrhythmias; history of symptomatic cardiovascular disease, stroke, structural cardiac abnormalities, or moderate-severe hypertensions; amphetamine hypersensitivity, allergy or intolerance; history (<6months) of suspected substance abuse or dependence; positive urine drug screen; or current use of other agents that have central nervous effects or affect performance.
Recruitment/selection of patients	Individuals enrolled as part of an earlier open label dose comparison trial (30, 50, 70 mg/day) for 3 weeks prior to randomisation into withdrawal phase.
Age, gender and ethnicity	Age - Mean (SD): 35.8 years (11.15). Gender (M:F): 50:66. Ethnicity: 91.4% white
Further population details	1. ADHD severity: Majority mild (ADHD-RS-IV scores at baseline all <22; mean score = 10.6 (SD = 4.87). Study specifies that "ADHD-RS-IV total scores and CGI-S ratings indicated a low level of ADHD symptom severity, with nearly all participants rated as 'not at all', 'borderline', or 'mildly ill'"). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness

Interventions	(n=60) Intervention 1: Lisdexamphetamine dimesylate - Stopping. Placebo. Method not described. Duration 6 weeks. Concurrent medication/care: Weekly clinic visits. Nothing further stated. Further details: 1. Duration of withdrawal: 1-3 months (6 weeks). 2. Prior length of treatment: 6-12 months (6-months + 3 week open label phase). 3. Study design: Blinded (Blinded). (n=56) Intervention 2: Lisdexamphetamine dimesylate - Continuing. Continued with LDX; 6, 23, and 27 participants received 30, 50, and 70 mg/day respectively. Duration 6 weeks. Concurrent medication/care: Weekly clinic visits. Nothing further stated. Further details: 1. Duration of withdrawal: 1-3 months (6 weeks). 2. Prior length of treatment: 6-12 months (6-months plus 3-week open label phase). 3. Study design: Blinded (Blinded).
Funding	Study funded by industry (Funded by Shire; Shire involved in the design, data collection, analysis and interpretation of the data)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING LDX versus CONTINUING LDX Protocol outcome 1: ADHD symptoms total at 1-2 weeks - Actual outcome for Adults (>18 years): ADHD-RS-IV at 6 weeks (LOCF); Group 1: mean 16.8 LS mean change (SD 1.35); n=60, Group 2: mean 1.6 LS mean change (SD 1.39); n=56; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Buitelaar 2012[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis according to DSM-IV (assessed using a structured clinical interview)

Stratum	Adults (>18 years): Adults 18-65 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with a diagnosis of ADHD according to DSM-IV criteria; a CAARS total score of ≥24 at screening of the original trial (Medori 2008). There were no specification in the inclusion criteria that participants had to have a clinically meaningful change in symptoms from treatment to be entered into the withdrawal phase; however all participants had received treatment for 1 year [query ok?]
Exclusion criteria	History of poor response or intolerance to MPH; presence of any current clinically unstable psychiatric condition; diagnosis of substance use disorder (abuse/dependence) according to DSM-IV criteria within the last 6-months; family history of schizophrenia or affective psychosis; serious illnesses; hyperthyroidism, myocardial infarction or stroke within 6-months of screening; history of seizures, glaucoma, or uncontrolled hypertension; participants with a treatment gap >30 days after the end of the open label phase immediately preceding the withdrawal phase.
Recruitment/selection of patients	Participants were selected for an original trial (Medori 2008), which was a 5-week double-blind, placebo-controlled, fixed dose, RCT of OROS methylphenidate. Participants who completed the trial or who discontinued due to poor tolerability were invited to participate in an open label phase of treatment for 7 weeks (also original trial). Those who completed the open label phase, were eligible to participate in the present study. This study consisted of an open label phase of treatment with OROS-MPH (unclear length of time). Those who had received treatment with OROS-MPH for at least 1 year across all phases of the study and had received a stable dose of OROS-MPH for 4 weeks at the end of the open label phase were eligible to enter a double-blind withdrawal phase. Participants began treatment in the open label phase on the same dose as they had received previously; however the dosage could be increased or decreased (to a maximum of 90 mg/day) according to optimal response and tolerance. Those who had received a break in treatment before the open label phase in the present study had their medication titrated from 18mg/day to a clinically optimal dose.
Age, gender and ethnicity	Age - Mean (SD): 36 years (10). Gender (M:F): 18:27. Ethnicity: Not reported
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (53% combined subtype in adulthood, baseline CAARS: O-SV score = 12.1 in stopping group and 16.5 in continuing group). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Methylphenidate modified release - Stopping. Placebo following treatment with OROS methylphenidate for at least 1 year. Duration 4 weeks. Concurrent medication/care: Not described Further details: 1. Duration of withdrawal: 2 days - 1 month (1 month). 2. Prior length of treatment: >12 months (>1 year). 3. Study design: Blinded (n=23) Intervention 2: Methylphenidate modified release - Continuing. Continuing treatment with OROS methylphenidate after at least 1 year of treatment. Duration 4 weeks. Concurrent medication/care: Not

	described Further details: 1. Duration of withdrawal: 2 days - 1 month (1 month). 2. Prior length of treatment: >12 months (> 1 year). 3. Study design: Blinded (Blinded).
Funding	Study funded by industry (Janssen-Cilag (EMEA; Johnson & Johnson))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING OROS-MPH versus CONTINUING OROS-MPH Protocol outcome 1: Quality of life at 1-2 weeks - Actual outcome for Adults (>18 years): Change in quality of life (Q-LES-Q; short form) at 4 weeks; Group 1: mean -2.7 (SD 12.4); n=22, Group 2: mean -6.5 (SD 11.4); n=23; Q-LES-Q short form unclear Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults (>18 years): Change in function (Sheehan disability scale) at 4 weeks; Group 1: mean 1.6 (SD 8.3); n=22, Group 2: mean 2.2 (SD 6.1); n=23; Sheehan disability scale 0-30 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: ADHD symptoms total at 1-2 weeks - Actual outcome for Adults (>18 years): Change in CAARS:S-SV total (self-reported) at 4 weeks; Group 1: mean 4 (SD 12); n=22, Group 2: mean 4.4 (SD 11.9); n=23; CAARS-S:SV unclear, possibly 0-54? Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults (>18 years): Number of patients who relapse (≥50% increase in symptoms from baseline on the CAARS:O-SV - observer rated) at 4 weeks; Group 1: 8/22, Group 2: 6/23; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study (subsidiary papers)	**Coghill 2014[13] (Banaschewski 2014[3])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=157)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR

Stratum	Children (0-17 years): Children 6-17 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children and young people enrolled in a previous open label safety trial of lisdexamphetamine. Children aged 6-17 years, primarily recruited from Europe but protocol adjusted to also include children recruited from sites in the US. All participants had at least moderate severity ADHD, defined as an ADHD-RS-IV score >/=28 at baseline of the original study. All participants completed at least 4 weeks of double-blind treatment followed by a 1-week post-treatment washout.
Exclusion criteria	Failure to respond to OROS-MPH therapy; failure to respond to more than one adequate course of amphetamine therapy; individuals whose previous therapy before the original trial provided effective control of symptoms with acceptable tolerability; people with comorbid psychiatric comorbidities with significant symptoms; participants who required dose adjustments, experienced unacceptable side effects or had an ADHD-RS-IV total score > 22 or a CGI-S score of 3 or more during the fixed dose phase (immediately prior to discontinuation)
Age, gender and ethnicity	Age - Mean (SD): 11 - 11.3 years (SD 2.63 - 2.58). Gender (M:F): 123 male; 34 female. Ethnicity: 95% white
Further population details	1. ADHD severity: Majority moderate (All participants had at least moderate severity ADHD, defined as an ADHD-RS-IV score >/=28 at baseline of the original study). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	Original trial was 4 weeks of dose optimisation, followed by 20-52 weeks of dose maintenance (longer for those who were enrolled in the original trial, prior to alterations to the trial protocol), and then a 2-week fixed dose period. The original trial protocol was amended to shorted the open label phase from 52 to 33 weeks and include a 2-week fixed dose phase followed by a 6-week randomised withdrawal phase.
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Lisdexamphetamine dimesylate - Stopping. Placebo administered in identical capsules. Capsule administered orally once daily at 7am. Duration 6 weeks. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: 1-3 months (Up to 6 weeks (but many people stopped early)). 2. Prior length of treatment: 1-3 months (2 weeks including 5 week dose optimisation)). 3. Study design: Blinded (Original trial was open label, withdrawal was blinded). (n=78) Intervention 2: Lisdexamphetamine dimesylate - Continuing. Drug administered in identical capsules to placebo once daily at 7am. Duration 6 weeks. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: 1-3 months (Up to 6 weeks). 2. Prior length of treatment: 1-3 months (2 weeks including 5 week dose optimisation)). 3. Study design: Blinded (Original trial was open label, withdrawal was blinded).

Funding	Study funded by industry (Funded by Shire; protocol and analysis plan written by Shire)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING LDX versus CONTINUING LDX

Protocol outcome 1: Quality of life at 1-2 weeks
- Actual outcome for Children (0-17 years): CHIP-CE (Achievement subscale) [LS-mean change in T score] at 6-weeks; Other: Effect size = .696; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (0-17 years): CHIP-CE (Risk avoidance subscale) [LS-mean change in T score] at 6-weeks; Other: Effect size = 0.829; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (0-17 years): CHIP-CE (Resilience subscale) [LS-mean change in T score] at 6-weeks; Other: Effect size = 0.275; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (0-17 years): CHIP-CE (Satisfaction subscale) [LS-mean change in T score] at 6-weeks; Other: Effect size = 0.636; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (0-17 years): CHIP-CE (Comfort subscale) [LS-mean change in T score] at 6-weeks; Other: Effect size = 0.348; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms total at 1-2 weeks
- Actual outcome for Children (0-17 years): ADHD-RS-IV (investigator completed) [change from baseline] at 6-weeks; Group 1: mean 14.5 (SD 9.95); n=73, Group 2: mean 1.9 (SD 6.97); n=73; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Behaviour/function at 1-2 weeks
- Actual outcome for Children (0-17 years): Weiss functional impairment rating scale (Parent report) (WFIRS-P) [assesses function in previous 4 weeks] at 6-weeks; Group 1: mean 0.71 (SD 0.387); n=65, Group 2: mean 0.58 (SD 0.329); n=63; WFIRS-P 0-3 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Huss 2014[22]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=489)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable

Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed diagnosis using DSM-IV criteria
Stratum	Adults (>18 years): Adults aged 18-60 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients (18–60 years) with diagnosis of ADHD, all types, with a confirmed childhood onset according to DSM-IV diagnostic criteria and a DSM-IV ADHD RS total score of ≥30 at screening and baseline were included in the study. Following the dose confirmation and optimisation phases of the trial, all participants who had experienced a clinical response to the study drug (defined as ≥30% reduction in ADHD-RS) and who still met inclusion criteria were re-randomised to the withdrawal phase
Exclusion criteria	Pre-existing cardiovascular or cerebrovascular diseases, or any other co-morbid psychiatric disorder requiring medical intervention/therapy or that might interfere with the study conduct at the time of enrolment; patients demonstrating a ≥30% improvement in DSM-IV ADHD RS total score at baseline relative to that at screening were also excluded from this study. Any psychological or behavioural therapies for the treatment of ADHD were discontinued at least 1 month prior to the screening visit. Patients who initiated these therapies within 3 months prior to screening visit for reasons other than ADHD were excluded from the trial. Additionally, patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgment were excluded from this study. Patients with use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment (whichever was longer), were excluded from the study. In patients receiving any psychotropic medications the minimum discontinuation period varied according to drug class as follows: 1 week prior to the screening visit for stimulants including MPH, antidepressants other than fluoxetine, antipsychotics, anticonvulsants for non-epilepsy uses, mood stabilizing medications such as lithium, and herbal preparations with psychotropic potential; 2 weeks prior to the screening visit for benzodiazepines, barbiturates, all other sedatives or hypnotics, and monoamine oxidase inhibitors and 4 weeks prior to the screening visit for fluoxetine. Other exclusion criteria included pregnancy, seizures, recent alcohol or drug abuse and patients with body mass index <18.5 kg/m2 or >35 kg/m2.
Recruitment/selection of patients	Participants recruited as part of a larger trial to evaluate the effectiveness of modified release methylphenidate
Age, gender and ethnicity	Age - Mean (SD): 35.4 years (11.38). Gender (M:F): 395:330. Ethnicity: 89.5% Caucasian, 2.5% Black, 2.5% Asian, 5.2% other (original trial only)
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (General population mean ADHD-RS at baseline = 39.2 (no SD), all responders to treatment at beginning of withdrawal phase). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness

Interventions	(n=123) Intervention 1: Methylphenidate - Stopping. Placebo following treatment with extended-release methylphenidate. During phase 1 of the trial, participants were randomised to receive either 40, 60, or 80 mg/day of MPH. Treatment was started at 20 mg/day and titrated until the assigned dose was reached over a 3-week period. After this time, participants received the dose for 6 weeks. During phase 2 of the trial, participants began treatment again at 20 mg/day, and then their dose was titrated to either 40, 60, or 80 mg/day over 3 weeks based on optimal response, and this dose was maintained for the remainder of this 5 week period (minimum 1 week). All participants were then receiving treatment with MPH for between 5 and 14 weeks, although may not always have been at optimal dose (minimum 1 week at optimal dose). Duration 6 months. Concurrent medication/care: No additional therapies, including rescue medication. Further details: 1. Duration of withdrawal: >3 months (6-months). 2. Prior length of treatment: 1-3 months (5-14 weeks, depending on randomisation in earlier parts of the trial). 3. Study design: Blinded (Blinded). (n=366) Intervention 2: Methylphenidate - Continuing. Continuing extended-release methylphenidate. Participants were randomised to their optimal dose (40, 60 or 80 mg/day) on an equal ratio based on optimal response (unclear how this was done on an equal basis and also based on optimal response). 114 participant received 40mg/day, 132 participants received 60mg, and 120 participants received 80mg. after prior treatment for 5-14 weeks. Participants were randomised to one of the 3 doses of treatment in an equal ratio. During phase 1 of the trial, participants were randomised to receive either 40, 60, or 80 mg/day of MPH. Treatment was started at 20 mg/day and titrated until the assigned dose was reached over a 3-week period. After this time, participants received the dose for 6 weeks. During phase 2 of the trial, participants began treatment again at 20 mg/day, and then their dose was titrated to either 40, 60, or 80 mg/day over 3 weeks based on optimal response, and this dose was maintained for the remainder of this 5 week period (minimum 1 week). All participants were then receiving treatment with MPH for between 5 and 14 weeks, although may not always have been at optimal dose (minimum 1 week at optimal dose). Duration 6 months. Concurrent medication/care: No other therapies allowed, including rescue medication Further details: 1. Duration of withdrawal: >3 months (6 months). 2. Prior length of treatment: 1-3 months (5-14 weeks). 3. Study design: Blinded (Blinded).
Funding	Study funded by industry (Novartis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING MPH-ER versus CONTINUING MPH-ER

Protocol outcome 1: ADHD symptoms total at 3-6 months
- Actual outcome for Adults (>18 years): Number of patients who experienced a ≥30% increase in symptoms AND who score was <30% improvement since the beginning of all of the trial phases (scores using the ADHD-RS) at 6-months; Group 1: 57/115, Group 2: 75/352; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Reduction in adverse outcomes at 3-6 months - Actual outcome for Adults (>18 years): Number of patients who experienced any adverse event at 6-months; Group 1: 44/121, Group 2: 197/361; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 1-2 weeks; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study (subsidiary papers)	**Michelson 2004[27] (Buitelaar 2007[9], Hazell 2006[19])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=416)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 18-months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV (K-SADS-PL)
Stratum	Children (0-17 years): Children aged 6 - 15 years
Subgroup analysis within study	Not stratified but pre-specified: Paper reports data for 2 phases: withdrawal following 3-months of treatment and withdrawal following 12-months of treatment. Overlap in the 2 groups (should not be pooled)
Inclusion criteria	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD as assessed by clinical history and confirmed by structured clinical interview and whose symptoms exceeded 1.5 SD above US age and gender norms.
Exclusion criteria	Patients with bipolar disorder or a psychotic illness; patients with unstable medical illness or patients with a condition that would require ongoing administration of a psychoactive medication (other than atomoxetine) during the study.
Recruitment/selection of patients	Following a washout and screening phase, participants were entered into an open-label phase of treatment with atomoxetine to a target dose of 1.2mg/kg per day administered twice daily. Further increases were allowed based on clinical response to a maximal dose of 1.8mg/kg per day. After 12 weeks, patients whose symptoms responded to treatment were randomised into a 9-month double-blind placebo controlled phase on the same dose as their final dose in the open label phase. Response was defined as >/= 25% reduction in ADHD symptoms (ADHD-RS-IV) and a CGI-S score of 1 or 2 at weeks 9 and 10 of the open label phase. After the double-blind phase, participants who received atomoxetine were re-randomised to either

	atomoxetine or placebo, to evaluate the effects of withdrawing treatment who have been taking atomoxetine for a longer time period.
Age, gender and ethnicity	Age - Mean (SD): 10.3 (2.3). Gender (M:F): 373:43. Ethnicity: Not reported
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (Majority of population combined subtype (73%); baseline ADHD-RS score = 15.8). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	Ba.
Indirectness of population	No indirectness
Interventions	(n=123) Intervention 1: Atomoxetine - Stopping. Placebo following 3-months treatment with atomoxetine on optimal dose (up to 1.8mg/day). Duration up to 9-months. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: >3 months (9 months). 2. Prior length of treatment: 1-3 months (3-months). 3. Study design: Blinded (Blinded following open label phase). (n=82) Intervention 2: Atomoxetine - Stopping. Placebo following 12-months treatment with atomoxetine on optimal dose (up to 1.8mg/day). Duration up to 6-months. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: >3 months (6 months). 2. Prior length of treatment: 6-12 months (12-months). 3. Study design: Blinded (Blinded). (n=292) Intervention 3: Atomoxetine - Continuing. Continuing atomoxetine following 3-months treatment with atomoxetine on optimal dose (up to 1.8mg/day). Duration up to 9-months. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: >3 months (9 months). 2. Prior length of treatment: 1-3 months (3-months). 3. Study design: Blinded (Blinded). (n=81) Intervention 4: Atomoxetine - Continuing. Continuing atomoxetine following 3-months treatment with atomoxetine on optimal dose (up to 1.8mg/day). Duration up to 6-months. Concurrent medication/care: None described Further details: 1. Duration of withdrawal: >3 months (6 months). 2. Prior length of treatment: 6-12 months (12 months). 3. Study design: Blinded (Blinded).
Funding	Study funded by industry (Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING ATX (3M) versus CONTINUING ATX (3M)

Protocol outcome 1: ADHD symptoms total at 3-6 months
- Actual outcome for Children (0-17 years): Change in symptom severity (ADHD-RS total; investigator rated) at 9 months follow-up; Group 1: mean 12.3 (SD 14.3); n=123, Group 2: mean 6.8 (SD 13.6); n=290; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No

indirectness - Actual outcome for Children (0-17 years): Number of patients who relapse (≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S) at 9 months follow-up; Group 1: 59/124, Group 2: 83/292; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: Reduction in adverse outcomes at 3-6 months - Actual outcome for Children (0-17 years): Number of patients with at least 1 new or worsened adverse event at 9 months follow-up; Group 1: 66/123, Group 2: 191/292; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING ATX (12M) versus CONTINUING ATX (12M) Protocol outcome 1: ADHD symptoms total at 3-6 months - Actual outcome for Children (0-17 years): Change in symptom severity (ADHD-RS total; investigator rated) at 6 months follow-up; Group 1: mean 7.8 (SD 12.4); n=81, Group 2: mean 1.7 (SD 9.1); n=77; ADHD-RS-IV total 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (0-17 years): Number of patients who relapse (≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S) at 6 months follow-up; Group 1: 16/82, Group 2: 6/81; Risk of bias: Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 1-2 weeks; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Prince 2000[30]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=25)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Kiddie SADS-E (DSM-IV)
Stratum	Children (0-17 years): Children and adolescents
Subgroup analysis within study	Not applicable
Inclusion criteria	Children and adolescents with ADHD between 6 and 17 years old who responded (as defined as a CGI-I score or 1 or 2 or a reduction in the DSM-IV ADHD rating scale of ≥30%) during an open label trial of

	nortriptyline (NT) over the course of 6 weeks.
Exclusion criteria	People with any clinically significant chronic medical condition, including a personal history of cardiovascular disease, a family history of non-geriatric cardiac disease, mental retardation (IQ <70), organic brain disorders, seizures, pregnant or nursing females, psychotic disorder of any type, bipolar disorder, current abuse or dependence on drugs and/or alcohol within the past 6 months, and current treatment with psychotropics (including anticonvulsants for behavioural control).
Recruitment/selection of patients	Identified through clinical referrals to a paediatric psychopharmacology clinic
Age, gender and ethnicity	Age - Mean (SD): 9.8 (92.6) (original sample). Gender (M:F): 28:7. Ethnicity: Not stated
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (Unclear. 59% with comorbid oppositional disorder, 13% with conduct disorder. No baseline symptom severity reported, however all positive responders to study drug). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	. Demographic data only reported for the original trial participants, and not specifically for those entering the discontinuation phase. Socioeconomic status = 2.3 (SD = 0.9). 57% of participants had previously received a trial of medication.
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Tricyclics - Stopping. Placebo to replace prior 6-week open label treatment with nortriptyline. During the open label phase, NT was titrated up to 1mg/kg/day by the end of week 1, and 2mg/kg/day by week 2, and maintained at 2mg/kg/day unless adverse events emerged of if the participant reported improved ADHD symptoms at a lower dose. Medication was taken before school and after dinner. Duration 3 weeks. Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2 days - 1 month (3 weeks). 2. Prior length of treatment: 1-3 months (6 weeks). 3. Study design: Blinded (Blinded, following open label treatment). Comments: Actual number of participants not provided; overall number in trial divided by 2 is reported here (n=11) Intervention 2: Tricyclics - Continuing. Continuing blinded nortriptyline treatment following 6-week open label treatment with nortriptyline. During the open label phase, NT was titrated up to 1mg/kg/day by the end of week 1, and 2mg/kg/day by week 2, and maintained at 2mg/kg/day unless adverse events emerged of if the participant reported improved ADHD symptoms at a lower dose. Medication was taken before school and after dinner. Duration 3 weeks. Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2 days - 1 month (3 weeks). 2. Prior length of treatment: 1-3 months (6 weeks). 3. Study design: Blinded (Blinded, following open label treatment).
Funding	Study funded by industry (Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING NORTRIPTYLINE versus CONTINUING NORTRIPTYLINE

Protocol outcome 1: CGI-I at 1-2 weeks - Actual outcome for Children (0-17 years): CGI-I at 3 weeks; Group 1: 3/12, Group 2: 8/11; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 1-2 weeks; ADHD symptoms total at 3-6 months; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study (subsidiary papers)	**Upadhyaya 2013[35] (Adler 2014[1], Camporeale 2013[11], Upadhyaya 2015[36])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=524)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 25 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Adults (>18 years): Adults aged 18-50 years
Subgroup analysis within study	Not applicable
Inclusion criteria	18-50 years of age; met DSM-IV-TR criteria for current and childhood ADHD as assessed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV; had a score of >/=2 on at least 6 items of either the inattentive or hyperactive core subscales of the CAARS-Inv-SV with adult ADHD prompts for current symptoms and of the CAARS-O-SV and had a score of >/=20 on CAARS-Inv-SV 18-item total score; a CGI-S rating of >/=4 (moderately ill) at the first two visits. Only those participants who responded to atomoxetine during the earlier phases of the trial (defined as a >/=30% reduction in their baseline CAARS-Inv-SV and a CGI ADHD-S score </=3 (minimally ill)
Exclusion criteria	Individuals who met DSM-IV-TR diagnostic criteria for any history of bipolar disorder, current major depression, a current anxiety disorder or any history of a psychotic disorder; current use of alcohol, drugs, or any prescribed or over the counter medication in a manner that the investigator considered indicative or chronic abuse or who met DSM-IV-TR criteria for alcohol or other substance dependence.
Recruitment/selection of patients	All participants were recruited from an early trial of atomoxetine. This trial consisted of a 4-week washout

	and screening phase, followed by a 12-week open label phase (ATX 40 mg/day with titration to 80 or 100 mg/day by week 8), followed by a 12-week double-blind maintenance of response phase (ATX 80 or 100 mg/day) that immediately preceded the withdrawal phase.
Age, gender and ethnicity	Age - Mean (SD): 33.1 years (9.4). Gender (M:F): 306:218. Ethnicity: 85.7% White; 11.1% Hispanic; 2.1% African
Further population details	1. ADHD severity: Majority moderate (Moderate and above before treatment (a CGI-S rating of >/=4 (moderately ill)); mild at time of randomisation). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness
Interventions	(n=258) Intervention 1: Atomoxetine - Stopping. Placebo. Duration 25 weeks. Concurrent medication/care: Not described Further details: 1. Duration of withdrawal: >3 months (25 weeks). 2. Prior length of treatment: 3-6 months (up to 6 months). 3. Study design: Blinded (Blinded). (n=266) Intervention 2: Atomoxetine - Continuing. 80 or 100 mg/day of atomoxetine, as based on random allocation to dose in previous segment of the trial. Duration 25 weeks. Concurrent medication/care: Not described Further details: 1. Duration of withdrawal: 2. Prior length of treatment: 3. Study design:
Funding	Study funded by industry (Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING ATX versus CONTINUING ATX

Protocol outcome 1: Quality of life at 3-6 months
- Actual outcome for Adults (>18 years): EQ-5D (UK index) at 25 weeks; Group 1: mean 0.9 (SD 0.1); n=258, Group 2: mean 0.9 (SD 0.2); n=266; EQ-5D 0-1 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms total at 3-6 months
- Actual outcome for Adults (>18 years): CAARS (self-report) at 25 weeks; Group 1: mean 16.7 (SD 10.4); n=258, Group 2: mean 14.1 (SD 8.4); n=266; CAARS-S-SV 0-18 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults (>18 years): CAARS (carer-report) at 25 weeks; Group 1: mean 17.9 (SD 10.5); n=258, Group 2: mean 16.2 (SD 10); n=266; CAARS-O-SV 0-18 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Reduction in adverse outcomes at 3-6 months
- Actual outcome for Adults (>18 years): Number of patients experiencing a treatment-related adverse event at 25 weeks; Group 1: 97/258, Group 2: 125/266; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Self-harm at > 3 months - Actual outcome for Adults (>18 years): Suicide-related events (including suicidal ideation and suicidal behaviour) at 25 weeks; Group 1: 3/258, Group 2: 6/266; Risk of bias: Very high; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; ADHD symptoms total at 1-2 weeks; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months

Study	**Waxmonsky 2014[37]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Mean duration 58.3 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV assessed by a 'comprehensive assessment' by a trained clinician, including an assessment of childhood onset
Stratum	Adults (>18 years): Adults >18 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Parents of children aged 5-12 years who, along with their children, were diagnosed with ADHD. Participants were required to have a score of ≥28 on the ADHD-RS along with at least moderate severity on the CGI-S. A 5 or more rating on the family subscale of the Sheehan Disability Scale was also require to demonstrate impaired family functioning. Medication was stopped prior to enrolment.
Exclusion criteria	Parents with medical (e.g. hypertension and other cardiovascular disease) or psychiatric (e.g. mania and substance use disorders) conditions that could be worsened by stimulants or who required psychotropic medications other than stimulants were excluded.
Recruitment/selection of patients	Parent of children with ADHD both recruited as part of a larger trial to investigate the effects of lisdexamphetamine on parent-child interactions.
Age, gender and ethnicity	Age - Mean (SD): 40.7 (5.5). Gender (M:F): 8:22. Ethnicity: 56% Hispanic or Latino; remainder not specified
Further population details	1. ADHD severity: Majority moderate (Participants were required to have a score of ≥28 on the ADHD-RS along with at least moderate severity on the CGI-S. Mean ADHD-RS total score = 39 (SD = 8.63)). 2. Secure

	estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	Demographic data only provided for the original trial, and not specifically for the withdrawal phase. Trial consisted of a medication optimisation phase (3 weeks), followed by a midpoint parent-child interaction assessment for 2 weeks (one week with parent on placebo one week on LDX). This means that half of all parents will have had a 1 week break from LDX prior to randomisation in the withdrawal phase of the trial. After 30 days of randomisation, parents completed another parent-child interaction assessment (one week one placebo, one week on LDX). All participants were responders to lisdexamphetamine (as defined by CGI score of 1 or 2 and ADHD-RS reduced by ≥30%
Indirectness of population	No indirectness: Half of all parents will have had a 1 week break from LDX prior to randomisation to the withdrawal phase of the trial
Interventions	(n=10) Intervention 1: Lisdexamphetamine dimesylate - Stopping. Placebo following treatment with Lisdexamphetamine for 4 or more weeks at optimal dose. During the 1st open label medicines optimisation phase, LDX was started at 30mg and could increase to 50mg for week 2, and 70mg for week 3. Optimal dose was defined as a physically tolerable dose that produced an ADHD-CGI of 1 or 2 plus a ≥30% reduction on the ADHD-RS. Titration ended early if the optimal dose was achieved before week 3. Duration 30 days. Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2 days - 1 month (30 days). 2. Prior length of treatment: 1-3 months (Minimum 4 weeks (maximum 5 weeks)). 3. Study design: Blinded Comments: Half of all participants experienced a 1-week break from treatment prior to randomisation into the withdrawal phase. Timing of withdrawal phase is unclear - text states this phases lasted 30 days, however diagram implies this may have been longer (n=9) Intervention 2: Lisdexamphetamine dimesylate - Continuing. Continuing lisdexamphetamine after at least 4 weeks at optimal dose. During the 1st open label medicines optimisation phase, LDX was started at 30mg and could increase to 50mg for week 2, and 70mg for week 3. Optimal dose was defined as a physically tolerable dose that produced an ADHD-CGI of 1 or 2 plus a ≥30% reduction on the ADHD-RS. Titration ended early if the optimal dose was achieved before week 3. Duration Minimum 30 days (maximum 8 weeks). Concurrent medication/care: Not stated Further details: 1. Duration of withdrawal: 2. Prior length of treatment: 3. Study design: Comments: Half of all participants experienced a 1-week break from treatment prior to randomisation into the withdrawal phase. Timing of withdrawal phase is unclear - text states this phases lasted 30 days, however diagram implies this may have been longer
Funding	Study funded by industry (Shire)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING LDX versus CONTINUING LDX	

Protocol outcome 1: CGI-I at 1-2 weeks - Actual outcome for Adults (>18 years): CGI-I at 30 days follow-up; Group 1: 3/10, Group 2: 7/9; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 1-2 weeks; ADHD symptoms total at 3-6 months; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Wilens 2006[43]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=177)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (0-17 years): Children aged 13-18 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatient children aged 13-18 years with ADHD (any subtype). All with a CGAS score of 41 - 70. All participants entering the withdrawal phase of the study responded positively to OROS methylphenidate during the open label dose optimisation phase of the study
Exclusion criteria	Participants taking medication at the time of enrolment; participants with a history of non-response to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems; clinically important electrocardiographic or blood pressure measurement abnormalities, or coexisting medical conditions or concurrent medications likely to interfere with the safe administration of methylphenidate; participants requiring clonidine or other α²adrenergic receptor agonists, tricyclic antidepressants; selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents; participants with Tourette's syndrome or a family history of Tourette's, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6-months prior to study enrolment, an eating disorder, or marked anxiety, tension, or agitation.

Recruitment/selection of patients	Participants recruited from 15 sites in the US
Age, gender and ethnicity	Age - Mean (SD): 14.6 years (1.5). Gender (M:F): 142:35. Ethnicity: 75.1% White, 13.6% Black, 11.3% other
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (ADHD-RS (Inv) score prior to treatment = 31.26 (all participants)). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	Participants were permitted to use a behavioural modification program during the trial, however were not permitted to alter the program following enrolment. Trial began with a 1-week washout period, and a 4-week open label medication optimisation phase prior to randomisation in the withdrawal phase.
Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Methylphenidate - Stopping. Placebo following treatment with OROS methylphenidate for 2 weeks following dose optimisation phase. during optimisation phase, OROS methylphenidate titrated to optimal dose beginning at 18mg one daily for a mean of 7 days (SD = 2). If criteria for improvement was not met but medication was tolerated, then medication was increased to 36 mg/day for a mean of 7 days (SD = 2). Subjects raised to final maximum dose of 72 mg/day if necessary and it was well tolerated. 8 participants received 18mg, 24 at 36 mg, 26 at 54 mg, 32 at 72 mg. Duration 2 weeks. Concurrent medication/care: Participants were permitted to use a behavioural modification program during the trial, however were not permitted to alter the program following enrolment (unclear how many participants this applied to). Further details: 1. Duration of withdrawal: 2 days - 1 month (2 weeks). 2. Prior length of treatment: 2-4 weeks (1 - 4 weeks, depending on time taken to reach optimal dose). 3. Study design: Blinded (Blinded following open label phase). (n=87) Intervention 2: Methylphenidate - Continuing. Continuing treatment with OROS methylphenidate for 2 weeks following dose optimisation phase. during optimisation phase, OROS methylphenidate titrated to optimal dose beginning at 18mg one daily for a mean of 7 days (SD = 2). If criteria for improvement was not met but medication was tolerated, then medication was increased to 36 mg/day for a mean of 7 days (SD = 2). Subjects raised to final maximum dose of 72 mg/day if necessary and it was well tolerated. 5 participants received 18mg, 25 at 36 mg, 24 at 54 mg, 33 at 72 mg. Duration 2 weeks. Concurrent medication/care: Participants were permitted to use a behavioural modification program during the trial, however were not permitted to alter the program following enrolment (unclear how many participants this applied to). Further details: 1. Duration of withdrawal: 2 days - 1 month (2 weeks). 2. Prior length of treatment: 2-4 weeks (1-4 weeks, depending on time taken to reach optimal dose). 3. Study design: Blinded (Blinded following open label phase).
Funding	Study funded by industry (McNeil Consumer and Specialty Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING OROS MPH versus CONTINUING OROS MPH	

Protocol outcome 1: ADHD symptoms total at 1-2 weeks - Actual outcome for Children (0-17 years): ADHD-RS (parent rated) at 2 weeks follow-up; Group 1: mean 20.84 (SD 13.58); n=90, Group 2: mean 16.65 (SD 11.07); n=87; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (0-17 years): Conners-Wells Adolescent Self-report of Symptoms Scale Score at 2 weeks follow-up; Group 1: mean 75.32 (SD 52.2); n=90, Group 2: mean 57.57 (SD 41.07); n=87; Conners Wells Adolescent Self-Report of Symptoms Scale 0-261 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: CGI-I at 1-2 weeks - Actual outcome for Children (0-17 years): CGI-I (score 1 or 2) at 2 weeks follow-up; Group 1: 28/90, Group 2: 45/87; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Study	**Wolraich 2001[45]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=187)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis confirmed with a diagnostic interview
Stratum	Children (0-17 years): Children 6-12 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 6-12 years with a clinical diagnosis of any subtype of ADHD. Participants who were taking methylphenidate or had taken it in the past had to have been on a total daily dose (IR or IR/SR combination) of between 10mg and 60mg.
Exclusion criteria	Children with an acute or chronic disease; children who were hypersensitive to methylphenidate, were having significant adverse experiences to methylphenidate, or were taking a medication that would interfere with the safe

	administration of methylphenidate; children with glaucoma, Tourette's syndrome, an ongoing seizure disorder, or a psychotic disorder; girls who had reached menarche.
Recruitment/selection of patients	Recruited through radio and newspapers advertisements
Age, gender and ethnicity	Age - Mean (SD): 9 years (1.8). Gender (M:F): Define. Ethnicity: 84.4% White; 7.4% Black; 0.4% Asian; 3.5% Hispanic; 4.3% other
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (73.4% combined subtype; baseline conners IOWA inattention/hyperactivity mean (SD) = 9.7 - 10.3 (3.7 - 4.1); baseline conners IOWA oppositional/defiant mean (SD) = 3.8 - 4.3 (4.2 - 4.5)). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Extra comments	Baseline demographics provided for the full sample, including a group that were switched to OROS MPH
Indirectness of population	Serious indirectness: Not clear that everyone who entered the trial will have experienced a positive response to treatment. 67.7% of participants will have previously been receiving MPH treatment within 4 weeks of the trial, and will have had their dose maintained. Others will have had MPH titrated to optimal response
Interventions	(n=95) Intervention 1: Methylphenidate - Stopping. Stopping MPH (placebo) following either titration to optimal dose (open label 1-4 week titration schedule) or at previously prescribed dose. Participants had either been receiving immediate release or combination of immediate release and slow release. Duration 4 weeks. Concurrent medication/care: Participants were permitted to receive behavioural interventions as long as these had been initiated prior to the study and were not altered during the duration of the study Further details: 1. Duration of withdrawal: 2 days - 1 month (4 weeks). 2. Prior length of treatment: 1-3 months (Minimum treatment duration 4 weeks (32% of the sample), others have previously been receiving treatment for unknown length of time.). 3. Study design: Blinded (Placebo). (n=97) Intervention 2: Methylphenidate - Continuing. Continuing IR MPH following either titration to optimal response over 4 weeks or following previously prescribed treatment. Participants were assigned to one of 3 treatment doses based on either optimal response during titration or conversion from previously prescribed dose (5mg, 10mg, 15mg). Duration 4 weeks. Concurrent medication/care: Participants were permitted to use a behavioural therapy during the trial, however were not permitted to alter the program following enrolment (unclear how many participants this applied to). Further details: 1. Duration of withdrawal: 2 days - 1 month (1 month). 2. Prior length of treatment: 1-3 months (Minimum treatment duration 4 weeks (32% of the sample), others have previously been receiving treatment for unknown length of time.). 3. Study design: Blinded (Placebo).
Funding	Study funded by industry (Study funded by ALZA corporation on behalf of Crescendo Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING MPH versus CONTINUING MPH	

Protocol outcome 1: ADHD symptoms total at 1-2 weeks - Actual outcome for Children (0-17 years): IOWA Conners inattention/overactivity (teacher rated) at 4 weeks; Group 1: mean 9.77 (SD 4.02); n=95, Group 2: mean 6.35 (SD 4.31); n=97; IOWA conners 0-15 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (0-17 years): IOWA Conners inattention/overactivity (parent rated) at 4 weeks; Group 1: mean 10.11 (SD 3.92); n=95, Group 2: mean 6.17 (SD 3.19); n=97; IOWA conners 0-15 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (0-17 years): IOWA Conners oppositional/defiance (teacher rated) at 4 weeks; Group 1: mean 5.38 (SD 5.13); n=95, Group 2: mean 2.5 (SD 3.7); n=97; IOWA conners 0-15 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (0-17 years): IOWA Conners oppositional/defiance (parent rated) at 4 weeks; Group 1: mean 8.6 (SD 4.82); n=95, Group 2: mean 4.98 (SD 3.81); n=97; IOWA conners 0-15 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: CGI-I at 1-2 weeks - Actual outcome for Children (0-17 years): Mean CGI-I at 4 weeks; Group 1: mean 2.48 (SD 1.67); n=95, Group 2: mean 4.19 (SD 1.45); n=97; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 1-2 weeks; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

D.2 Drug holidays

Study	**Martins 2004[25]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Brazil; Setting: Recruited from an ADHD outpatient clinic (university hospital)
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Semi-structured interview (K-SADS-E) modified to assess DSM-IV criteria
Stratum	Children (0-17 years): Age 6-14 years
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD diagnosis using DSM-IV, age between 6-14 years, male gender, education level between 1st and 8th elementary grade

Exclusion criteria	Presence of a significant neurological or clinical disease; presence of bipolar disorder or substance use/dependence disorder; use of any psychiatric medication in the last 6-months, including methylphenidate; estimate IQ lower than 70 (assessed using WISC-III)
Age, gender and ethnicity	Age - Range of means: 9 - 9.6 (2.2 - 2.8). Gender (M:F): 100% male. Ethnicity: Majority European-Brazilian (77%)
Further population details	1. ADHD severity: Not applicable / Not stated / Unclear (Basal T-score in attention on the CBCL = 72 (9), and on the teacher report form = 74 (11)). 2. Secure estate: Not applicable / Not stated / Unclear (Not stated).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Methylphenidate - Stopping. Methylphenidate on weekdays with placebo administered blindly on weekends. The initial dose of MPH was 0.3 mg/kg/day on the first week. The dose was raised to 0.50 mg/kg/day on the second week and to 0.70 mg/kg/day on the third and fourth weeks, unless the emergence of adverse effects pre- vented the increase. MPH was administered orally, in individual doses, twice a day, after breakfast and lunch (James et al. 2001). Both methylphenidate and placebo pills were of the same shape and colour. A 1-week supply of pills was provided for each patient in blister packs labelled with their names, date, time of administration, and schedule. he initial dose of MPH was 0.3 mg/kg/day on the first week. The dose was raised to 0.50 mg/kg/day on the second week and to 0.70 mg/kg/day on the third and fourth weeks, unless the emergence of adverse effects prevented the increase. MPH was administered orally, in individual doses, twice a day, after breakfast and lunch. Both methylphenidate and placebo pills were of the same shape and colour. A 1-week supply of pills was provided for each patient in blister packs labelled with their names, date, time of administration, and schedule. Duration 4 weeks. Concurrent medication/care: Not described Further details: 1. Duration of withdrawal: 1-2 days (including weekend) (Weekend). 2. Prior length of treatment: 2-4 weeks (0-4 weeks). 3. Study design: Blinded (Blinded). (n=21) Intervention 2: Methylphenidate - Continuing. Methylphenidate received 7 days a week. The initial dose of MPH was 0.3 mg/kg/day on the first week. The dose was raised to 0.50 mg/kg/day on the second week and to 0.70 mg/kg/day on the third and fourth weeks, unless the emergence of adverse effects prevented the increase. MPH was administered orally, in individual doses, twice a day, after breakfast and lunch. A 1-week supply of pills was provided for each patient in blister packs labelled with their names, date, time of administration, and schedule. Duration 4 weeks. Concurrent medication/care: Not described Further details: 1. Duration of withdrawal: 1-2 days (including weekend) (Weekend). 2. Prior length of treatment: 2-4 weeks (0-4 weeks). 3. Study design: Blinded (Blinded).
Funding	Equipment / drugs provided by industry (Hospital research fund supported the project. Industry provided the drug and placebo 'at no cost and without restrictions'.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STOPPING MPH versus CONTINUING MPH

Protocol outcome 1: ADHD symptoms total at 1-2 weeks
- Actual outcome for Children (0-17 years): Conners abbreviated rating scale (ABRS) - Parent rating at 4 weeks. Ratings directed towards symptoms over the final weekend; Other: Effect size = 0.26 (looks as if scores are higher in the MPH group, but analysis detected no difference) (p value 0.26) Conners ABRS 0-30 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (0-17 years): Conners abbreviated rating scale (ABRS) - Teacher rating at 4 weeks. Ratings directed towards symptoms on the first day back after the weekend; Other: Effect size = 0.002 (no discernible difference between the 2 groups on the return to school. Data only displayed on a graph). (p value 0.99); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Reduction in adverse outcomes at 1-2 weeks
- Actual outcome for children (0-17 years): Barkley side effect rating scale – Parent rating at 4 weeks. Ratings directed towards symptoms over the final weekend. SMD = 0.45; 95% CI = -0.16 – 1.06) (calculated from t-score); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at 1-2 weeks; Quality of life at 3-6 months; ADHD symptoms total at 3-6 months; CGI-I at 1-2 weeks; CGI-I at 3-6 months; Behaviour/function at 1-2 weeks; Behaviour/function at 3-6 months; Reduction in adverse outcomes at 3-6 months; Serious adverse outcomes at Any timepoint; Emotional dysregulation at 1-2 weeks; Academic outcomes at >3 months; Substance use at > 3 months; Self-harm at > 3 months

Appendix E: Forest plots

E.1 Withdrawal from pharmacological treatment

E.1.1 Evidence for children and young people

E.1.1.1 Evidence for withdrawing methylphenidate

Figure 3: ADHD symptoms at 2 weeks (as assessed using Conners Wells Adolescent Self-report of symptoms Scale; range 0-261; high is poor outcome)

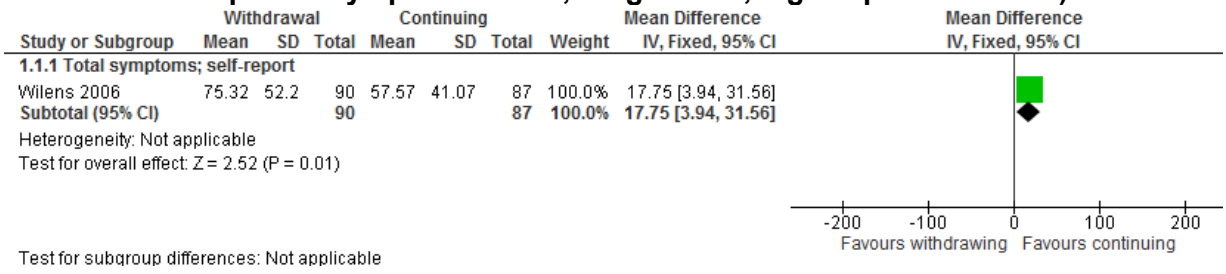


Figure 4: ADHD symptoms at 2 weeks (as assessed using ADHD-RS; parent rated; range 0-54; high is poor outcome)

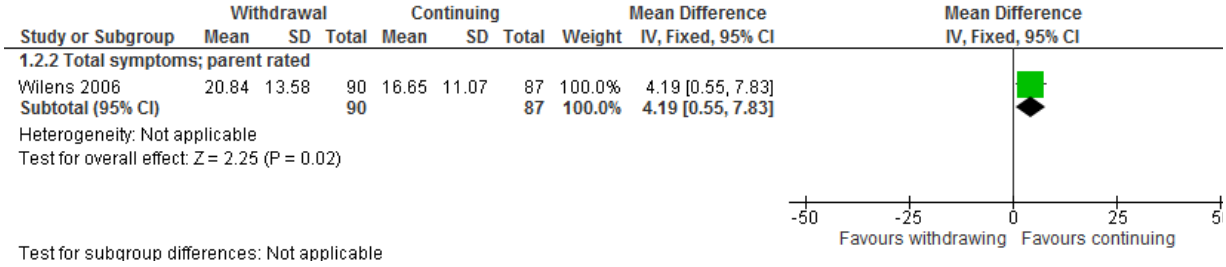


Figure 5: CGI-I at 2 weeks (number of participants rated as 'much improved' or 'very much improved')

E.1.1.2 Evidence for withdrawing methylphenidate in participants who may not have all experienced a positive response to methylphenidate

Figure 6: ADHD symptoms at 4 weeks (as assessed by the IOWA Conners scale; range 0-15; high is poor outcome)

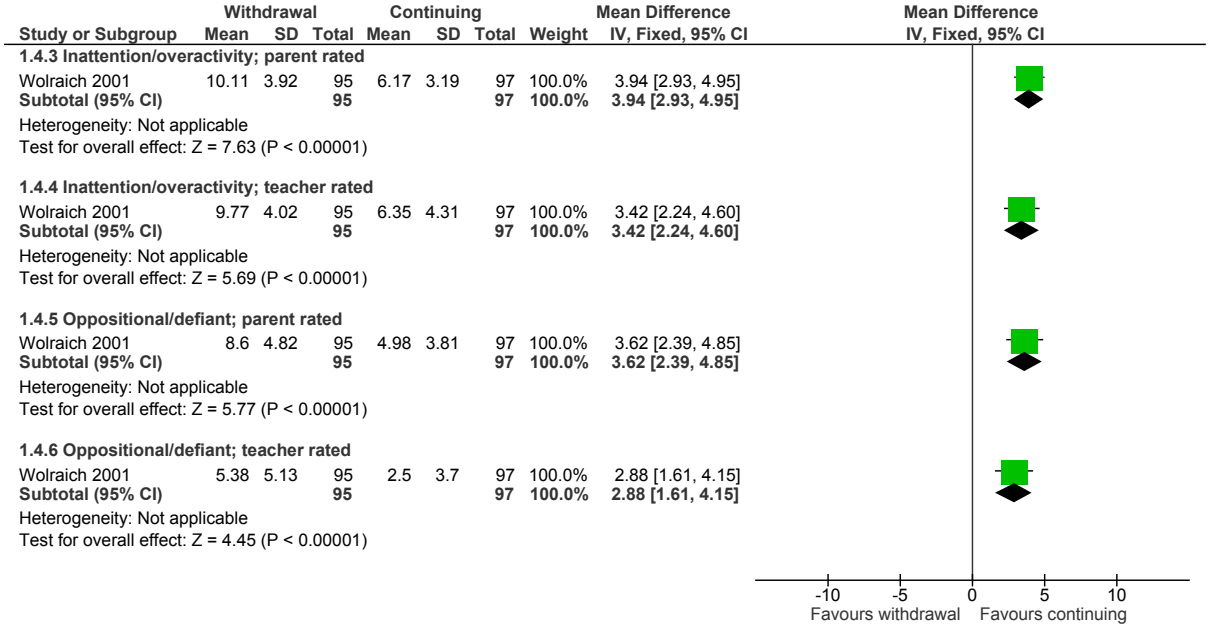
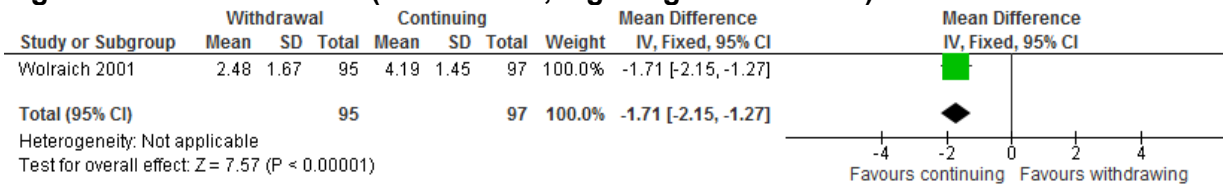


Figure 7: CGI-I at 4 weeks (mean score, high is good outcome)



E.1.1.3 Evidence for withdrawing Atomoxetine

Figure 8: Change in ADHD symptoms at 6-9-months (as assessed by ADHD-RS-IV; range 0-54; high is poor outcome)

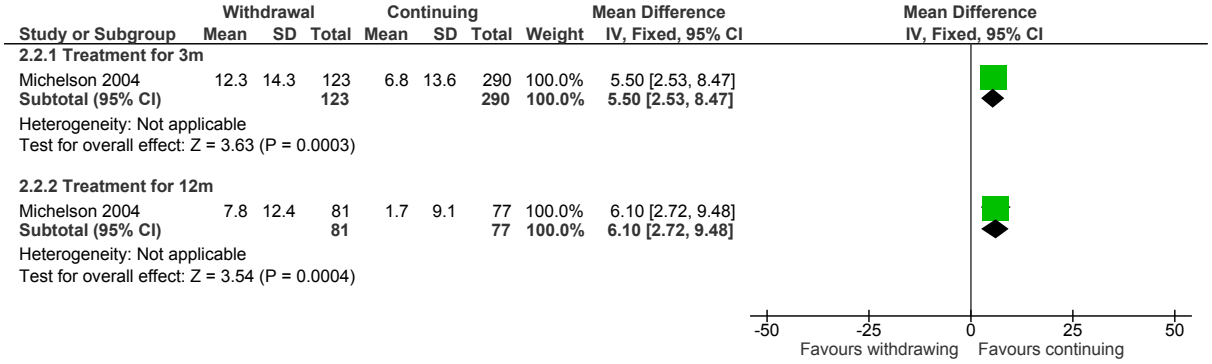


Figure 9: ADHD symptoms (relapse) at 6-9 months (number of participants who experienced a ≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S)

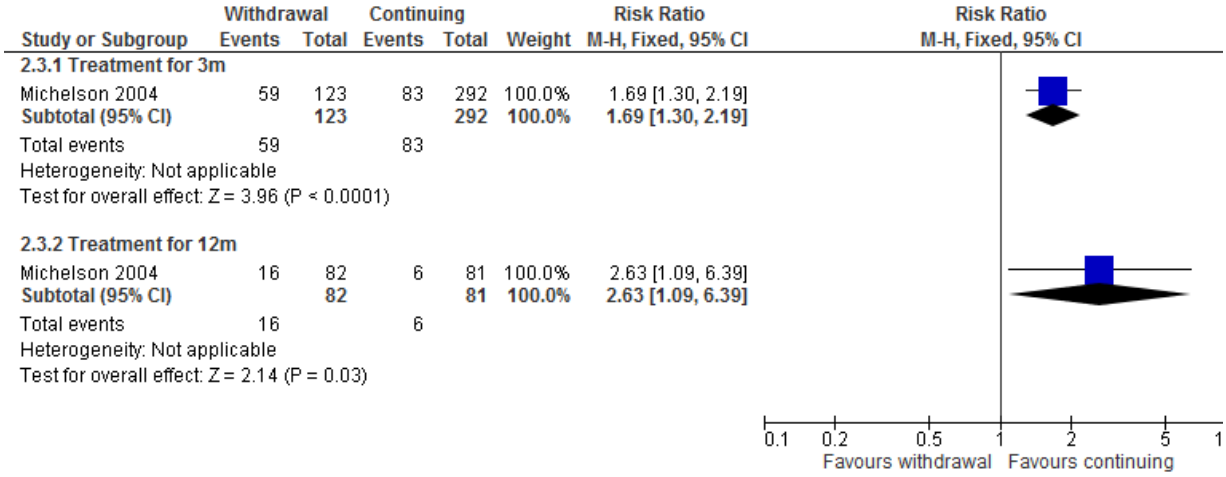


Figure 10: Adverse outcomes at 9-months (number of people who experienced at least 1 new or worsened adverse event)

E.1.1.4 Evidence for withdrawing Lisdexamphetamine

Figure 11: Change in ADHD symptoms at 6 weeks (as assessed by ADHD-RS-IV; range 0-54; high is poor outcome)

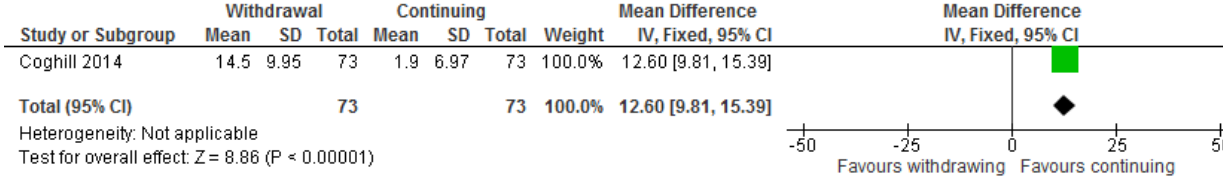
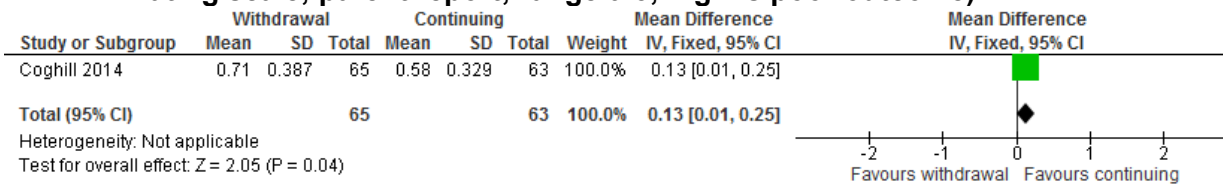
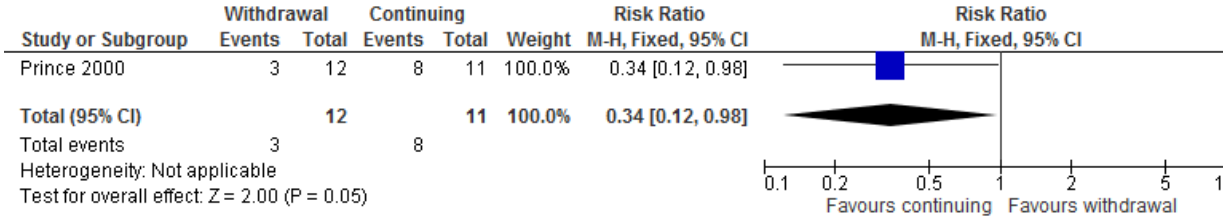


Figure 12: Behaviour at 6 weeks (as assessed by the Weiss functional impairment rating scale; parent report; range 0-3; high is poor outcome)



E.1.1.5 Evidence for withdrawing nortriptyline

Figure 13: CGI-I at 3 weeks (number of participants who were rated as 'much improved' or 'very much improved')



E.1.2 Evidence in adults

E.1.2.1 Evidence for withdrawing methylphenidate

Figure 14: Health-related quality of life at 4 weeks (as assessed by Q-LES-Q short form; range is unclear; assumed that high is good outcome but unclear)

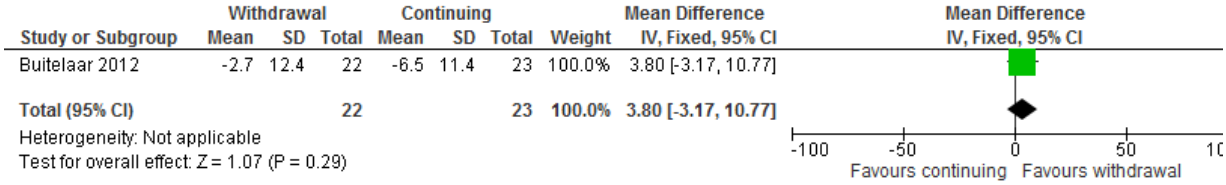


Figure 15: Change in ADHD symptoms at 4 weeks (as assessed by CAARS:S-SV; self-report; range 0-54; high is poor outcome)

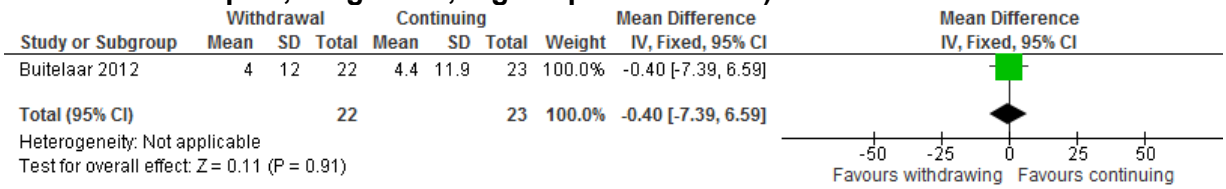


Figure 16: ADHD symptoms (relapse) at 4 weeks (≥50% increase in symptoms from baseline on CAARS:O-SV/CGI-I of 'much worse' or 'very much worse'/ worsening AISRS score so that relative improvement relative to baseline severity was <15% improvement for 2 consecutive visits by the second study) and 6 months (≥30% increase in ADHD-RS and score<30% improvement since baseline)

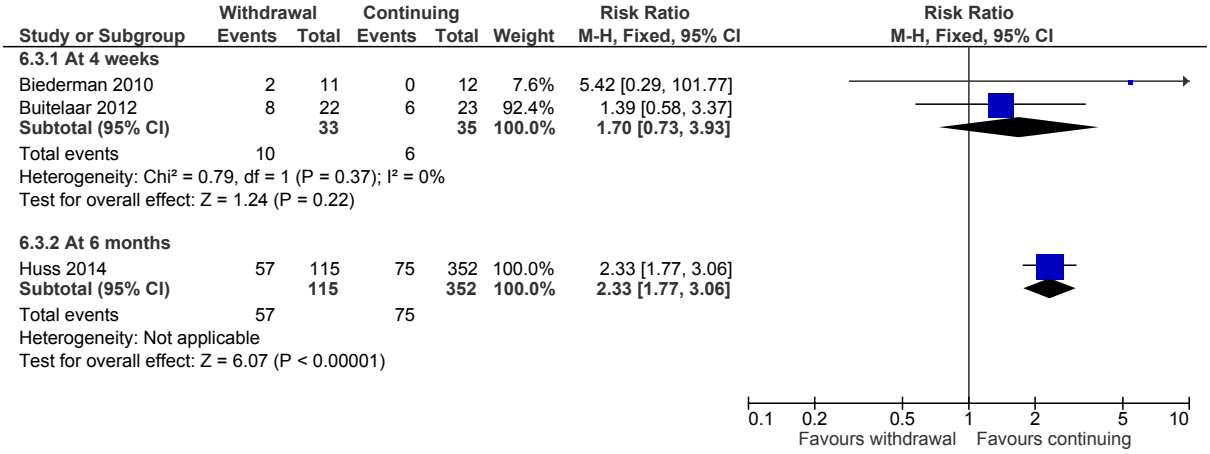


Figure 17: Change in function at 4 weeks (as assessed by the Sheehan disability scale; range 0-30; high is poor outcome)

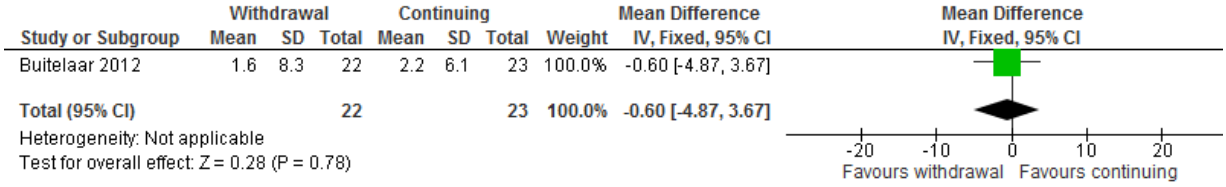


Figure 18: Adverse outcomes at 6 months (as assessed by the number of participants who experienced any adverse event)

E.1.2.2 Evidence for withdrawing Atomoxetine

Figure 19: Health related quality of life at 25 weeks (as assessed by EQ-5D; range 0-1; high is good outcome)

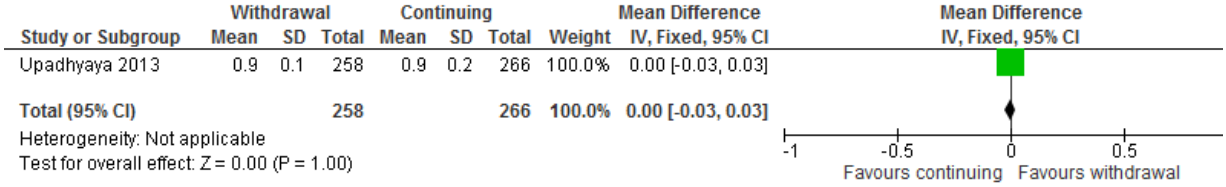


Figure 20: ADHD symptoms at 25 weeks (as assessed by CAARS; range 0-18; high is poor outcome)

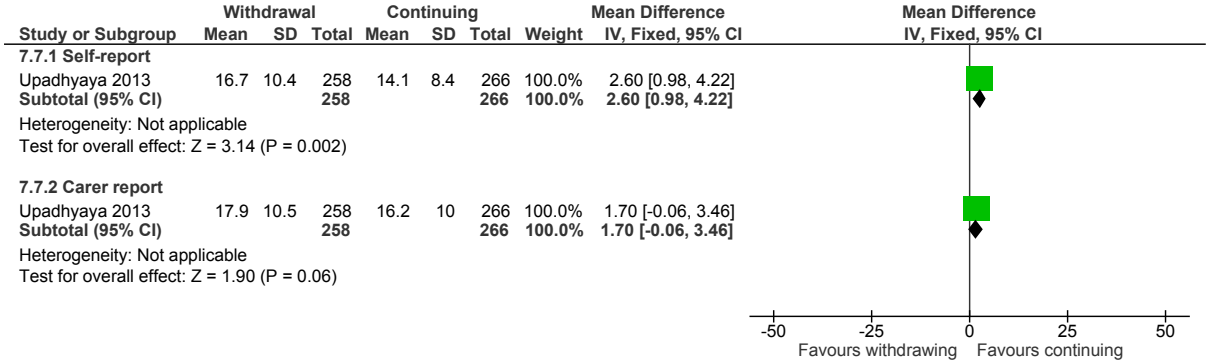


Figure 21: Adverse outcomes at 25 weeks (number of participants who experienced a treatment-related adverse event)

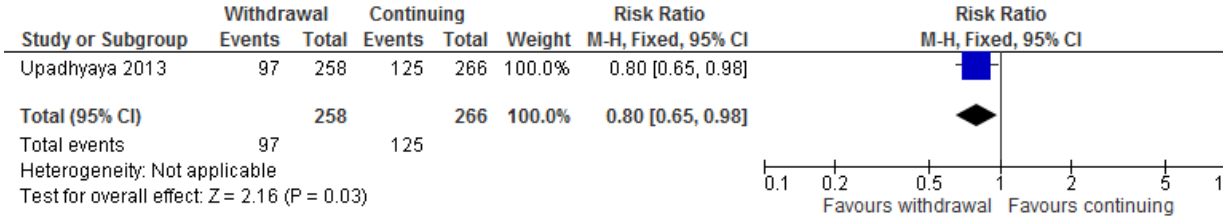
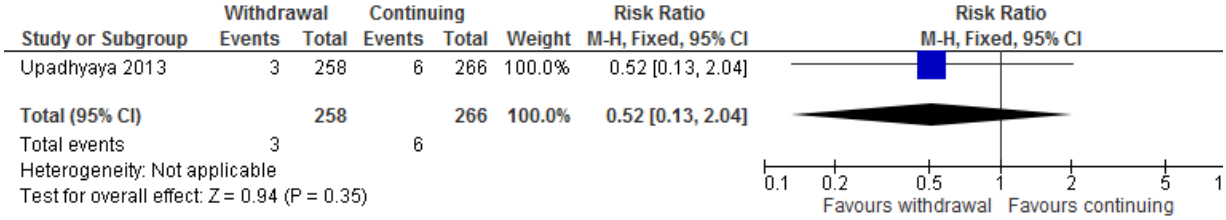


Figure 22: Self-harm at 25 weeks (as assessed by number of participants who experienced 'suicide-related events', including suicidal ideation and suicidal behaviour)



E.1.2.3 Evidence for withdrawing Lisdexamphetamine

Figure 23: Change in ADHD symptoms at 4 weeks (as assessed by ADHD-RS-IV; range 0-54; high is poor outcome)

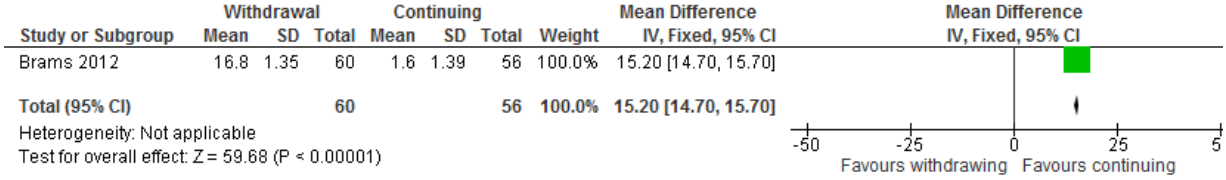
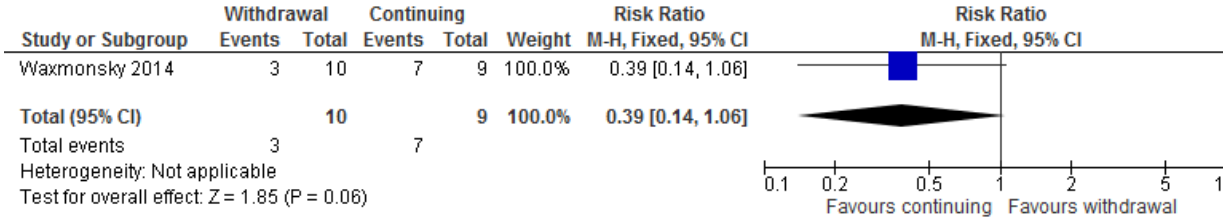


Figure 24: CGI-I at 4 weeks (number of participants who were rated as 'much improved' or 'very much improved')



E.2 Drug holidays

E.2.1 Weekend breaks from pharmacological treatment

Figure 25: ADHD symptoms (assessed using the Conners' Abbreviated Rating Scale; scale 0 – 5, higher scores indicates poorer outcome)

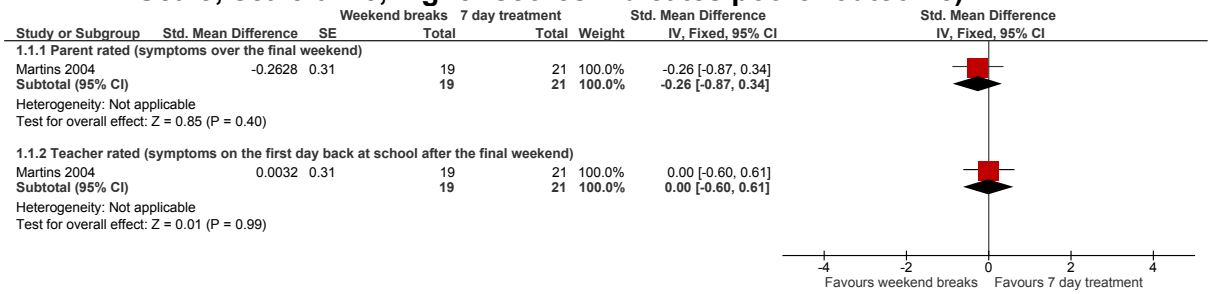
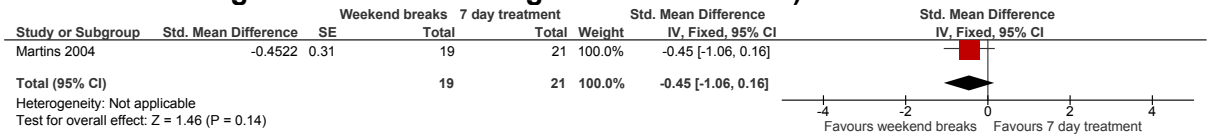


Figure 26: Mean number of adverse events on the final weekend (assessed using the Side effect Rating Scale; unclear scale range and direction (possibly 0-5 with higher scores indicating more side effects)



Appendix F: GRADE tables

F.1 Withdrawal from pharmacological treatment

Table 21: Clinical evidence profile: Stopping methylphenidate versus continuing methylphenidate in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping methylphenidate vs. continuing methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD symptoms (1-2 weeks) - Total symptoms; self-report (follow-up mean 2 weeks; measured with: Conners Wells Adolescent Self-Report of Symptoms Scale: 0-261. High is poor outcome; range of scores: 0-261; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	90	87	-	MD 17.75 higher (3.94 to 31.56 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (1-2 weeks) - Total symptoms; parent rated (follow-up mean 2 weeks; measured with: ADHD-RS: Parent rated; 0-54. High is poor outcome; range of scores: 0-54; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	90	87	-	MD 4.19 higher (0.55 to 7.83 higher)	⊕⊕⊕O MODERATE	CRITICAL
CGI-I (follow-up mean 2 weeks; assessed with: (number of people who are much improved or very much improved (score 1 or 2))												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[b]	no serious imprecision	none	28/90 (31.1%)	45/87 (51.7%)	RR 0.6 (0.42 to 0.87)	207 fewer per 1000 (from 67 fewer to 300 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[b] Outcome varies from protocol; rather than number of people who were rated as being 'much worse' or 'very much worse', this outcome is the number of people who improved following continuation or withdrawal from treatment

Table 22: Clinical evidence profile: Stopping methylphenidate versus continuing methylphenidate in participants who may not have all experienced a positive response to methylphenidate in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping methylphenidate vs. continuing methylphenidate in participants who may not have all experienced a positive response to methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD symptoms (1-2 weeks) - Inattention/overactivity; parent rated (Copy) (follow-up mean 4 weeks; measured with: IOWA conners: 0-15. High is poor outcome; range of scores: 0-15; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	95	97	-	MD 3.94 higher (2.93 to 4.95 higher	⊕⊕OO LOW	CRITICAL
ADHD symptoms (1-2 weeks) - Inattention/overactivity; teacher rated (Copy) (follow-up mean 4 weeks; measured with: IOWA conners: 0-15. High is poor outcome; range of scores: 0-15; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	95	97	-	MD 3.42 higher (2.24 to 4.60 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (1-2 weeks) - Oppositional/defiant; teacher rated (Copy) (follow-up mean 4 weeks; measured with: IOWA conners: 0-15. High is poor outcome; range of scores: 0-15; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	95	97	-	MD 3.62 higher (2.39 to 4.85 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (1-2 weeks) - Oppositional/defiant; parent rated (Copy) (follow-up mean 4 weeks; measured with: IOWA conners: 0-15. High is poor outcome; range of scores: 0-												

15; Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	95	97	-	MD 2.88 higher (1.61 to 4.15 higher)	⊕⊕OO LOW	CRITICAL
CGI-I (follow-up mean 4 weeks; measured with: Mean score on the CGI-I; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	95	97	-	MD 1.71 lower (2.15 to 1.27 lower)	⊕⊕OO LOW	CRITICAL

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

Table 23: Clinical evidence profile: Stopping atomoxetine versus continuing atomoxetine in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stopping atomoxetine vs. continuing atomoxetine**	**Control**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (Treatment for 3m) (follow-up mean 9 months; measured with: Change in ADHD-RS-IV; range of scores: 0-54; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	123	290	-	MD 5.5 higher (2.53 to 8.47 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (change at 6-9 months) - Treatment for 12m (follow-up mean 6 months; measured with: change in ADHD-RS-IV; range of scores: 0-54; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	81	77	-	MD 6.1 higher (2.72 to 9.48 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (relapse; treatment for 3m) (follow-up mean 9 months; assessed with: Number of people who 'relapsed'; defined by ≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S)												

1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[b]	no serious imprecision	none	59/123 (48%)	83/292 (28.4%)	RR 1.69 (1.3 to 2.19)	196 more per 1000 (from 85 more to 338 more)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (relapse; treatment for 12m) (follow-up mean 6 months; assessed with: Number of people who 'relapsed'; defined by ≥50% increase in ADHD-RS-IV and ≥2 increase in CGI-S)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[b]	Serious[a]	none	16/82 (19.5%)	6/81 (7.4%)	RR 2.63 (1.09 to 6.39)	121 more per 1000 (from 7 more to 399 more)	⊕⊕OO LOW	CRITICAL
Adverse outcomes (follow-up mean 9 months; assessed with: Number of participants with at least 1 new or worsened adverse event)												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	Serious[a]	none	66/123 (53.7%)	191/292 (65.4%)	RR 0.82 (0.68 to 0.99)	118 fewer per 1000 (from 7 fewer to 209 fewer)	⊕⊕OO LOW	CRITICAL

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[b] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[c] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 24: Clinical evidence profile: Lisdexamphetamine versus continuing Lisdexamphetamine in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stopping lisdexamphetamine vs. continuing lisdexamphetamine**	**Control**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (follow-up mean 6 weeks; measured with: change in ADHD-RS-IV; range of scores: 0-54; Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	Serious[b]	no serious imprecision	none	73	73	-	MD 12.6 higher (9.81 to 15.39 higher)	⊕OOO VERY LOW	CRITICAL
Behaviour at 1-2 weeks (follow-up mean 6 weeks; measured with: Weiss functional impairment rating scale (Parent report) (WFIRS-P) [assesses function in previous 4 weeks; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[a]	no serious inconsistency	Serious[b]	Serious[c]	none	65	63	-	MD 0.13 higher (0.01 to 0.25	⊕OOO VERY	IMPORTANT

										higher)[4]	LOW	

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Clinical evidence profile: Nortriptyline versus continuing Nortriptyline in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping Nortriptyline vs. continuing Nortriptyline	Control	Relative (95% CI)	Absolute		
CGI-I (follow-up mean 3 weeks; assessed with: The number of people who are much improved or very much improved; score of 1-2)												
1	randomised trials	Serious[a]	no serious inconsistency	Serious[b]	Serious[c]	none	3/12 (25%)	8/11 (72.7%)	RR 0.34 (0.12 to 0.98)	480 fewer per 1000 (from 15 fewer to 640 fewer)	⊕OOO VERY LOW	CRITICAL

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence profile: Stopping methylphenidate versus continuing methylphenidate in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping methylphenidate vs. continuing methylphenidate	Control	Relative (95% CI)	Absolute		
Health related quality of life (follow-up mean 4 weeks; measured with: Change in Q-LES-Q (short form); range of scores: ?-?; Better indicated by higher values)												

1	randomised trials	Serious[b]	no serious inconsistency	Serious[c]	Serious[d]	none	22	23	-	MD 3.8 higher (3.17 lower to 10.77 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (follow-up mean 4 weeks; measured with: Change in CAARS:S-SV total (self-reported) ; range of scores: 0-84; Better indicated by lower values)												
1	randomised trials	Serious[b]	no serious inconsistency	Serious[c]	no serious imprecision	none	22	23	-	MD 0.4 lower (7.39 lower to 6.59 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (relapse) (follow-up mean 4 weeks; assessed with: the number of patients who relapse (defined as ≥50% increase in symptoms from baseline on the CAARS:O-SV in one study; and CGI-I score of 'much worse' or 'very much worse' or a worsening in the AISRS score so that relative improvement relative to baseline severity was <15% improvement for 2 consecutive visits by the second study))												
2	randomised trials	Serious[b]	no serious inconsistency	Serious[c]	Serious[d]	none	10/33 (30.3%)	6/35 (17.1%)	RR 1.7 (0.73 to 3.93)	120 more per 1000 (from 46 fewer to 502 more)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (relapse) (follow-up mean 6 months; assessed with: Number of patients who experienced a ≥30% increase in ADHD-RS and whose score was <30% improvement since the beginning of all of the trial phases)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[c]	no serious imprecision	none	57/115 (49.6%)	75/352 (21.3%)	RR 2.33 (1.77 to 3.06)	283 more per 1000 (from 164 more to 439 more)	⊕⊕⊕O MODERATE	CRITICAL
Behaviour (follow-up mean 4 weeks; measured with: Change in function (Sheehan disability scale); range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[c]	very serious[d]	none	22	23	-	MD 0.6 lower (4.87 lower to 3.67 higher)	⊕OOO VERY LOW	IMPORTANT
Adverse outcomes (follow-up mean 6 months; assessed with: Number of patients who experienced any adverse event)												
1	randomised trials	Serious[b]	no serious inconsistency	Serious[c]	no serious imprecision	none	44/121 (36.4%)	197/361 (54.6%)	RR 0.67 (0.52 to 0.86)	180 fewer per 1000 (from 76 fewer to 262 fewer)	⊕⊕OO LOW	CRITICAL

[a] Unclear if participants' score were transformed into a percentage, or if raw scores were used (range of raw scores is 14-70)
[b] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[d] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: Stopping Atomoxetine versus continuing Atomoxetine in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping Atomoxetine vs. continuing Atomoxetine	Control	Relative (95% CI)	Absolute		
Health related quality of life (follow-up mean 25 weeks; measured with: EQ-5D; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	258	266	-	MD 0 higher (0.03 lower to 0.03 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
ADHD symptoms (follow-up mean 25 weeks; measured with: CAARS (self-report); range of scores: 0-18; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	258	266	-	MD 2.6 higher (0.98 to 4.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (follow-up mean 25 weeks; measured with: CAARS (carer-report); range of scores: 0-18; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	258	266	-	MD 1.7 higher (0.06 lower to 3.46 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse outcomes (follow-up mean 25 weeks; assessed with: Number of patients experiencing a treatment-related adverse event)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[b]	Serious[a]	none	97/258 (37.6%)	125/266 (47%)	RR 0.8 (0.65 to 0.98)	94 fewer per 1000 (from 9 fewer to 164 fewer)	⊕⊕OO LOW	CRITICAL
Self-harm (follow-up mean 25 weeks; assessed with: Number of participants experiencing Suicide-related events (including suicidal ideation and suicidal behaviour))												
1	randomised trials	Serious[c]	no serious inconsistency	Serious[b]	no serious imprecision	none	3/258 (1.2%)	6/266 (2.3%)	RR 0.52 (0.13 to 2.04)	11 fewer per 1000 (from 20 fewer to 23 more)	⊕⊕OO LOW	IMPORTANT

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[b] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect

population or outcomes
[c] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 28: Clinical evidence profile: Lisdexamphetamine versus continuing lisdexamphetamine in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping lisdexamphetamine vs continuing lisdexamphetamine	Control	Relative (95% CI)	Absolute		
ADHD symptoms (follow-up mean 4 weeks; measured with: Change in ADHD-RS-IV; range of scores: 0-54; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[a]	no serious imprecision	none	60	56	-	MD 15.2 higher (14.7 to 15.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
CGI-I (follow-up mean 4 weeks; assessed with: number of people who are 'much improved' or 'very much improved' (i.e. score of 1 or 2))												
1	randomised trials	very serious[b]	no serious inconsistency	no serious indirectness	Serious[c]	none	3/10 (30%)	7/9 (77.8%)	RR 0.39 (0.14 to 1.06)	474 fewer per 1000 (from 669 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL

[a] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[b] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[c] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.2 Drug holidays

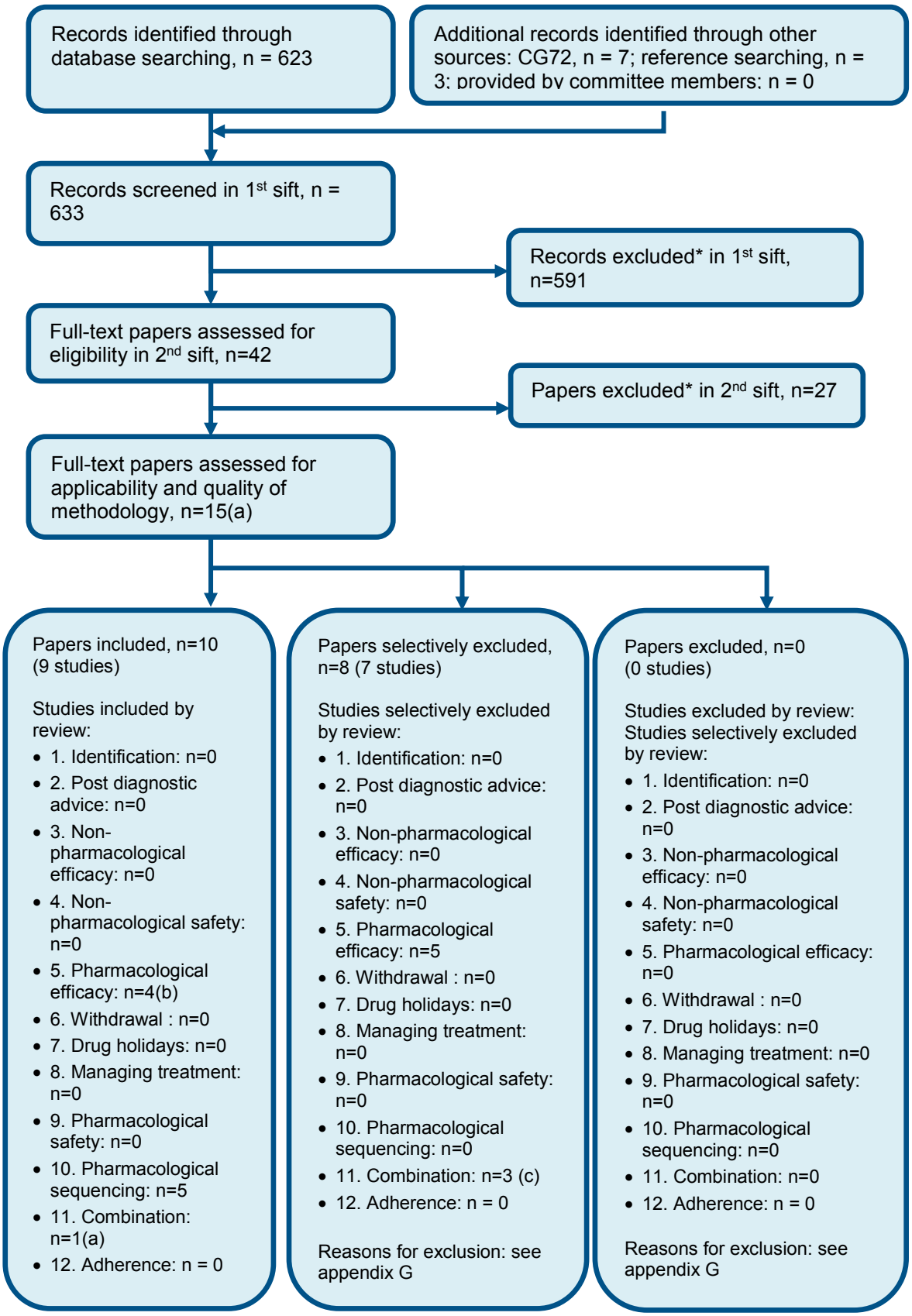
Table 29: Clinical evidence profile: Weekend breaks from treatment vs. 7 day treatment

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Weekend breaks**	**7 day treatment**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms - Parent rated (symptoms over the final weekend) (follow-up mean 4 weeks; measured with: Conners Abbreviated Rating Scale; range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	21	-	SMD 0.26 lower (0.87 lower to 0.34 higher)	VERY LOW	CRITICAL
ADHD symptoms - Teacher rated (symptoms on the first day back at school after the final weekend) (follow-up mean 4 weeks; measured with: Conners Abbreviated Rating Scale; range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19	21	-	SMD 0 higher (0.6 lower to 0.61 higher)	VERY LOW	CRITICAL
Number of adverse events on the final weekend of the trial (follow-up mean 4 weeks; measured with: Barkley's side effect rating scale; range of scores: 0-9; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	21	-	SMD 0.45 higher (0.16 lower to 1.06 higher)	VERY LOW	CRITICAL

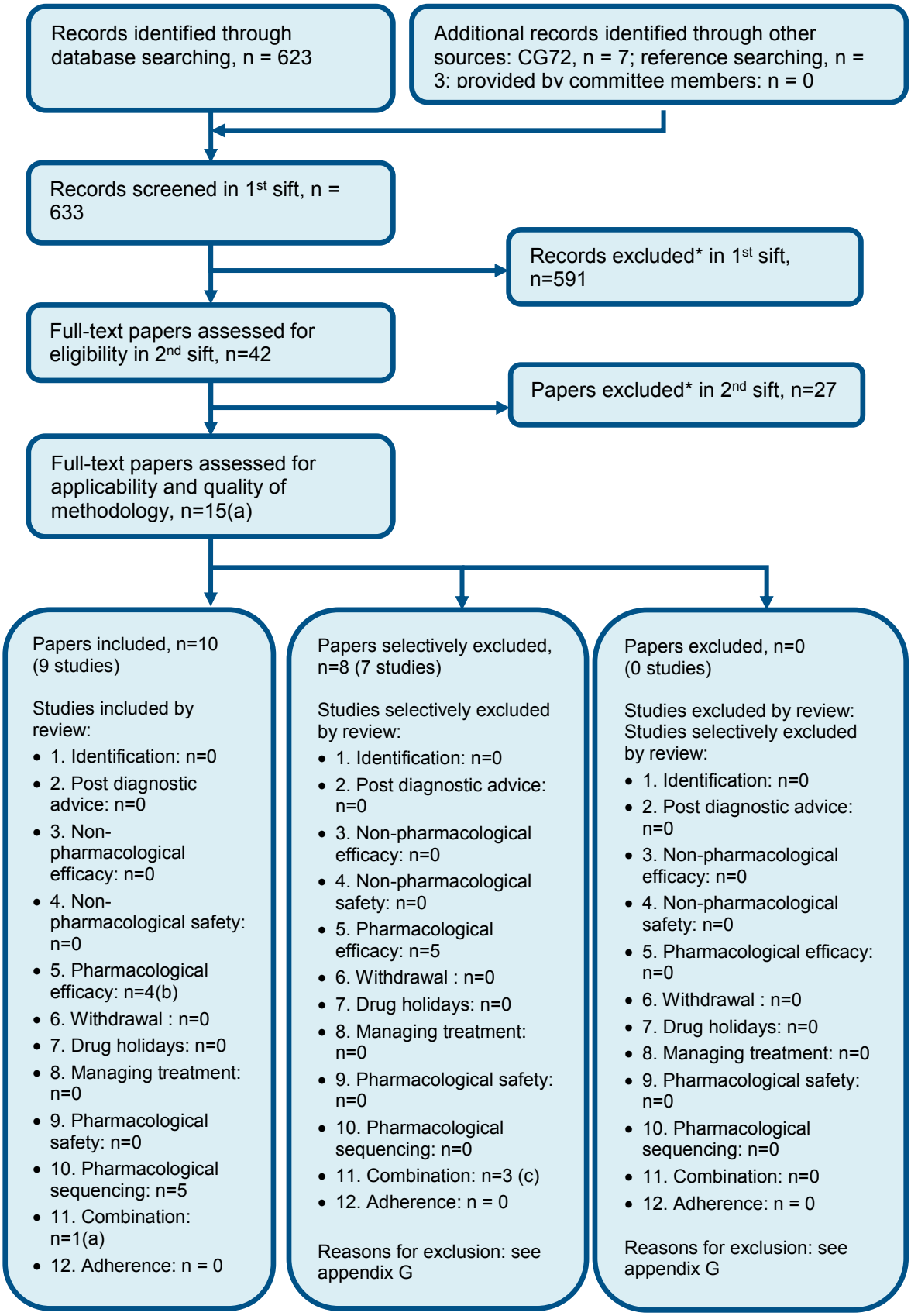
Appendix G: Health economic evidence selection

G.1 Withdrawal from pharmacological treatment



** Non-relevant population, intervention, comparison, design or setting; non-English language*
(a) Note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.
(b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included under Q5 only.
(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in this flowchart.

G.2 Drug holidays



* Non-relevant population, intervention, comparison, design or setting; non-English language

(a) note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.
(b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included under Q5 only.
(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in this flowchart.

Appendix H: Health economic evidence tables

H.1 Withdrawal from pharmacological treatment

None.

H.2 Drug holidays

None.

Appendix I: Excluded studies

I.1 Withdrawal from pharmacological treatment

I.1.1 Excluded clinical studies

Table 30: Studies excluded from the clinical review

Study	Exclusion reason
Adler 2008[2]	Incorrect study design
Biederman 2007[4]	Incorrect interventions
Brams 2011[6]	Withdrawal phase is a randomised crossover with no data reported following the first treatment allocation
Brown 2010[8]	Withdrawal phase is a randomised crossover with no data reported following the first treatment allocation
Chen 2011[12]	Incorrect study design
Dopfner 2004[14]	Inappropriate comparison
Fox 2014[15]	No relevant outcomes
Giblin 2011[16]	No relevant outcomes
Greenhill 2006[17]	Crossover phase is <minimum duration; parallel phase has an inappropriate washout
Haas 2008[18]	Not guideline condition
Hoebert 2009[20]	Incorrect study design
Huss 2014[21]	Same trial as other Huss study, no withdrawal data provided
Kent 2013[23]	Incorrect interventions
Mccarthy 2009[26]	Incorrect study design
Murray 2011[28]	Open label phase followed by 2 day crossover (1 day drug, 1 day placebo). 1 day
Reyes 2006[31]	Not guideline condition
Sandler 2008[32]	Inappropriate comparison
Sandler 2010[33]	Incorrect interventions
Swanson 2006[34]	Incorrect population (only 37% of participants experienced a positive response to the study drug prior to randomisation)
Wigal 2009[39]	Withdrawal phase was a crossover, with no data provided after the first phase
Wigal 2010[38]	Withdrawal phase is a crossover design, with no data provided following the first phase
Wigal 2010[42]	Withdrawal phase is a randomised crossover with no data reported following the first treatment allocation
Wigal 2011[40]	Withdrawal phase is a crossover with no data provided after the first phase
Wigal 2011[41]	Crossover with no data provided at the end of phase 1
Williamson 2014[44]	Withdrawal phase was a crossover with no data provided following first phase

I.1.2 Excluded health economic studies

None

I.2 Drug holidays

I.2.1 Excluded clinical studies

Table 31: Studies excluded from the clinical review

Study	Exclusion reason
Adler 2008[2]	Incorrect study design
Adler 2014[1]	Incorrect interventions
Banaschewski 2014[3]	Incorrect interventions
Biederman 2007[4]	Incorrect interventions
Biederman 2010[5]	Incorrect interventions
Brams 2011[6]	Incorrect interventions
Brams 2012[7]	Incorrect interventions
Brown 2010[8]	Incorrect interventions
Buitelaar 2007[9]	Incorrect interventions
Buitelaar 2012[10]	Incorrect interventions
Camporeale 2013[11]	Incorrect interventions
Chen 2011[12]	Incorrect study design
Coghill 2014[13]	Incorrect interventions
Dopfner 2004[14]	Inappropriate comparison
Fox 2014[15]	No relevant outcomes
Giblin 2011[16]	No relevant outcomes
Gittelman Klein 2008[24]	No relevant outcomes
Greenhill 2006[17]	Incorrect interventions
Haas 2008[18]	Not guideline condition
Hazell 2006[19]	Incorrect interventions
Hoebert 2009[20]	Incorrect study design
Huss 2014[21]	Incorrect interventions
Huss 2014[22]	Incorrect interventions
Kent 2013[23]	Incorrect interventions
Mccarthy 2009[26]	Incorrect study design
Michelson 2004[27]	Incorrect interventions
Murray 2011[28]	Incorrect interventions
Prince 2000[30]	Incorrect interventions
Reyes 2006[31]	Not guideline condition
Sandler 2008[32]	Inappropriate comparison
Sandler 2010[33]	Incorrect interventions
Swanson 2006[34]	Incorrect interventions
Upadhyaya 2013[35]	Incorrect interventions
Upadhyaya 2015[36]	Incorrect interventions
Waxmonsky 2014[37]	Incorrect interventions
Wigal 2009[39]	Incorrect interventions
Wigal 2010[38]	Incorrect interventions

Study	Exclusion reason
Wigal 2010[42]	Incorrect interventions
Wigal 2011[40]	Incorrect interventions
Wigal 2011[41]	Incorrect interventions
Wilens 2006[43]	Incorrect interventions
Williamson 2014[44]	Incorrect interventions
Wolraich 2001[45]	Incorrect interventions

I.2.2 Excluded economic studies

None.

Appendix J: Research recommendations

J.1 Discontinuation of long term ADHD medication

Research question: What is the clinical and cost effectiveness of discontinuing long term ADHD medication?

Why this is important:

ADHD medication including methylphenidate is often given for periods of years without good evidence of whether prolonged therapy is effective or safe. The majority of studies supporting its use in the first place are only 2-3 months in duration. ADHD medication is typically discontinued in later teenage years; evidence is required of the benefit of continued prescribing in this age group.

Criteria for selecting high-priority research recommendations:

PICO question	Population: children, young people and adults with ADHD who have been taking ADHD medication for at least 18 months Intervention(s): cessation of ADHD medication (placebo) Comparison: continuation of ADHD medication Outcome(s): quality of life, ADHD symptoms (total, inattention, hyperactivity) assessed by neutral observer and reported as continuous and dichotomous responder outcomes, behavioural measures, discontinuations, serious adverse events
Importance to patients or the population	Guide decisions that patients are forced to make with little direct evidence about whether to stop or continue medication
Relevance to NICE guidance	Inform more specific recommendations on when and whether to discontinue medication
Relevance to the NHS	Reduce unnecessary prescribing or prevent inappropriate cessation of treatment
National priorities	NICE ADHD guideline
Current evidence base	Currently withdrawal studies, as identified in this evidence review, almost exclusively include participants who have been stabilised on medication for weeks rather than months
Equality	N/A
Study design	RCT, results sub-grouped by medication originally taken, follow-up at least 12 months post withdrawal
Feasibility	N/A
Other comments	N/A
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.