Fokuseret spørgsmål 3: Methylphenidat vs. placebo for ADHD

uality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
ADHD symptoms (measured with: ADHD-RS. Self-rated; Better indicated by lower values)												
13	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	1110	776	-	SMD 0.56 lower (0.68 to 0.43 lower)	⊕⊕OO LOW	IMPORTANT
ADHD symptoms (follow-up 5-24 weeks; measured with: Connor's Adult ADHD Rating Scale. Investigator rated; Better indicated by lower values)												
8	randomised trials	serious[3]	no serious inconsistency	serious	no serious imprecision	none	518	334	-	SMD 0.50 lower (0.69 to 0.32 lower)	⊕⊕OO LOW	IMPORTANT
ADHD Function (Global Assessment of Function) Investigator rated (follow-up 2-7 weeks; measured with: Global Assessment of Function 10-100 (GAF); Better indicated by lower values)												
4	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	245	125	-	SMD 0.87 lower (1.2 to 0.55 lower)	⊕⊕OO LOW	IMPORTANT
ADHD Function (CGI Investigator rated). (follow-up 4-13 weeks; measured with: Clinical Global Impression (CGI); Better indicated by lower values)												
4	randomised trials	serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	451	193	-	SMD 0.36 lower (0.53 to 0.19 lower)	⊕⊕OO LOW	IMPORTANT
Any drug use (follow-up 12-24 weeks; Better indicated by lower values)												
3	randomised trials	serious[7]	no serious inconsistency	serious[8]	no serious imprecision	none	63	66	-	SMD 0.87 higher (0.34 to 2.23 higher)	⊕⊕OO LOW	
Cocaine use (follow-up 10 weeks; assessed with: Proportion of positive weeks for cocaine)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/32 (0%)	0/33 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Cocaine use (follow-up 14 weeks; assessed with: Positive weeks urine samples)												
1	randomised trials	serious[10]	no serious inconsistency	serious[11]	no serious imprecision	none	0/53 (0%)	0/53 (0%)	-	-	⊕⊕OO LOW	IMPORTANT
								0%		-		
Anxiety (follow-up 2-24 weeks; measured with: (HAM-A, Beck, SLC-90 scales). Investigator rated; Better indicated by lower values)												
10	randomised trials	serious[12]	no serious inconsistency	serious[13]	no serious imprecision	none	667	511	-	SMD 0.05 higher (0.16 lower to 0.25 higher)	⊕⊕OO LOW	IMPORTANT
Depression (measured with: (Hamilton, Beck, and SCL-90 scales). Investigator rated.; Better indicated by lower values)												
11	randomised trials	serious[13]	no serious inconsistency	serious[12]	no serious imprecision	none	675	519	-	SMD 0.10 higher (0.08 lower to 0.28 higher)	⊕⊕OO LOW	IMPORTANT
Quality of life												

0	No evidence available					none	-	-	-	-		
								0%		-		
Sleep												
0	No evidence available					none	-	-	-	-		
								0%		-		
Crime												
0	No evidence available					none	-	-	-	-		
								0%		-		
Mortality (follow-up 9 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[14]	no serious imprecision	none	1/544 (0.18%)	0/181 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Insomnia (follow-up 5-24 weeks)												
17	randomised trials	serious[15]	no serious inconsistency	serious[16]	no serious imprecision	none	338/2072 (16.3%)	103/1150 (9%)	OR 2.13 (1.66 to 2.73)	84 more per 1000 (from 51 more to 122 more)	⊕⊕OO LOW	CRITICAL
								10.3%		94 more per 1000 (from 57 more to 136 more)		
Decreased appetite (+"anorexia")												
17	randomised trials	serious[17]	no serious inconsistency	serious[18]	no serious imprecision	none	597/2103 (28.4%)	88/1175 (7.5%)	OR 4.95 (3.87 to 6.33)	211 more per 1000 (from 164 more to 264 more)	⊕⊕OO LOW	
								7.1%		203 more per 1000 (from 157 more to 255 more)		
Dry mouth (follow-up 5-24 weeks)												
14	randomised trials	serious[19]	no serious inconsistency	serious[20]	no serious imprecision	none	432/1963 (22%)	49/996 (4.9%)	OR 5.53 (4.01 to 7.62)	173 more per 1000 (from 123 more to 234 more)	⊕⊕OO LOW	CRITICAL
								3.9%		144 more per 1000 (from 101 more to 197 more)		
Nausea												
9	randomised trials	serious[21]	no serious inconsistency	serious[22]	no serious imprecision	none	168/1316 (12.8%)	36/697 (5.2%)	OR 2.79 (1.9 to 4.1)	80 more per 1000 (from 42 more to 131 more)	⊕⊕OO LOW	
								5%		78 more per 1000 (from 41		

										more to 127 more)		
Cardiovascular complications (follow-up 6-24 weeks)												
7	randomised trials	serious[23]	no serious inconsistency	serious[24]	no serious imprecision	none	69/546 (12.6%)	18/398 (4.5%)	OR 3.25 (1.85 to 5.73)	88 more per 1000 (from 35 more to 168 more)	⊕⊕OO LOW	CRITICAL
								4.1%		81 more per 1000 (from 32 more to 156 more)		
Sexual (reduced libido, erectile dysfunction) (follow-up 6-24 weeks)												
3	randomised trials	serious[25]	no serious inconsistency	serious[26]	no serious imprecision	none	23/318 (7.2%)	2/214 (0.9%)	OR 4.1 (1.2 to 14.05)	28 more per 1000 (from 2 more to 108 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Urinary difficulties (follow-up 6-24 weeks)												
4	randomised trials	serious[12]	no serious inconsistency	serious[27]	no serious imprecision	none	23/353 (6.5%)	5/216 (2.3%)	OR 2.45 (0.83 to 7.24)	32 more per 1000 (from 4 fewer to 123 more)	⊕⊕OO LOW	CRITICAL
								2.2%		30 more per 1000 (from 4 fewer to 118 more)		
Palpitations												
7	randomised trials	serious[28]	no serious inconsistency	serious[12]	no serious imprecision	none	116/1233 (9.4%)	14/545 (2.6%)	OR 3.72 (1.83 to 7.56)	64 more per 1000 (from 20 more to 141 more)	⊕⊕OO LOW	
								3.7%		88 more per 1000 (from 29 more to 188 more)		
Systolic blood pressure (follow-up 3-24 weeks; measured with: Monitor; Better indicated by lower values)												
14	randomised trials	serious[29]	no serious inconsistency	serious[12]	no serious imprecision	none	1003	905	-	SMD 0.15 higher (0.06 to 0.25 higher)	⊕⊕OO LOW	CRITICAL
Diastolic blood pressure (measured with: Monitor; Better indicated by lower values)												
13	randomised trials	serious[29]	no serious inconsistency	serious[30]	no serious imprecision	none	902	840	-	SMD 0.15 higher (0.05 to 0.24 higher)	⊕⊕OO LOW	CRITICAL
Pulse (measured with: Monitor; Better indicated by lower values)												
14	randomised trials	serious[29]	no serious inconsistency	serious[30]	no serious imprecision	none	955	856	-	SMD 0.38 higher (0.27 to 0.48 higher)	⊕⊕OO LOW	CRITICAL

Suicide attempt (follow-up 9 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[14]	no serious imprecision	none	1/542 (0.18%)	0/180 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Suicidal ideation C-SSRS. (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[31]	no serious imprecision	none	1/68 (1.5%)	1/73 (1.4%)	-	14 fewer per 1000 (from 14 fewer to 14 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Used date of birth and sex to randomise in one study. Randomising not sufficient descibed in seven studies. All patients were able to break the randomization code in one small study. Incomplete data in one study. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult in one study. Particpants judged to be low or non responders by the investigator were excluded from one study.

[2] None responders to MPH excluded in tree studies. Only responders to MPH in earlier 6 week phase in one study. Unclear if earlier nonresponders to MPh was excluded in one study. Strict inclusion no comorbidity in one study.

[3] Known non-responders excluded in tree studies.

[4] Exclusion criteria was nown non-responders to MPH in two studies.

[5] Unclear randomising in seven studies. Unclear blinding in two studies. All patients were able to break the randomization code in one small study. I one study no medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult. In this study no data for the crossover phase 11/50 persons. Use of LOCF when reporting final outcomes in one study.

[6] Unclear blinding of personel in one study.

[7] Addiction serverity index scale and "psychiatric symptoms" was not reported in one study. Insuffieciente data in one study. Use of LOCF when reporting final outcomes in one study. Only described "randomizing was stratified by site and by amount of recent cocaine use" in one study.

[8] Very selected sample e.g. only ptts. addicted to amphetamines in one study. High rate of dropout â€“ 10/55 completed (2 placebo, 8MPH) in one study.

[9] Randomizing unclear was stratified by site and by amount of recent cocaine use.

[10] Unclear randomizing

[11] Exclusion criteria: Known sensitivity to MPHExclusion criteria. Large dropout.

[12] Unclear randomising in six studies. Unclear blinding in two studies. I one study no medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult. In this study no data for the crossover phase 11/50 persons. Use of LOCF when reporting final outcomes in one study. No explanation was provided

[13] Only responders to MPH in earlier 6 week phase was included in one study. Eclusion criteria was nown non-responders to MPH in two studies. In one study they use LOCF for missing data. In tihis study persons who had participated in a previous drug trial in the last 30 days and individuals treated with any psychopharmacological drug in addition to study medication were not included.

[14] Particpants judged to be low or non responders by the investigator were excluded from the study

[15] Used date of birth and sex to randomise in one study. LOCF reporting used for side effects in one study. Unclear randomising in nine studies. Unclear blinding in five studies. Numbers for randomising chosen from a hat in one study. Drop out rate different i PBO and higher in MPH due to AE in one study. No medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult in one study. No data for the crossover phase and no data for 11/50 in one study. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult in one study.

[16] Non-responders to MPH excluded in five studies. Only responders to MPH in earlier 6 week phase in one study. Very selected sample e.g. only ptts. addicted to amphetamines in one study. Known sensitivity to MPH was an exclusion criteria in one study. High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%) in one study. Large dropout in MPH 29% and only 8% in PBO in one study. Unclear if non-responders to MPH were excluded in one study. Strict inclusion no comorbidity.

[17] Used date of birth and sex to randomise in one study. LOCF reporting used for side effects in one study. Unclear randomising in eight studies. Unclear blinding in five studies. Numbers for randomising chosen from a hat in one study. Drop out rate different i PBO and higher in MPH due to AE in one study. No medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult in one study. No data for the crossover phase and no data for 11/50 in one study. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult in one study.

[18] Non-responders to MPH excluded in four studies. Only responders to MPH in earlier 6 week phase in one study. Very selected sample e.g. only ptts. addicted to amphetamines in one

study. Known sensitivity to MPH was an exclusion criteria in one study. High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%) in one study. Large dropout in MPH 29% and only 8% in PBO in one study. Unclear if non-responders to MPH were excluded in one study. Strict inclusion no comorbidity in one study.

[19] Used date of birth and sex to randomise in one study. LOCF reporting used for side effects in one study. Unclear randomising in seven studies. Unclear blinding in four studies. Drop out rate different i PBO and higher in MPH due to AE in one study. No medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult in one study. No data for the crossover phase and no data for 11/50 in one study. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult in one study.

[20] Non-responders to MPH excluded in four studies. Only responders to MPH in earlier 6 week phase in one study. Very selected sample e.g. only ptts. addicted to amphetamines in one study. Known sensitivity to MPH was an exclusion criteria in one study. High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%) in one study. Unclear if non-responders to MPH were excluded in one study. Strict inclusion no comorbidity in one study.

[21] Used date of birth and sex to randomise in one study. LOCF reporting used for side effects in one study. Drop out rate different i PBO and higher in MPH due to AE in one study. Unclear randomising in four studies study. Unclear blinding in two studies. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult in one study.

[22] None responders to MPH excluded in tree studies. Particpants judged to be low or non responders by the investigator were excluded from one study. High drop out rate, 110 of 363. lower 24% in intervention than control group (43%). Large dropout in MPH 29% and only 8% in PBO in one study. Unclear if non-responders to MPH are excluded in one study. Strict inclusion no comorbidity.

[23] Unclear randomising in tree studies. Unclear blinding in two studies.

[24] Only responders to MPH in earlier 6 week phase in one study. High rate of dropout â€“ 10/55 completed (2 placebo, 8MPH) in one study. Very selected sample e.g. only ptts. addicted to amphetamines in one study. High drop out rate, 110 of 363. lower 24% in intervention than control group (43%) in one study. Strict inclusion no comorbidity in one study. Excluded if ealier nonresponders to MPH in one study.Â

[25] Unclear randomising in two studies. Unclear blinding in one study.

[26] High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%) in one study. Strict inclusion no comorbidity and excluded if ealier nonresponders to MPH in one study.

[27] High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%) in one study. Only responders to MPH in earlier 6 week phase in one study.

[28] Unclear randomising in tree studies.

[29] Unclear randomising in seven studies. Used date of birth and sex to randomise in one study. Randomising numbers chosen from a hat in one study, LOCF reporting used for side effects and cardiovascular results in one study. Unclear blinding i tree studies. No data for the crossover phase i one study. No data for 11/50 persons in one study. No medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult in one study. Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult. High drop out rate in one study, 110 of 363. lower 24% in intervention than control group (43%). AE is weakly reported in one study.

[30] None responders to MPH excluded in four studies. Drop out rate different i PBO and higher in MPH due to AE in one study. Some patients were self-referrals in one study. Unclear if nonresponders to MPH are excluded in one study.

[31] Strict inclusion no comorbidity.Excluded if ealier nonresponders to MPH.Â

Fokuseret spørgsmål 5: Atomoxetin vs. placebo for ADHD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine versus placebo	Control	Relative (95% CI)	Absolute		
Funktion, observatÃ¸rvurdering (follow-up 12 weeks; measured with: (CGI-skala); Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	216	219	-	MD 0.37 lower (0.57 to 0.17 lower)	⊕⊕OO LOW	IMPORTANT
ADHD symptomer, observatÃ¸r-vurdering (follow-up 12-26 weeks; measured with: CAARS:O; Better indicated by lower values)												
4	randomised trials	very serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	727	727	-	SMD 0.28 lower (0.38 to 0.17 lower)	⊕OOO VERY LOW	IMPORTANT
QoL (follow-up 12-25 weeks; measured with: AAQoL,self-rated; Better indicated by lower values)												
2	randomised trials	very serious[5]	no serious inconsistency	serious[6]	no serious imprecision	none	455	456	-	SMD 0.26 higher (0.13 to 0.39 higher)	⊕OOO VERY LOW	CRITICAL
Anxiety and depression (follow-up 25 weeks; assessed with: EQ-D5)												
1	randomised trials	serious[7]	no serious inconsistency	serious[8]	no serious imprecision	none	0/226 (0%)	0/258 (0%)	-	-	⊕⊕OO LOW	IMPORTANT
								0%		-		
Depression (follow-up 12 weeks; measured with: The Montgomery-Ã…sberg Depression Rating Scale (MADRS) 10 item investigator rated range from 0-60; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[9]	none	192	196	-	SMD 0.08 lower (0.28 lower to 0.12 higher)	⊕OOO VERY LOW	IMPORTANT
Depression (follow-up 10 weeks; assessed with: HAM-D 17 change from baseline)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[10]	no serious imprecision	none	0/124 (0%)	0/124 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Anxiety (follow-up 10 weeks; assessed with: HAM-A change from baseline)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[10]	no serious imprecision	none	0/124 (0%)	0/124 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Anxiety (follow-up 24 weeks; assessed with: State-trait Axiety Inventory (STAI-State) self-rated 40 items questionaire. Rates from 1-4)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/125 (0%)	0/135 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Anxiety (follow-up 24 weeks; assessed with: State-trait Axiety Inventory (STAI-Traite) self-rated 40 items questionaire. Rates from 1-4)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/125 (0%)	0/135 (0%)	-	-	⊕⊕⊕O MODERATE	
								0%		-		
Marijuana Reduced days using relative to baseline. (N) (follow-up 12 weeks)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/19 (0%)	0/19 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Marijuana. The Habits Timeline Followback (TLFB) (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/26 (0%)	0/20 (0%)	-	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
Alkohol. The Habits Timeline Followback (TLFB)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/119 (0%)	0/121 (0%)	-	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
Drugs: The Habits Timeline Followback (TLFB) (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/2 (0%)	0/2 (0%)	-	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
Alcohol relapse												
1	randomised trials					none	64/68 (94.1%)	69/72 (95.8%)	-	958 fewer per 1000 (from 958 fewer to 958 fewer)		IMPORTANT
								0%		-		
Crime												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Sleep												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
								0%		-		
Serious adverse events (follow-up 24 weeks)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/266 (0%)	7/234 (3%)	-	30 fewer per 1000 (from 30 fewer to 30 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Seriours adverse events (follow-up 24 weeks)												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/266 (1.5%)	1/234 (0.43%)	-	4 fewer per 1000 (from 4 fewer to 4 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Nausea (adverse events) (follow-up 6-26 weeks)												
7	randomised trials	very serious[12]	no serious inconsistency	serious[13]	no serious imprecision	none	290/1403 (20.7%)	71/1356 (5.2%)	OR 4.46 (2.89 to 6.86)	145 more per 1000 (from 85 more to 222 more)	⊕OOO VERY LOW	CRITICAL

								5.6%		153 more per 1000 (from 90 more to 233 more)		
Dry mouth (adverse events) (follow-up 6-26 weeks)												
8	randomised trials	very serious[14]	no serious inconsistency	serious[11]	no serious imprecision	none	254/1422 (17.9%)	67/1339 (5%)	OR 4.09 (3.07 to 5.46)	127 more per 1000 (from 89 more to 173 more)	⊕OOO VERY LOW	CRITICAL
								5.8%		143 more per 1000 (from 101 more to 194 more)		
Headache (adverse events)												
7	randomised trials	serious[15]	no serious inconsistency	serious[16]	no serious imprecision	none	163/1153 (14.1%)	142/1076 (13.2%)	OR 1.09 (0.78 to 1.52)	10 more per 1000 (from 26 fewer to 56 more)	⊕⊕OO LOW	CRITICAL
								12.8%		10 more per 1000 (from 25 fewer to 54 more)		
Fatigue (adverse events)												
6	randomised trials	serious[17]	no serious inconsistency	serious[16]	serious[18]	none	102/1056 (9.7%)	62/1029 (6%)	OR 1.64 (1.1 to 2.45)	35 more per 1000 (from 6 more to 76 more)	⊕OOO VERY LOW	CRITICAL
								7.3%		41 more per 1000 (from 7 more to 89 more)		
Decreased appetite (adverse events) (follow-up 6-26 weeks)												
5	randomised trials	serious[19]	no serious inconsistency	serious[13]	no serious imprecision	none	135/1118 (12.1%)	31/1076 (2.9%)	OR 4.69 (3.13 to 7.04)	93 more per 1000 (from 56 more to 144 more)	⊕⊕OO LOW	CRITICAL
								3.4%		108 more per 1000 (from 65 more to 165 more)		
Insomnia (adverse events) (follow-up 6-26 weeks)												
8	randomised trials	very serious[14]	serious[20]	serious[16]	no serious imprecision	none	182/1422 (12.8%)	86/1339 (6.4%)	OR 1.94 (1.23 to 3.04)	53 more per 1000 (from 14 more to 108 more)	⊕OOO VERY LOW	CRITICAL
								7.2%		59 more per 1000 (from 15 more to 119 more)		
Dizziness (adverse events) (follow-up 6-26 weeks)												
8	randomised trials	no serious risk of bias[12]	no serious inconsistency	serious[16]	no serious imprecision	none	106/1422 (7.5%)	39/1339 (2.9%)	OR 2.5 (1.7 to 3.67)	41 more per 1000 (from 19 more to 70 more)	⊕⊕⊕O MODERATE	CRITICAL
								3.1%		43 more per 1000 (from 21 more to 74 more)		
Constipation (adverse events) (follow-up 10-26 weeks)												

5	randomised trials	serious[21]	no serious inconsistency	serious[16]	no serious imprecision	none	79/894 (8.8%)	35/797 (4.4%)	OR 2.12 (1.4 to 3.22)	45 more per 1000 (from 17 more to 85 more)	⊕⊕OO LOW	CRITICAL
								4.3%		44 more per 1000 (from 16 more to 83 more)		
Somnolence (adverse events) (follow-up 6-26 weeks)												
6	randomised trials	serious[22]	no serious inconsistency	serious[13]	no serious imprecision	none	71/1133 (6.3%)	34/1057 (3.2%)	OR 1.81 (1.18 to 2.76)	25 more per 1000 (from 6 more to 52 more)	⊕⊕OO LOW	CRITICAL
								2.9%		22 more per 1000 (from 5 more to 47 more)		
Irritability (adverse events) (follow-up 6-26 weeks)												
5	randomised trials	serious[11]	no serious inconsistency	serious[16]	no serious imprecision	none	59/790 (7.5%)	31/771 (4%)	OR 1.87 (1.19 to 2.94)	32 more per 1000 (from 7 more to 69 more)	⊕⊕OO LOW	CRITICAL
								4.1%		33 more per 1000 (from 7 more to 71 more)		
Erectile dysfunction (adverse events) (follow-up 6-26 weeks)												
5	randomised trials	serious[23]	no serious inconsistency	serious[13]	no serious imprecision	none	53/944 (5.6%)	7/927 (0.8%)	OR 6.35 (2.96 to 13.65)	39 more per 1000 (from 14 more to 87 more)	⊕⊕OO LOW	CRITICAL
								0.4%		21 more per 1000 (from 8 more to 48 more)		
Decreased libido (adverse events)												
3	randomised trials	serious[24]	no serious inconsistency	serious[13]	no serious imprecision	none	33/439 (7.5%)	8/383 (2.1%)	OR 3.46 (1.56 to 7.64)	48 more per 1000 (from 11 more to 119 more)	⊕⊕OO LOW	CRITICAL
								1.9%		44 more per 1000 (from 10 more to 110 more)		
Sweating (adverse events)												
5	randomised trials	serious[25]	no serious inconsistency	serious[6,13]	no serious imprecision	none	46/966 (4.8%)	3/875 (0.3%)	OR 8.01 (2.99 to 21.46)	23 more per 1000 (from 7 more to 65 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Systolisk BT (adverse events) (Better indicated by lower values)												
2	randomised trials	serious[26]	no serious inconsistency	serious[6,13]	no serious imprecision	none	524	516	-	MD 1.57 higher (1.08 lower to 4.22 higher)	⊕⊕OO LOW	CRITICAL
Diastolisk BT (adverse events) (Better indicated by lower values)												
2	randomised trials	serious[26]	no serious inconsistency	serious[6,13]	no serious imprecision	none	524	516	-	MD 1.75 higher (0.77 to 2.74	⊕⊕OO LOW	CRITICAL

										higher)		
Puls (adverse events) (Better indicated by lower values)												
2	randomised trials	serious[26]	no serious inconsistency	serious[6,13]	no serious imprecision	none	524	516	-	MD 4.7 higher (3.49 to 5.91 higher)	⊕⊕OO LOW	CRITICAL
Seriours adverse events (follow-up 6 weeks)												
1	randomised trials					none	0/74 (0%)	1/73 (1.4%)	-	14 fewer per 1000 (from 14 fewer to 14 fewer)		CRITICAL
								0%		-		
Cardiovascular adverse events (follow-up 6 weeks)												
1	randomised trials	serious[11]	no serious inconsistency	serious[24]	no serious imprecision	none	5/73 (6.8%)	3/73 (4.1%)	-	41 fewer per 1000 (from 41 fewer to 41 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Unclear blinding of ATX and blinding of capsuels in one study. Unclear randomization

[2] Participants was excluded if earlier failure to ATX or stimulant in one study. Only responders to ATX in an earlier study was included. (n=38) in one study was Marijuana Dependent.

[3] Randomization unclear in two studies. Unclear if the participants was blinded to ATX in one study due to lead in period with open label ATX in both groups. Unclear blinding of ATX and PBO capsuels in another study. Failure to response to ATX or stimulants was an exclusion criteria in one study. Only participants who responded on ATX in an earlier study

[4] Participants (n=38) in one study was Marijuana Dependent.

[5] Unclear blinding of ATX and PBO capsuels in one study. The other study included only patients who responded on ATX in an earlier study and unclear if the participants was blinded to ATX in this study due to lead in period with open label ATX in both groups.

[6] Only responders to ATX in an earlier study was included.

[7] Blinding of participants unclear - ATX treatment - all patients in lead in period. Only patients who responded on ATX in earlier study was included. Blinding not described.

[8] Excluded all patients who was non-responders in an earlier study

[9] Unclear results on Depression in one study (n=38).

[10] Excluded if response to placebo in lead in phase

[11] Unclear blinding of personal

[12] Randomization unclear in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. Responders to placebo in lead in period was excluded in one study.

[13] Failure to respond at ATX or stimulants or non responders to ATX in an earlier study was an exclusion criteria.

[14] Randomization unclear in two studies. Blinding of capsuels unclear in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. Responders to placebo in lead in period was excluded in one study.

[15] Randomization unclear in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. Only responders to ATX in an earlier study was included in one study.

[16] Failure to respond at ATX or stimulants or non responders to ATX in an earlier study was an exclusion criteria. Participants (n=38) in one study was Marijuana Dependent.

[17] Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. Only responders to ATX in an earlier study was included in one study.

[18] Different estimates in one study (n=266)

[19] Unclear randomizing in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in two studies. Only responders to ATX in an earlier study was included in one study. Responders to placebo in lead in phase was excluded.

[20] Different estimates in two studies. One with all participants (n=38) Marijuana dependent.

[21] Randomization unclear in one study. Blinding of capsuels unclear in one study. Blinding of personal unclear in one study. Earlier non-responders to ATX or stimulants was excluded in one study. Responders to placebo in lead in period was excluded in one study.

[22] Randomization unclear in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. All participants treated with ATX in lead in period and non-responders to ATX was excluded in one study.

[23] Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in to studies. Responders to placebo in lead in period was excluded in one study.
[24] Unclear randomizing and blinding of personal in one study. Earlier non-responders to ATX or stimulants was excluded in one study. Responders to placebo in lead in phase was excluded.
[25] Unclear randomizing in one study. Blinding of personal unclear in two studies. Earlier non-responders to ATX or stimulants was excluded in one study. Only responders to ATX in an earlier study was included in one study. Responders to placebo in lead in phase was excluded.
[26] Blinding of personal unclear in one study. Responders to placebo in lead in period was excluded in one study. All patients starts with ATX and only patients who had effect of ATX was included.

Fokuseret spørgsmål 6: Atomoxetin vs. placebo for ADHD og internaliserende symptomer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetin	Control	Relative (95% CI)	Absolute		
ADHD symptoms (follow-up 16 weeks; assessed with: CAARS:O)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Functioning (follow-up 16 weeks; assessed with: CGI-I-O-S)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Functioning (assessed with: GAF)												
0	No evidence available					none	-	-	-	-		
								0%		-		
Anxiety (internalizing symptoms) (follow-up 16 weeks; assessed with: STAI - Trait. State-Trait-Anxiety-Inventory self-rated)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Anxiety (internalizing symptoms) (follow-up 16 weeks; assessed with: STAI - State. State-Trait-Anxiety-Inventory self-rated)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Quality of Life (follow-up 16 weeks; assessed with: AAQoL)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Depression (a part of internalization symptoms)												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Sleep												
0	No evidence available					none	-	-	-	-		
								0%		-		
Drug or medication abuse												
0	No evidence available					none	-	-	-	-		
								0%		-		
Mortality												
0	No evidence available					none	-	-	-	-		
								0%		-		

Crime												
0	No evidence available					none	-	-	-	-		
								0%		-		
Serious adverse events (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Headache (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/212 (20.3%)	30/211 (14.2%)	-	142 fewer per 1000 (from 142 fewer to 142 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Insomnia (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/212 (17%)	19/211 (9%)	-	90 fewer per 1000 (from 90 fewer to 90 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Dry mouth (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/212 (15.6%)	9/211 (4.3%)	-	43 fewer per 1000 (from 43 fewer to 43 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Somnolence (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/212 (5.2%)	7/211 (3.3%)	-	33 fewer per 1000 (from 33 fewer to 33 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Nausea (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/212 (16%)	16/211 (7.6%)	-	76 fewer per 1000 (from 76 fewer to 76 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased appetite (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/212 (10.4%)	12/211 (5.7%)	-	57 fewer per 1000 (from 57 fewer to 57 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Constipation (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/212 (7.5%)	8/211 (3.8%)	-	38 fewer per 1000 (from 38 fewer to 38 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Dizziness (adverse events) (follow-up 16 weeks)												
1	randomised	serious[1]	no serious	no serious	no serious	none	16/212	5/211	-	24 fewer per 1000	⊕⊕⊕O	CRITICAL

	trials		inconsistency	indirectness	imprecision		(7.5%)	(2.4%)		(from 24 fewer to 24 fewer)	MODERATE	
								0%		-		
Fatique (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/212 (6.1%)	12/211 (5.7%)	-	57 fewer per 1000 (from 57 fewer to 57 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Initial insomnia (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/212 (5.7%)	6/211 (2.8%)	-	28 fewer per 1000 (from 28 fewer to 28 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Irritability (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/212 (5.2%)	15/211 (7.1%)	-	71 fewer per 1000 (from 71 fewer to 71 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Anxiety (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/212 (4.7%)	13/211 (6.2%)	-	62 fewer per 1000 (from 62 fewer to 62 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Pharyngolaryngeal Pain (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/212 (4.2%)	12/211 (5.7%)	-	57 fewer per 1000 (from 57 fewer to 57 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Anxiety (adverse events) (follow-up 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/224 (0%)	0/218 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Erectile dysfunction (adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/113 (5.3%)	1/113 (0.88%)	-	9 fewer per 1000 (from 9 fewer to 9 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Al participants get placebo 2 weeks after randomization. Participant with more than 25% decrease of social anxiety to placebo treatment were excluded in some of the anxiety analysis.

Fokuseret spørgsmål 7: Lisdexamfetamin vs. placebo for ADHD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisdexamphetamine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD kernesymptomer (follow-up 2-10 weeks; measured with: ASRS/CAARS:S; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	558	385	-	SMD 0.8 lower (0.93 to 0.66 lower)	⊕⊕OO LOW	IMPORTANT
Quality of Life (follow-up 10 weeks; assessed with: AAQoL (scale 0-100))												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	0/79 (0%)	0/75 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Sleep (global PSQI scores) (follow-up 4 weeks; assessed with: PSQI: 19 items self-rated and 5 items roommate questions))												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/341 (0%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Sleep Onset in minutes (follow-up 4 weeks; assessed with: PSQI: 19 items self-rated and 5 items roommate questions))												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/356 (0%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Sleep Duration in Hours (follow-up 4 weeks; assessed with: PSQI 19 items self-rated and 5 items roommate questions))												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/356 (0%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Mortality												
0	No evidence available					none	-	-	-	-		
								0%		-		
Drug or medication abuse												
0	No evidence available					none	-	-	-	-		
								0%		-		
Crime												
0	No evidence available					none	-	-	-	-		NOT IMPORTANT
								0%		-		
Internalizing symptoms												
0	No evidence available					none	-	-	-	-		
								0%		-		
Functioning (assessed with: CGI)												
0	No evidence available					none	-	-	-	-		
								0%		-		
Functioning (assessed with: GAF)												

0	No evidence available					none	-	-	-	-		
								0%		-		
Anorexia (adverse events) (follow-up 4-10 weeks)												
2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	22/437 (5%)	0/142 (0%)	RR 7.46 (0.98 to 56.7)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Increased heart rate (adverse events) (follow-up 4-10 weeks)												
2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	11/437 (2.5%)	2/142 (1.4%)	OR 2.26 (0.51 to 9.95)	17 more per 1000 (from 7 fewer to 110 more)	⊕⊕OO LOW	CRITICAL
								1.3%		16 more per 1000 (from 6 fewer to 103 more)		
Anxiety (adverse events) (follow-up 2-4 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	24/490 (4.9%)	1/194 (0.5%)	OR 4.27 (0.88 to 20.6)	16 more per 1000 (from 1 fewer to 91 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Insomnia (adverse events) (follow-up 2-10 weeks)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	83/569 (14.6%)	11/274 (4%)	OR 2.24 (0.79 to 6.41)	46 more per 1000 (from 8 fewer to 171 more)	⊕⊕OO LOW	CRITICAL
								4.3%		48 more per 1000 (from 9 fewer to 181 more)		
Irritability (adverse events) (follow-up 2-10 weeks)												
3	randomised trials	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	11/211 (5.2%)	5/212 (2.4%)	OR 2.16 (0.76 to 6.14)	26 more per 1000 (from 6 fewer to 106 more)	⊕⊕OO LOW	CRITICAL
								3.8%		41 more per 1000 (from 9 fewer to 157 more)		
Decreased appetite (adverse events) (follow-up 2-10 weeks)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	137/569 (24.1%)	8/274 (2.9%)	OR 9.36 (4.35 to 20.17)	190 more per 1000 (from 86 more to 348 more)	⊕⊕OO LOW	CRITICAL
								1.7%		122 more per 1000 (from 53		

										more to 242 more)		
Fatigue (adverse events) (follow-up 2-10 weeks)												
4	randomised trials	serious[1]	serious[5]	serious[2]	no serious imprecision	none	24/569 (4.2%)	22/274 (8%)	OR 0.5 (0.25 to 0.97)	38 fewer per 1000 (from 2 fewer to 59 fewer)	⊕OOO VERY LOW	CRITICAL
								8.4%		40 fewer per 1000 (from 2 fewer to 62 fewer)		
Headache (adverse events) (follow-up 10 weeks)												
3	randomised trials	serious[4]	serious[6]	serious[2]	no serious imprecision[7]	none	22/211 (10.4%)	7/212 (3.3%)	OR 3.15 (1.37 to 7.23)	64 more per 1000 (from 12 more to 165 more)	⊕OOO VERY LOW	CRITICAL
								2.6%		52 more per 1000 (from 9 more to 136 more)		
Nausea (adverse events) (follow-up 2-10 weeks)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[7]	none	30/569 (5.3%)	6/274 (2.2%)	OR 1.8 (0.7 to 4.63)	17 more per 1000 (from 6 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL
								3.1%		23 more per 1000 (from 9 fewer to 98 more)		
Dry mouth (adverse events) (follow-up 2-10 weeks)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	123/569 (21.6%)	9/274 (3.3%)	OR 6.96 (3.33 to 14.55)	158 more per 1000 (from 69 more to 298 more)	⊕⊕OO LOW	CRITICAL
								2%		104 more per 1000 (from 44 more to 209 more)		
Feeling jittery (adverse events) (follow-up 10 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	12/308 (3.9%)	0/259 (0%)	OR 11.52 (1.57 to 84.73)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Pulse (adverse events) (follow-up 4-10 weeks; Better indicated by lower values)												
2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none[3]	437	266	-	MD 3.65 higher (2.28 to 5.03 higher)	⊕⊕OO LOW	CRITICAL
Systolic blood pressure (adverse events) (follow-up 4-10 weeks; Better indicated by lower values)												

2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	437	266	-	MD 1.21 higher (0.12 lower to 2.54 higher)	⊕⊕OO LOW	CRITICAL
Diastolic blood pressure (adverse events) (follow-up 4-10 weeks; Better indicated by lower values)												
2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	437	266	-	MD 0.04 higher (1.06 lower to 1.14 higher)	⊕⊕OO LOW	CRITICAL
Weight decreased (adverse events) (follow-up 10 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	8/79 (10.1%)	0/80 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Chest tightness (adverse events) (follow-up 4 weeks)												
1	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	1/17 (5.9%)	0/15 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Stomach pain (adverse events) (follow-up 4 weeks)												
1	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	1/17 (5.9%)	0/15 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Teeth grinding (adverse events) (follow-up 4 weeks)												
1	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	2/17 (11.8%)	0/15 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Tachycardia (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/358 (1.1%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Blood pressure (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/358 (2.8%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Palpitations (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/358 (1.7%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Dyspnea (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/358 (2.2%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Hyperhidrosis (adverse events) (follow-up 10 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	5/79 (6.3%)	0/80 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Change in Weight lb. (adverse events) (follow-up 2 weeks)												

1	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	0/115 (0%)	0/117 (0%)	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Sleep nightmare (adverse events) (follow-up 4 weeks; assessed with: PSQI 19 items self-rated and 5 items roommate questions))												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/368 (0.54%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Poor quality sleep (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/358 (0.28%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Abnormal dreams (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/358 (0.28%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Hypersomnia (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/358 (0.28%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Sleep disorder (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/358 (0.56%)	2/62 (3.2%)	-	32 fewer per 1000 (from 32 fewer to 32 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Middle insomnia (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/358 (3.6%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Somnolence (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/358 (0.28%)	2/62 (3.2%)	-	32 fewer per 1000 (from 32 fewer to 32 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Early morning awekening (adverse events) (follow-up 4 weeks)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/358 (0.28%)	0/62 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Acne (adverse events) (follow-up 4 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	1/17 (5.9%)	0/15 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Serious adverse events (follow-up 10 weeks)												

2	randomised trials	serious[4]	no serious inconsistency	serious[3]	no serious imprecision	none	18/437 (4.1%)	26/142 (18.3%)	-	183 fewer per 1000 (from 183 fewer to 183 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Treatment emergent serious adverse event (follow-up 10 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Selections bias: Randomizing not described in two studies

[2] Selections bias: Earlier lack of response to amphetamine therapy was an exclusion criteria in two studies

[3] Selections bias: Earlier lack of response to amphetamine therapy was an exclusion criteria in one study

[4] Selections bias: Randomizing not described in one study

[5] Heterogeneity. I2 = 68 % point estimates are very scattered + large 95%CI

[6] Heterogeneity. I2 = 80% point estimates are very scattered + large 95%CI

[7] Large (95 % CI)

Fokuseret spørgsmål 15: Kognitiv adfærdsterapi + medicin vs. medicin for ADHD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT+medication versus medication alone	Control	Relative (95% CI)	Absolute		
Funktionsniveau/GAF (CGI-skala), 3 mÃ¥neder FU, independent evaluator (follow-up mean 3 months; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	24	28	-	MD 0.95 lower (1.44 to 0.46 lower)	⊕⊕OO LOW	
Beck Depression Scale, self-assessment (follow-up mean 3 months; Better indicated by lower values)												
2	randomised trials	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	31	32	-	MD 7.41 lower (12.94 to 1.87 lower)	⊕⊕OO LOW	
Beck Anxiety Scale, self-assessment (follow-up mean 3 months; Better indicated by lower values)												
2	randomised trials	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	31	32	-	MD 4.14 lower (6.68 to 1.61 lower)	⊕⊕OO LOW	
ADHD symptomer (DuPaul) Independent evaluator (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	16	15	-	SMD 0.6 lower (1.32 lower to 0.12 higher)	⊕⊕OO LOW	
ADHD symptomer (BCS/CBS), self-assessment (follow-up mean 3 months; Better indicated by lower values)												
2	randomised trials	serious				none	31	32	-	SMD 1 lower (1.53 to 0.47 lower)		
Depression (Hamilton), independent assessor (Better indicated by lower values)												
1	no methodology chosen					none	16	15	-	MD 5.56 lower (9.71 to 1.41 lower)		
Anxiety, Hamilton Scale, independent observer (Better indicated by lower values)												
1	no methodology chosen					none	16	15	-	MD 5.68 lower (10.32 to 1.04 lower)		

[1] Unclear randomization in both studies, large drop-out in one study.

[2] Small numbers

[3] Unclear randomisation in both studies, large drop out rate in one study, self-assessment of subjective outcome

[4] Unclear randomisation, self-assessment of subjective outcome.