

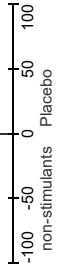
1 Non-Stimulant vs. placebo

1.1 ADHD-symptoms (critical)

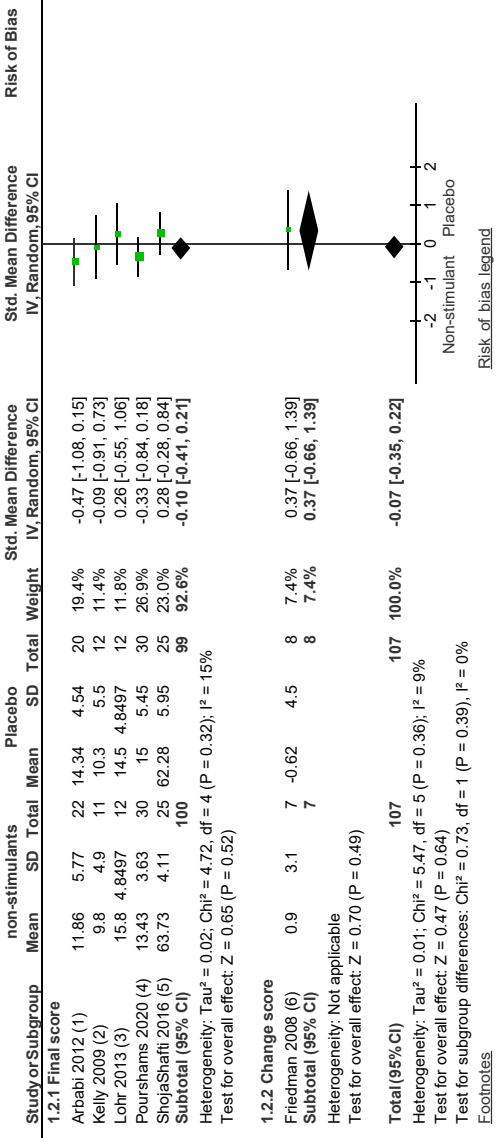
| Study or Subgroup | non-stimulants | | Placebo | | Total | Weight | Mean Difference IV, Random, 95% CI | Risk of Bias |
|-------------------|----------------|----|---------|----|-------|--------|---------------------------------------|--------------|
| | Mean | SD | Mean | SD | | | | |
| Total (95% CI) | 0 | | 0 | | 0 | | Not estimable | |

Heterogeneity: Not applicable
 Test for overall effect: Not applicable

Risk of bias legend



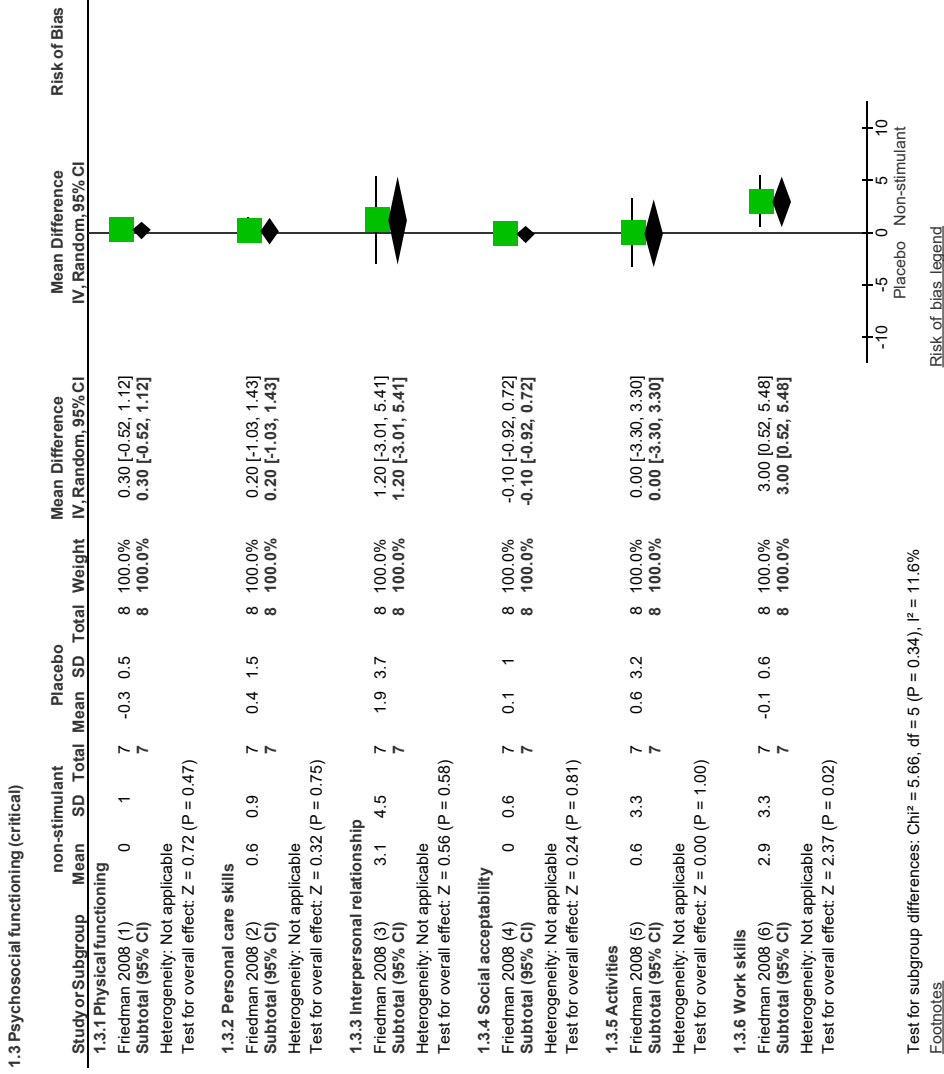
1.2 Psychotic symptoms (critical)



Non-stimulant Placebo

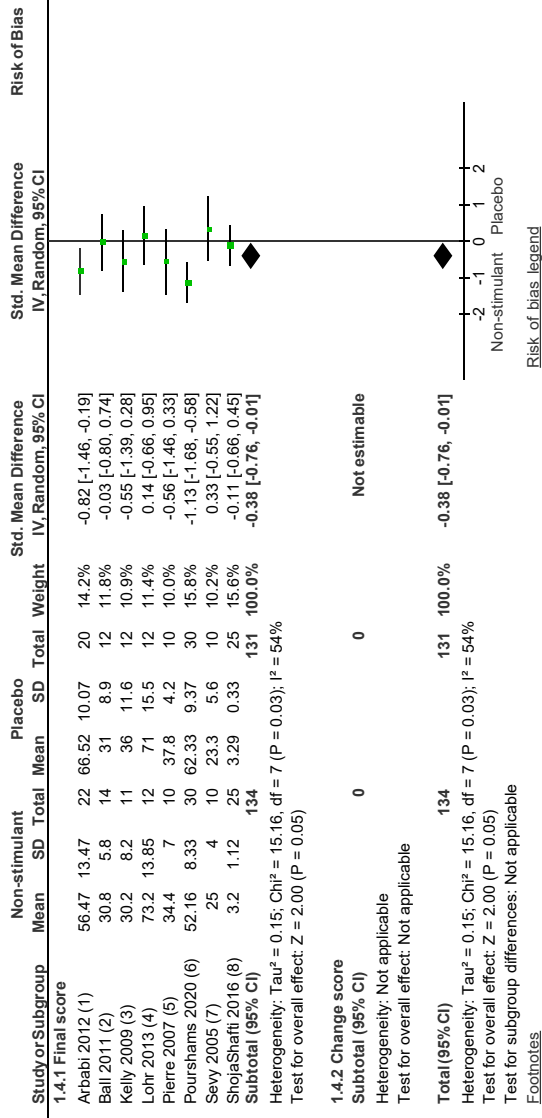
Risk of bias legend

Footnotes:
 (1) Modafinil, PANSS positive, lower is better
 (2) Atomoxetine, BPRS, lower is better
 (3) Modafinil, Afloest på graf (fig 3), PANSS positive, lower is better
 (4) Atomoxetine, PANSS positive, lower is better
 (5) modafinil, Data from LOCF. SAPS (scale for assessment of positive symptoms), lower is better
 (6) Atomoxetine, Data from observed cases, PANSS, lower is better

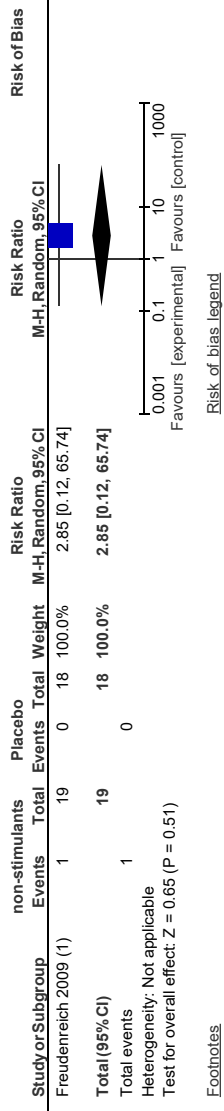


Footnotes
 (1) Atomoxetine, changes score (observed cases), SLOF, higher is better
 (2) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (3) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (4) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (5) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (6) atomoxetine, changes scores (observed cases), SLOF, higher is better

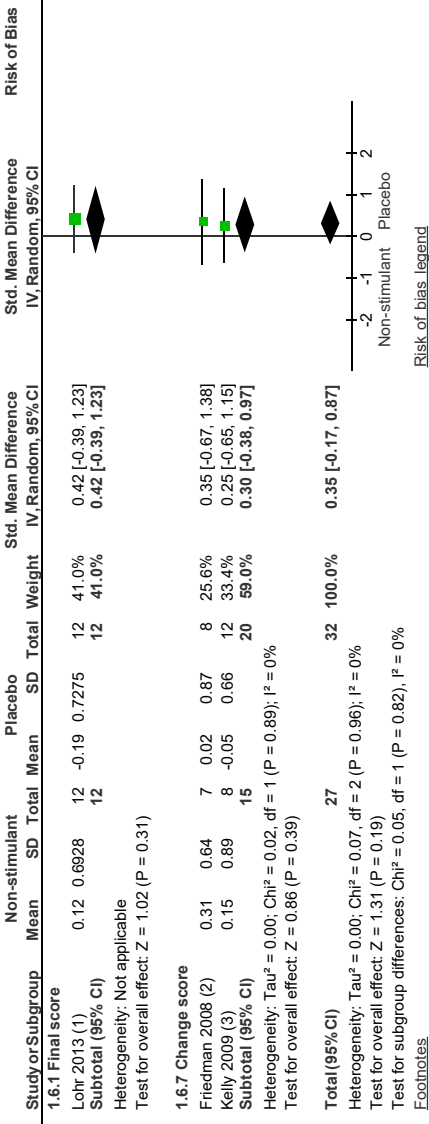
1.4 Global symptoms/functioning (important)



1.5 Psychiatric hospitalization

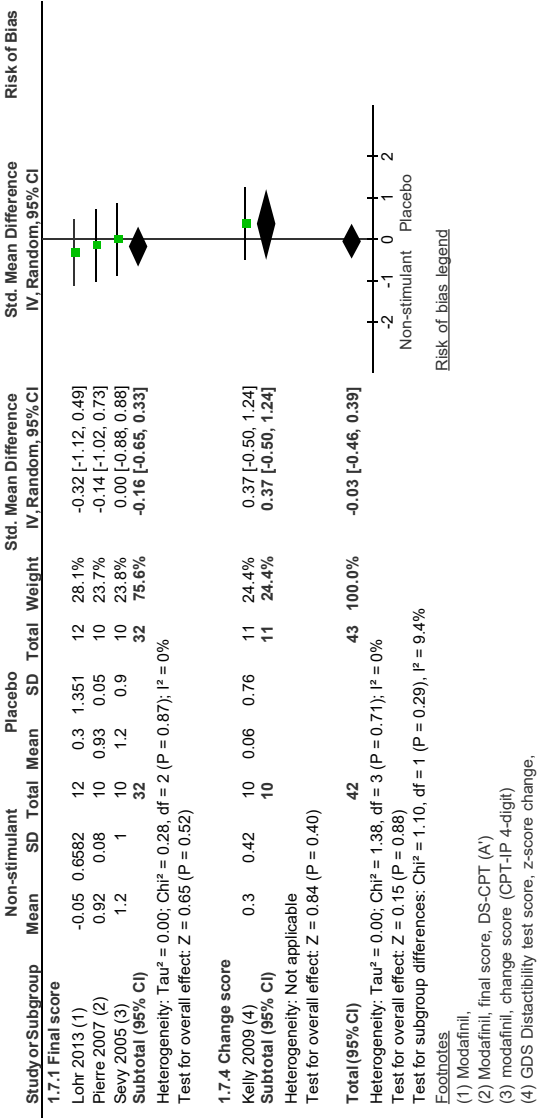


1.6 Executive functions (important)

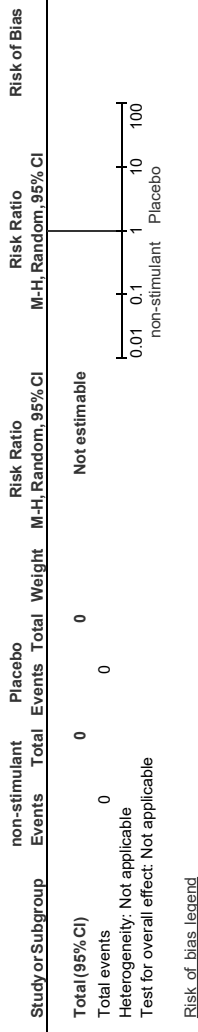


Footnotes:
 (1) Modafinil, NP-composite executive,
 (2) Atomoxetine, Tower of London, change score,
 (3) Woodcock-Johnson planning test, z-score change

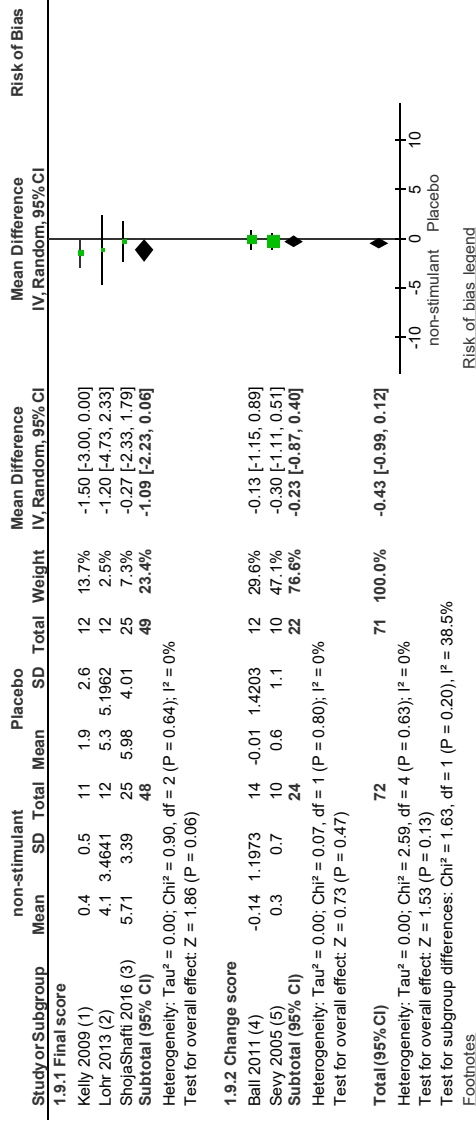
1.7 Attention (important)



1.8 Extrapyramidal side effects (important)

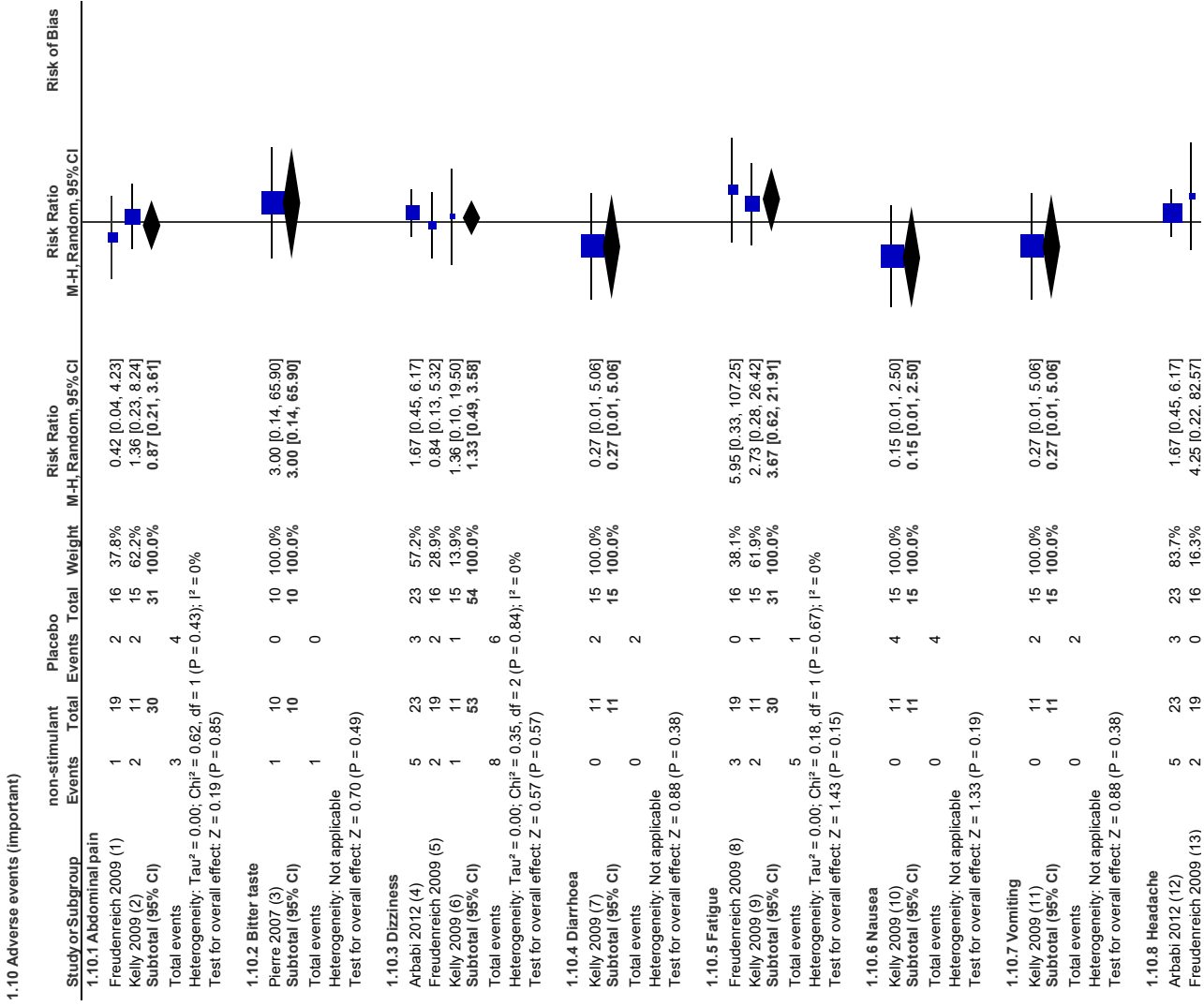


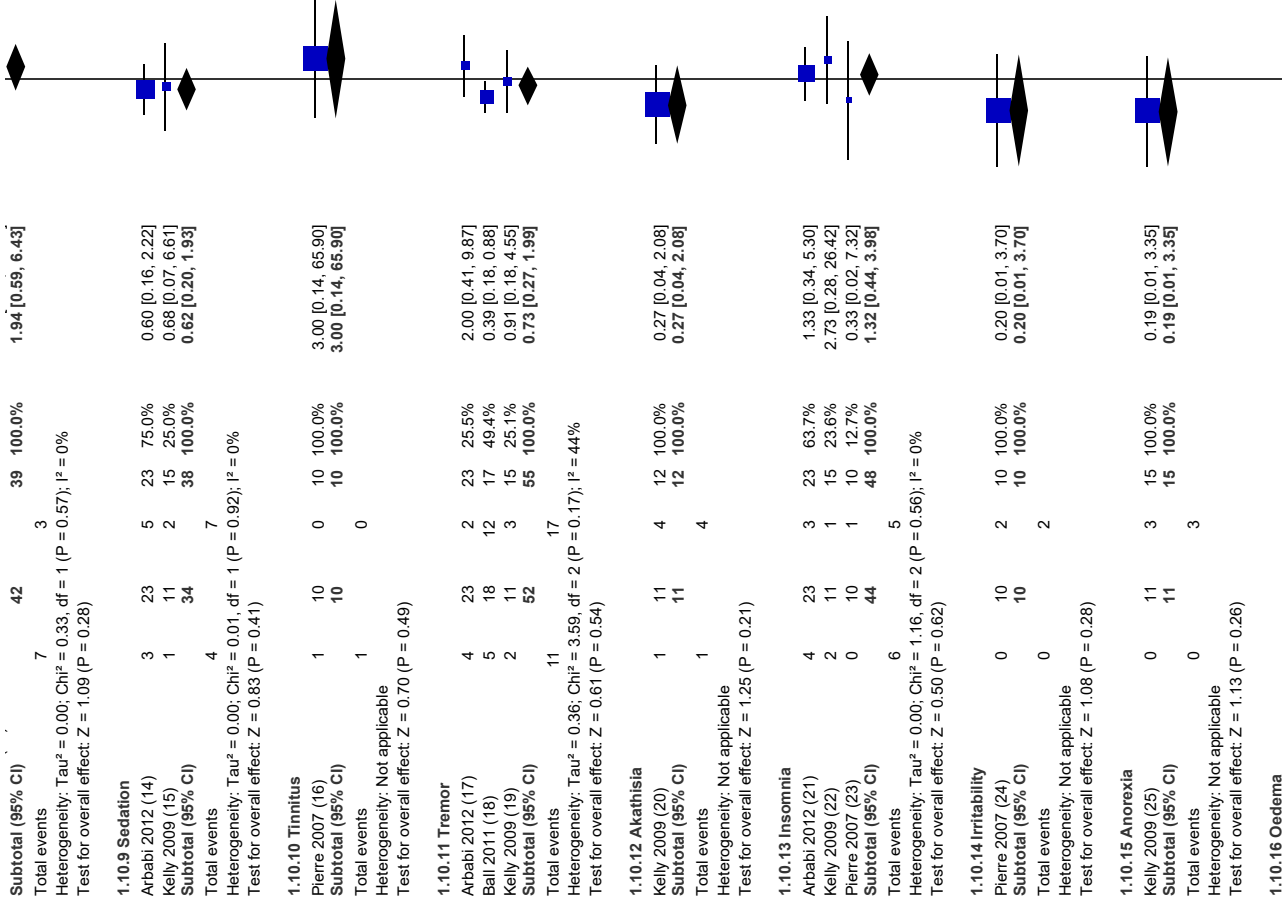
1.9 Extrapryramidal side effects (important)

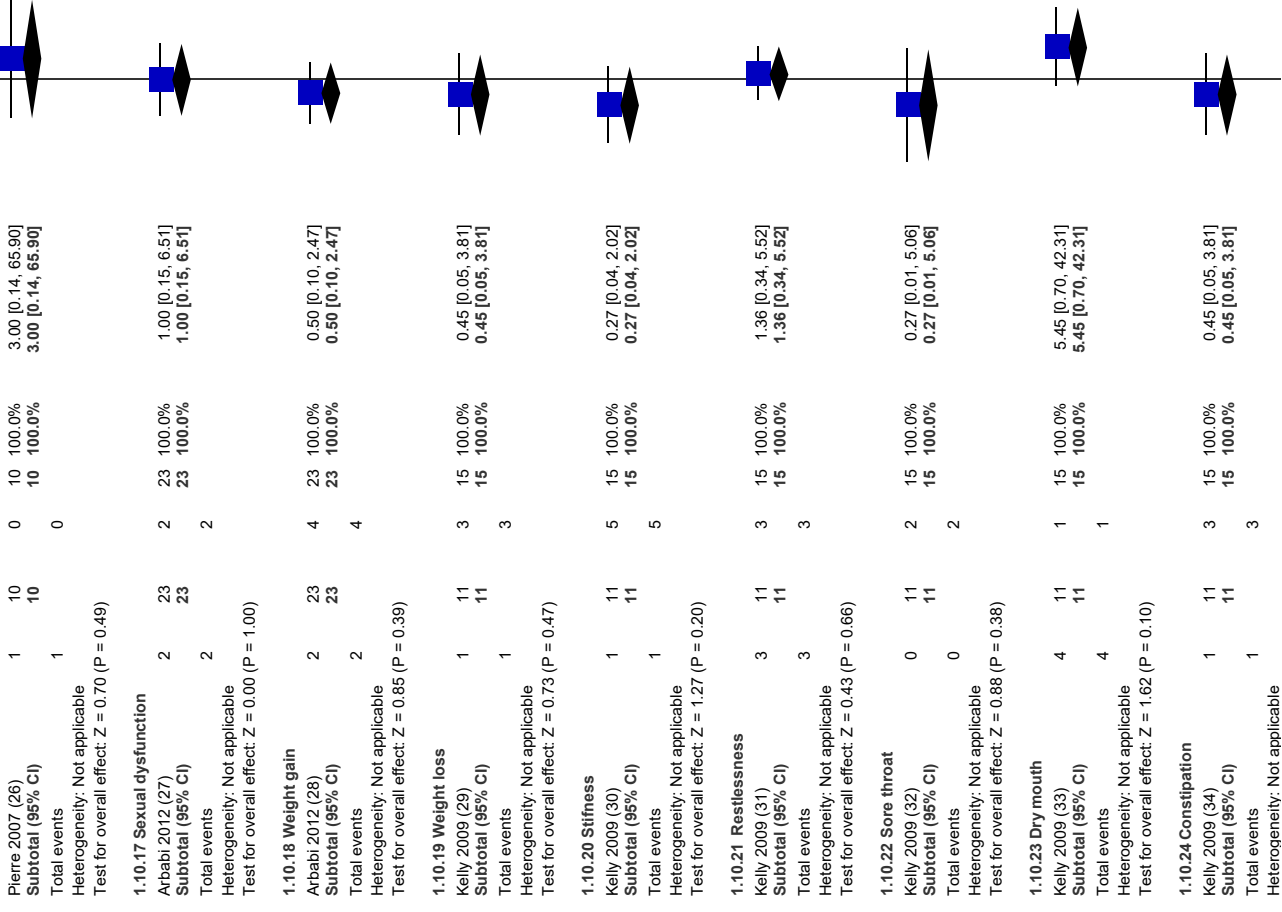


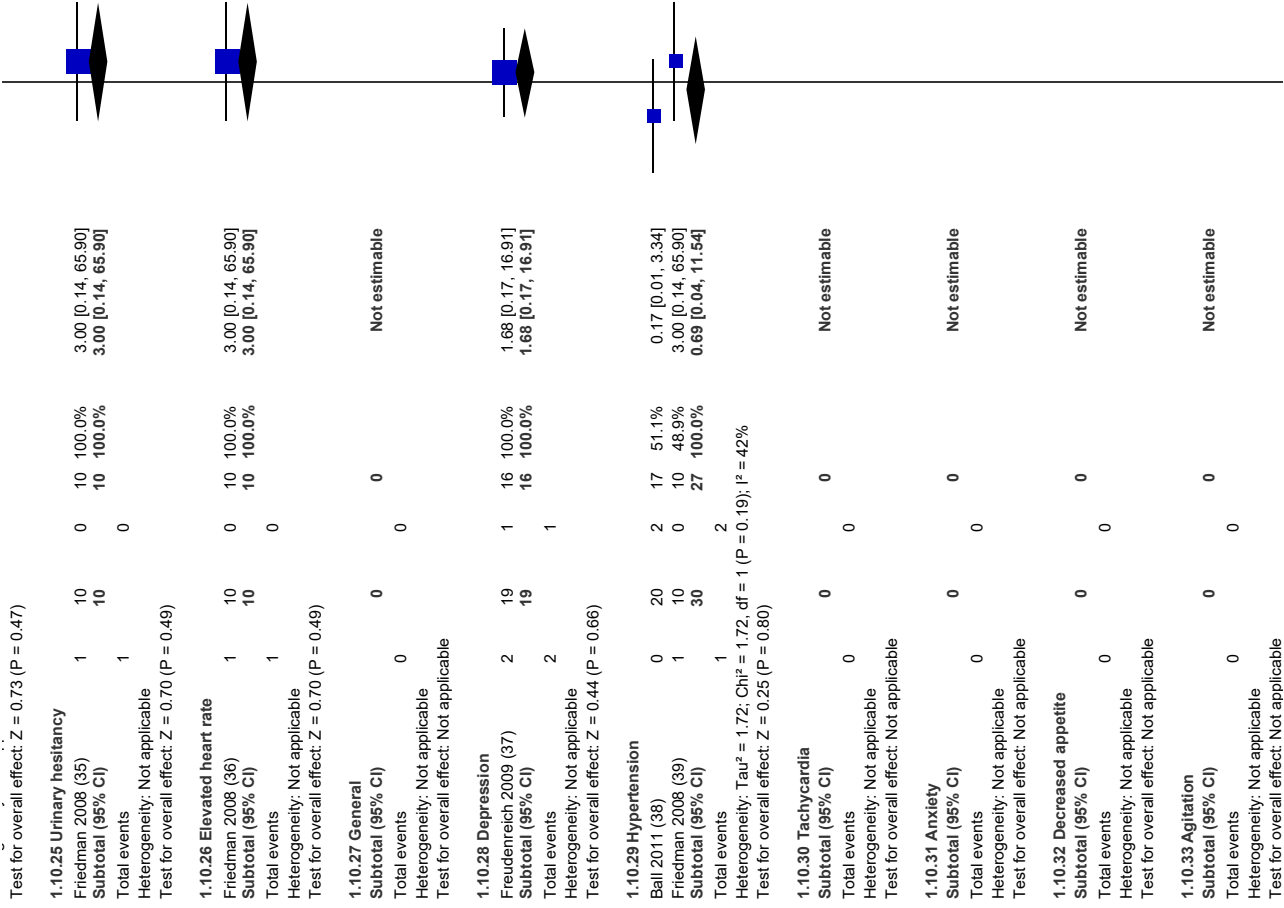
Risk of bias legend

Footnotes
 (1) atomoxetine, Simpson Angus Scale, Lower is better
 (2) Modafinil, SAS, aflæst på fig 2 day-56, final score, lower is better
 (3) Modafinil, Simpson Angus Scale, final score, lower is better
 (4) atomoxetine, Simpson Angus Extrapryramidal symptoms Scale, umiddelbart change score
 (5) Modafinil, Modified Simpson Angus Scale, change

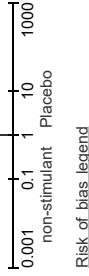








| | | | |
|---|---|---|---|
| 1-10.34 Euphoric mood | | | |
| Subtotal (95% CI) | 0 | 0 | 0 |
| Total events | 0 | 0 | 0 |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Not applicable | | | |
| 1-10.35 Psychotic disorders | | | |
| Subtotal (95% CI) | 0 | 0 | 0 |
| Total events | 0 | 0 | 0 |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Not applicable | | | |



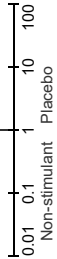
Test for subgroup differences: Chi² = 21.77, df = 27 (P = 0.75), I² = 0%

Footnotes

- (1) Modafinil
- (2) atomoxetine
- (3) Modafinil
- (4) Modafinil
- (5) Modafinil
- (6) atomoxetine
- (7) atomoxetine
- (8) modafinil
- (9) atomoxetine
- (10) atomoxetine
- (11) atomoxetine
- (12) Modafinil
- (13) Modafinil
- (14) Modafinil
- (15) atomoxetine
- (16) Modafinil
- (17) Modafinil
- (18) atomoxetine
- (19) atomoxetine
- (20) atomoxetine
- (21) Modafinil
- (22) atomoxetine
- (23) Modafinil
- (24) Modafinil
- (25) atomoxetine
- (26) Modafinil
- (27) Modafinil
- (28) Modafinil
- (29) atomoxetine
- (30) atomoxetine
- (31) atomoxetine
- (32) atomoxetine
- (33) atomoxetine
- (34) atomoxetine
- (35) atomoxetine
- (36) atomoxetine
- (37) Modafinil
- (38) atomoxetine
- (39) atomoxetine

1.11 Suicidal behavior (important)

| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Risk Ratio | | Risk of Bias |
|---|---------------|-------|---------|-------|-------|--------|---------------------|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | |
| Total (95% CI) | 0 | 0 | 0 | 0 | 0 | 0 | Not estimable | | |
| Total events | 0 | 0 | 0 | 0 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | | |



Risk of bias legend

1.12 Substance use (important)

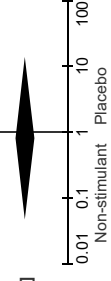
| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Risk Ratio | | Risk of Bias |
|---|---------------|-------|---------|-------|-------|--------|---------------------|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | |
| Total (95% CI) | 0 | 0 | 0 | 0 | 0 | 0 | Not estimable | | |
| Total events | 0 | 0 | 0 | 0 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | | |



Risk of bias legend

1.13 Post hoc: Serious adverse events

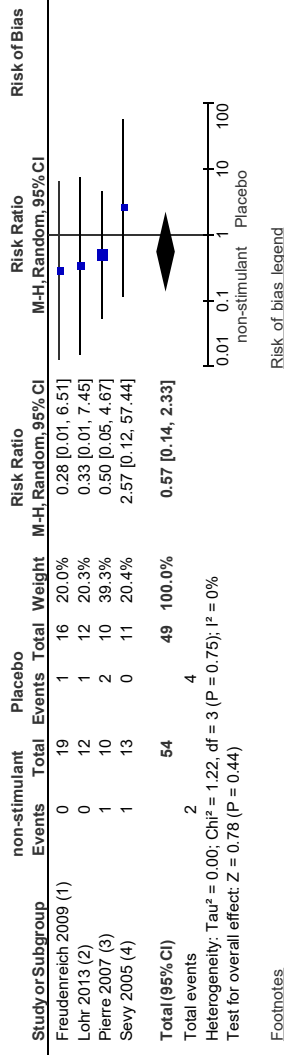
| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Odds Ratio | | Risk of Bias |
|--|---------------|-------|---------|-------|--------|--------|---------------------|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | |
| Freudenreich 2009 (1) | 1 | 19 | 1 | 16 | 100.0% | 0.83 | [0.05, 14.48] | | |
| Total (95% CI) | 1 | 19 | 1 | 16 | 100.0% | 0.83 | [0.05, 14.48] | | |
| Total events | 1 | 1 | 1 | 1 | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | | | | | |



Footnotes

(1) Modafinil

1.14 Post hoc: worsening psychosis

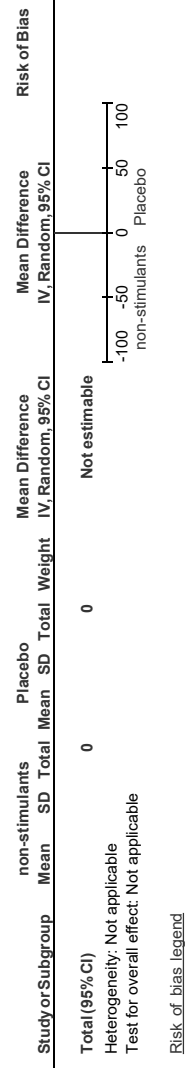


Footnotes

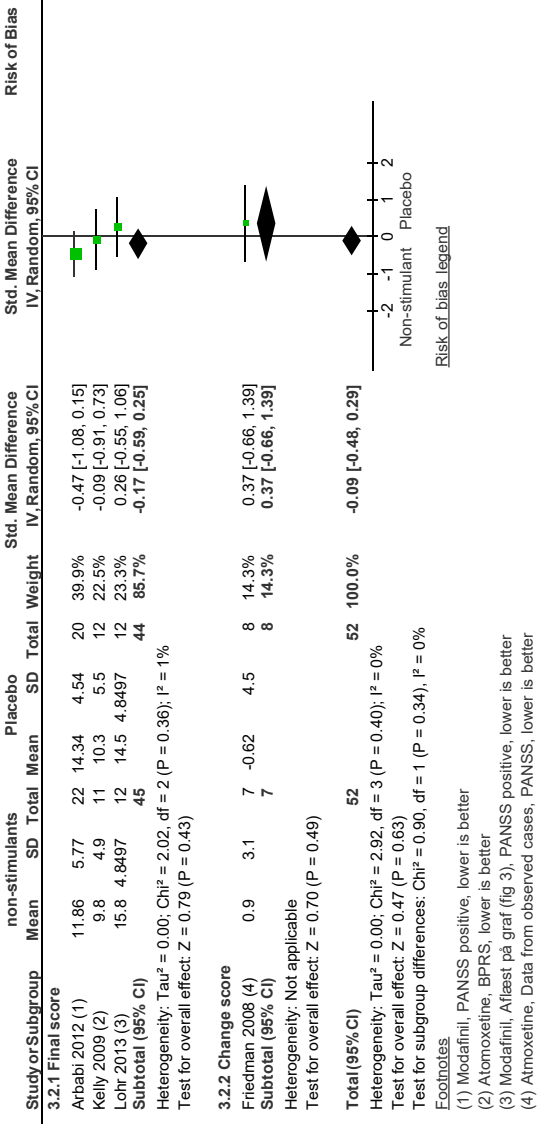
- (1) Modafinil
- (2) Modafinil
- (3) Modafinil
- (4) Modafinil

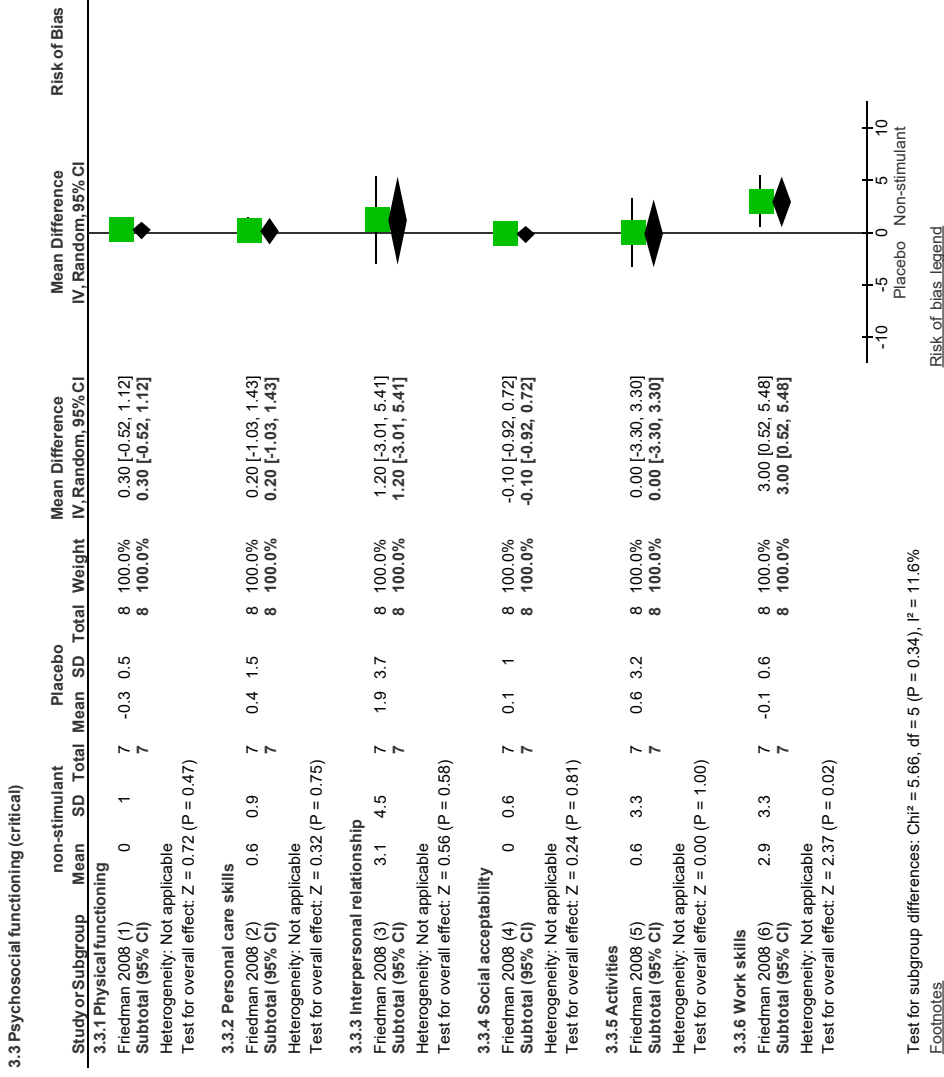
3 Sensitivitsanalyse: Non-Stimulant vs. placebo

3.1 ADHD-symptoms (critical)



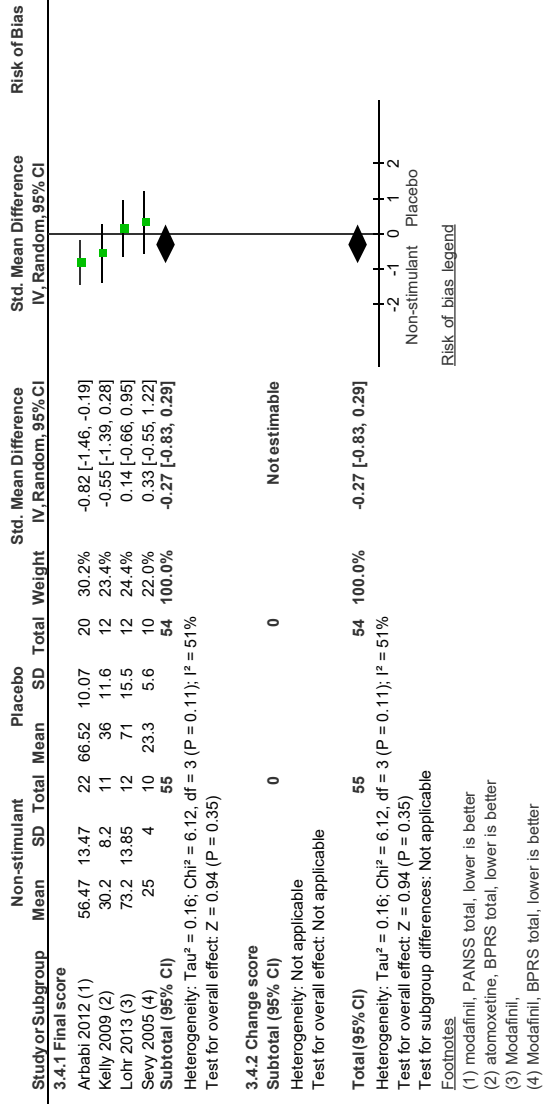
3.2 Psychotic symptoms (critical)



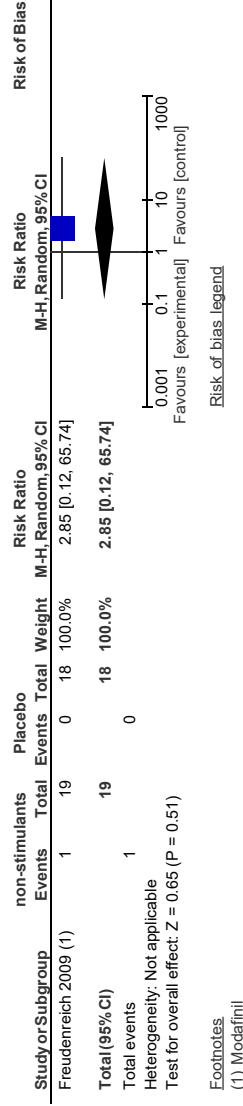


Footnotes
 (1) Atomoxetine, changes score (observed cases), SLOF, higher is better
 (2) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (3) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (4) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (5) atomoxetine, changes scores (observed cases), SLOF, higher is better
 (6) atomoxetine, changes scores (observed cases), SLOF, higher is better

3.4 Globally symptoms/functioning (important)



3.5 Psychiatric hospitalization



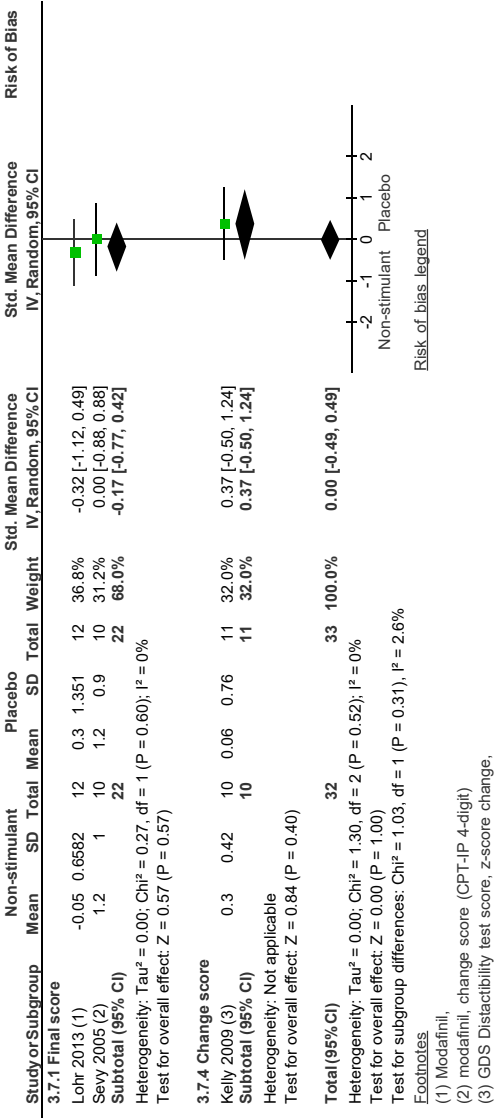
3.6 Executive functions (important)

| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Risk of Bias |
|---|---------------|--------|---------|--------|-----------|---------------|--|--------------------|
| | Mean | SD | Mean | SD | | | | |
| 3.6.1 Final score | | | | | | | | |
| Lohr 2013 (1) | 0.12 | 0.6928 | -0.19 | 0.7275 | 12 | 41.0% | 0.42 [-0.39, 1.23] | |
| Subtotal (95% CI) | 12 | | | | 12 | 41.0% | 0.42 [-0.39, 1.23] | |
| Heterogeneity: Not applicable Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | | | |
| 3.6.7 Change score | | | | | | | | |
| Friedman 2008 (2) | 0.31 | 0.64 | 7 | 0.02 | 0.87 | 8 | 25.6% | 0.35 [-0.67, 1.38] |
| Kelly 2009 (3) | 0.15 | 0.89 | 8 | -0.05 | 0.66 | 12 | 33.4% | 0.25 [-0.65, 1.15] |
| Subtotal (95% CI) | 15 | | | | 20 | 59.0% | 0.30 [-0.38, 0.97] | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 1 (P = 0.89); I ² = 0% Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | | | |
| Total (95% CI) | 27 | | | | 32 | 100.0% | 0.35 [-0.17, 0.87] | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.07, df = 2 (P = 0.96); I ² = 0% Test for overall effect: Z = 1.31 (P = 0.19) Test for subgroup differences: Chi ² = 0.05, df = 1 (P = 0.82), I ² = 0% | | | | | | | | |

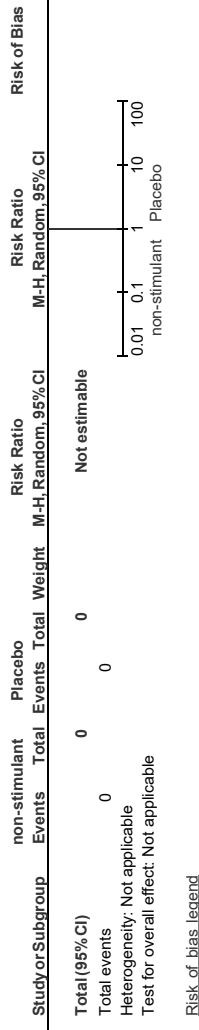
Footnotes

- (1) Modafinil, NP-composite executive,
- (2) Atomoxetine, Tower of London, change score,
- (3) Woodcock-Johnson planning test, z-score change

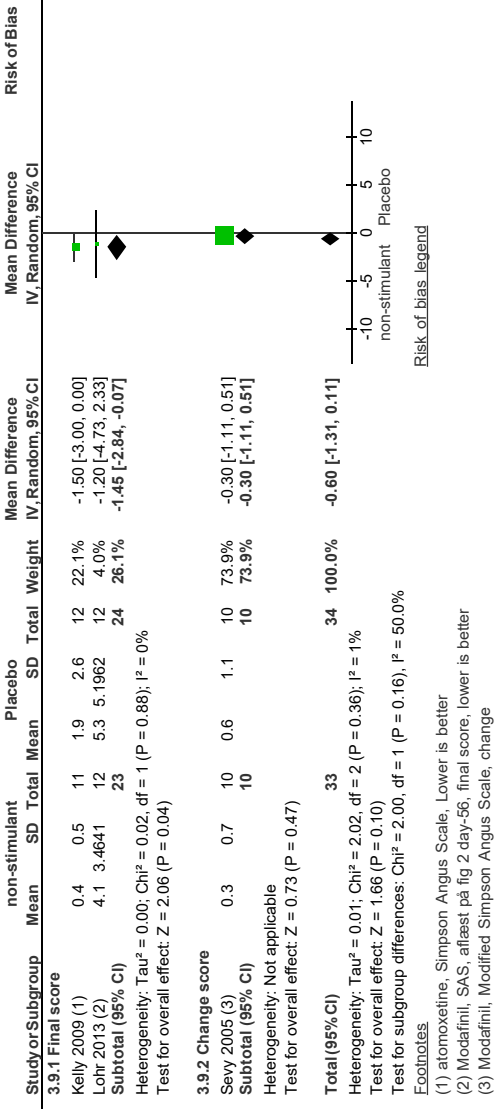
3.7 Attention (important)

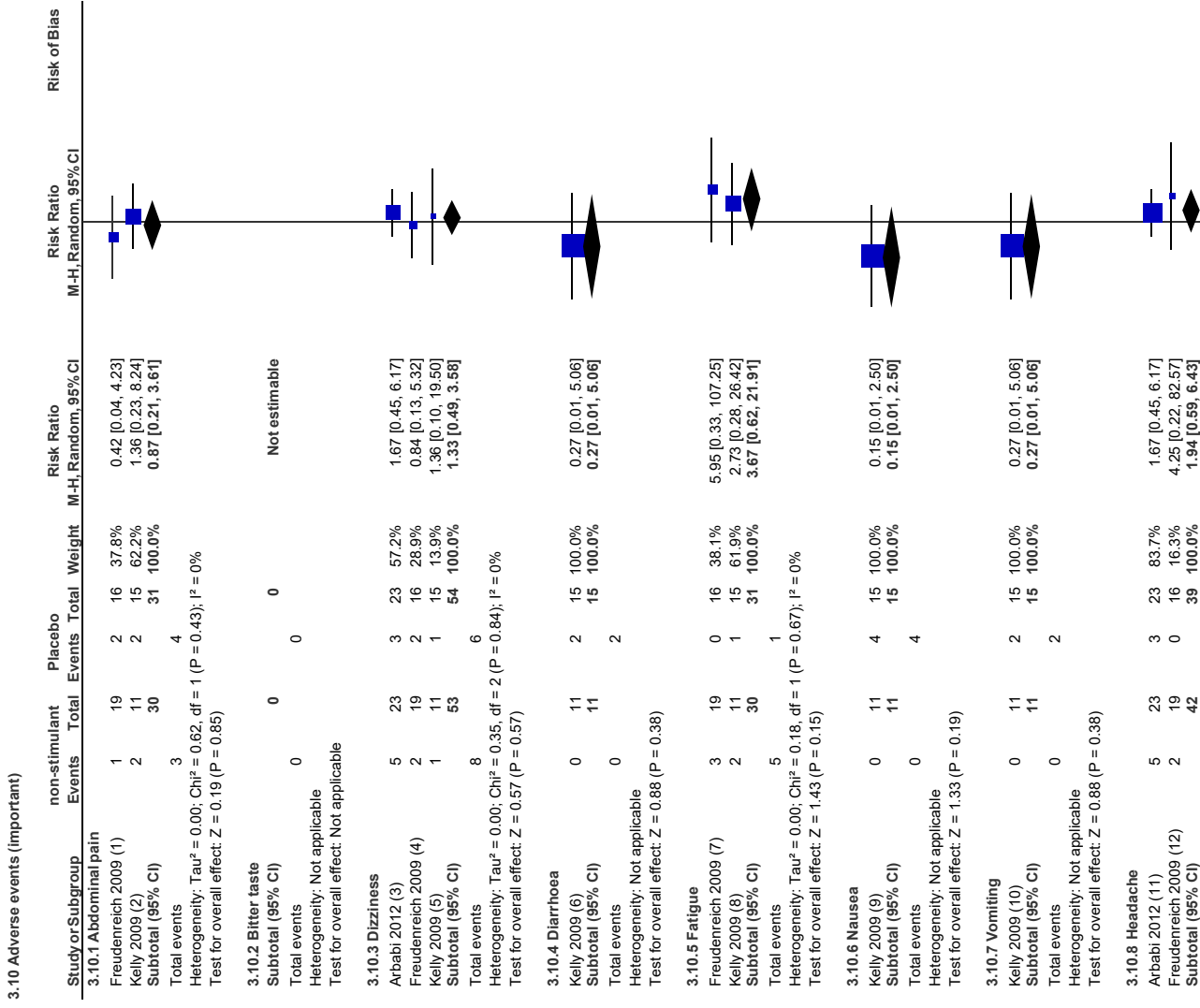


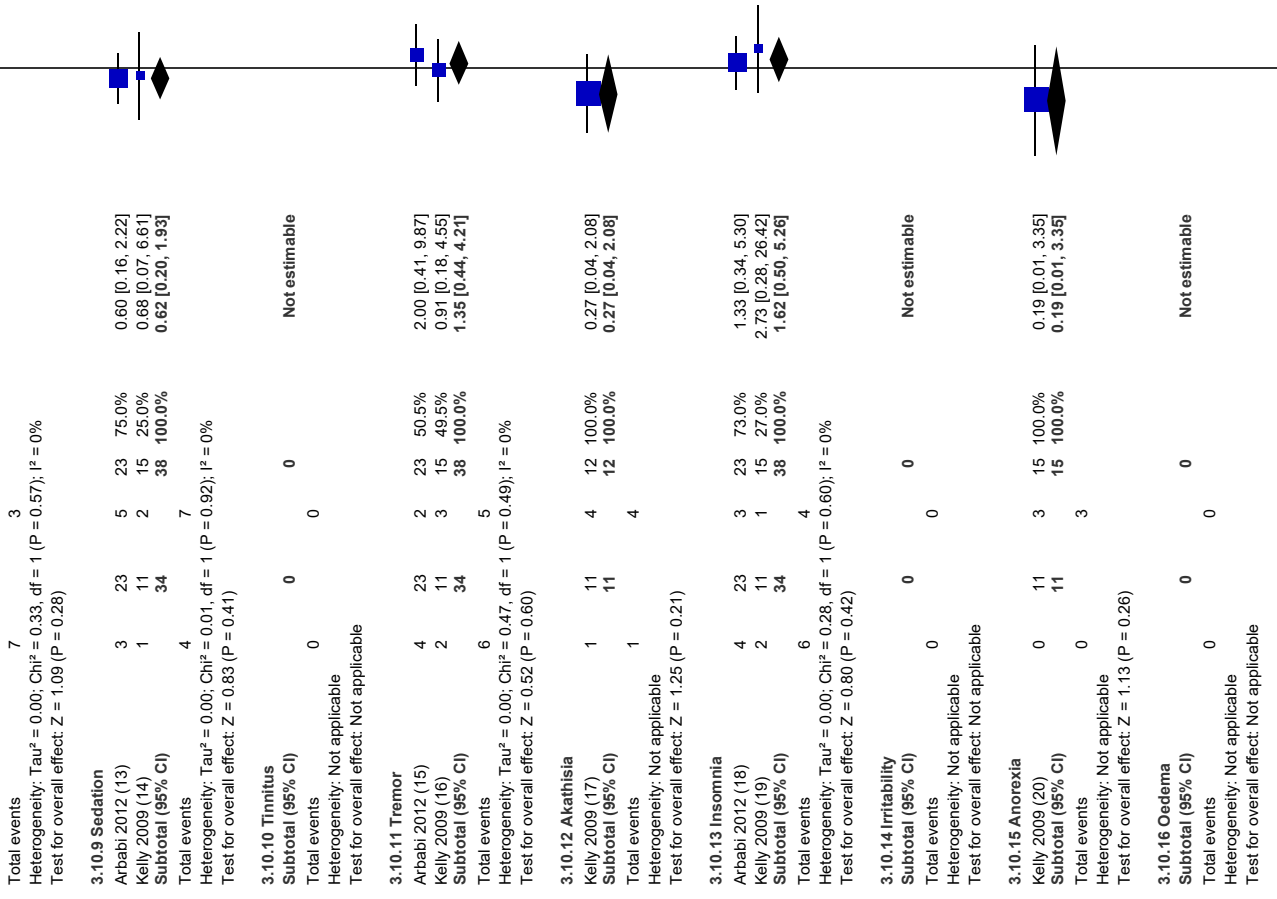
3.8 Extrapyramidal side effects (important)

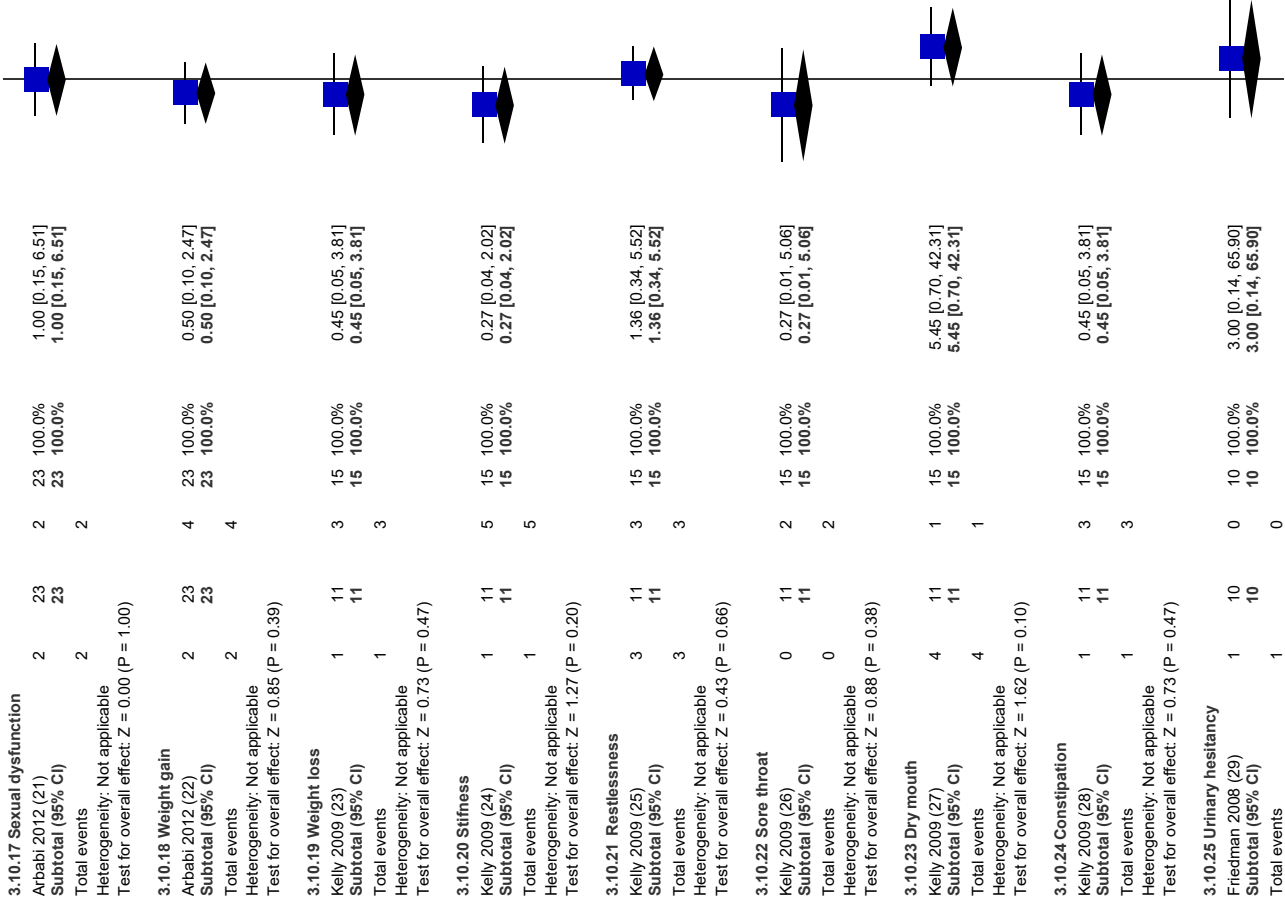


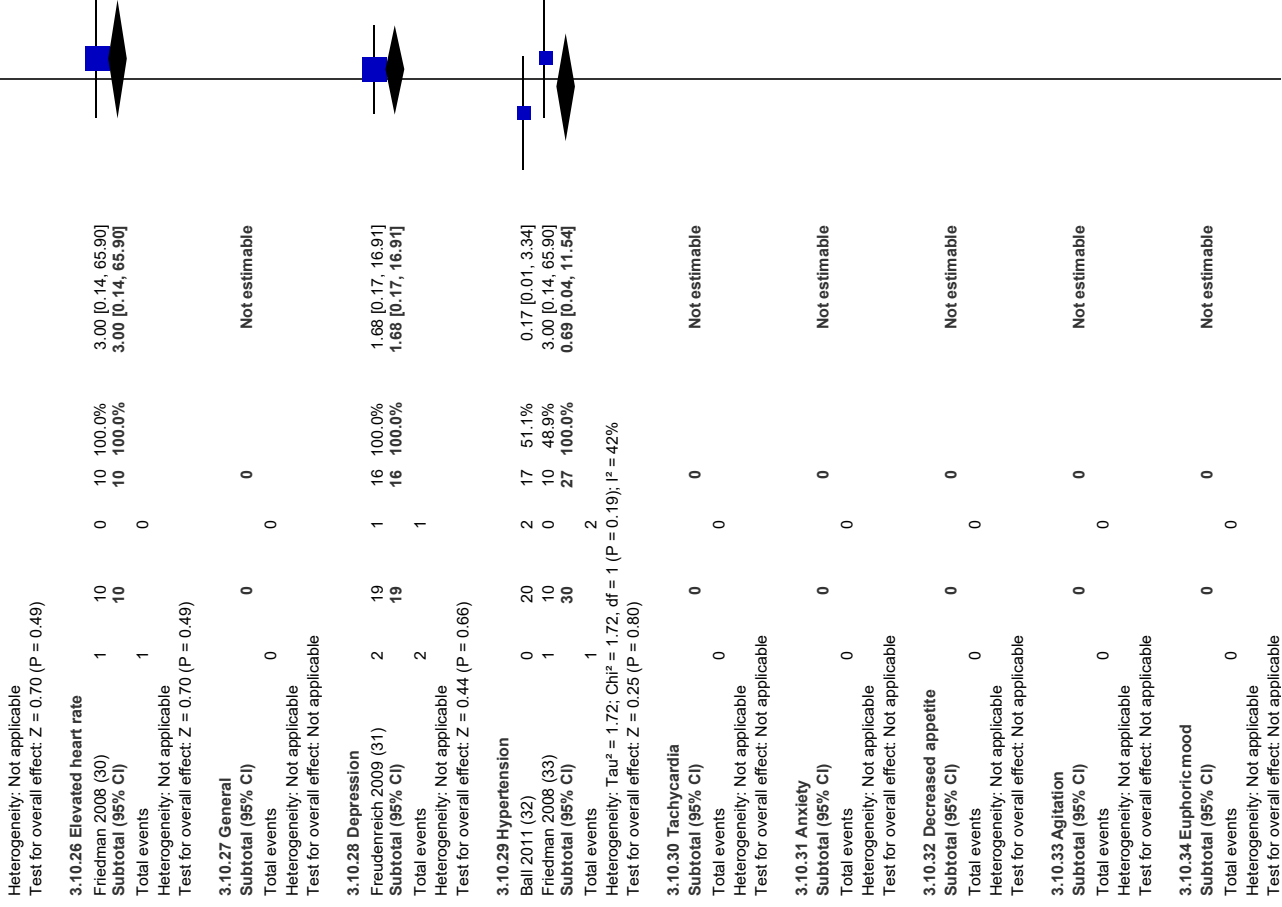
3.9 Extrapyramidal side effects (important)

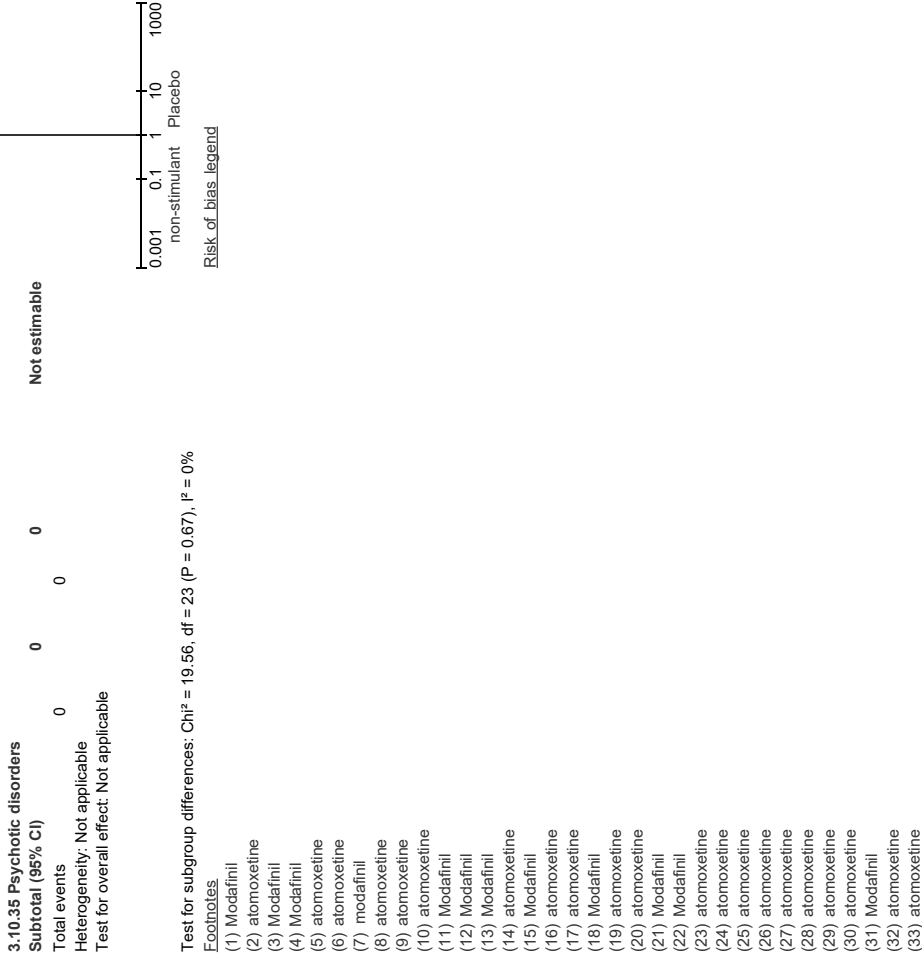






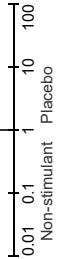






3.11 Suicidal behavior (important)

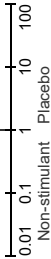
| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Risk Ratio | | M-H, Random, 95% CI | Risk Ratio | | M-H, Random, 95% CI | Risk of Bias |
|---|---------------|-------|---------|-------|-------|--------|---------------------|---------------------|---------------------|------------|--|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | | | | | |
| Total (95% CI) | 0 | 0 | 0 | 0 | 0 | 0 | Not estimable | | | | | | |
| Total events | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | | | | | | |



Risk of bias legend

3.12 Substance use (important)

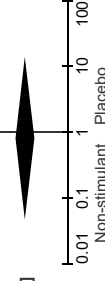
| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Risk Ratio | | M-H, Random, 95% CI | Risk Ratio | | M-H, Random, 95% CI | Risk of Bias |
|---|---------------|-------|---------|-------|-------|--------|---------------------|---------------------|---------------------|------------|--|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | | | | | |
| Total (95% CI) | 0 | 0 | 0 | 0 | 0 | 0 | Not estimable | | | | | | |
| Total events | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | | | | | | |



Risk of bias legend

3.13 Post hoc: Serious adverse events

| Study or Subgroup | Non-stimulant | | Placebo | | Total | Weight | Odds Ratio | | M-H, Random, 95% CI | Odds Ratio | | M-H, Random, 95% CI | Risk of Bias |
|--|---------------|-------|---------|-------|--------|--------|---------------------|---------------------|---------------------|------------|--|---------------------|--------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI | | | | | |
| Freudenreich 2009 (1) | 1 | 19 | 1 | 16 | 100.0% | 0.83 | [0.05, 14.48] | | | | | | |
| Total (95% CI) | 1 | 19 | 1 | 16 | 100.0% | 0.83 | [0.05, 14.48] | | | | | | |
| Total events | 1 | 1 | 1 | 1 | 1 | | | | | | | | |
| Heterogeneity: Not applicable | | | | | | | | | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | | | | | | | | | |



Footnotes

(1) Modafinil

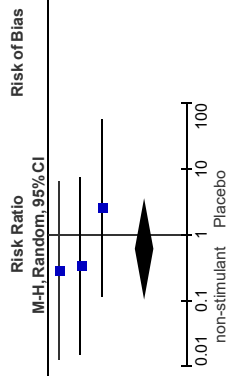
3.14 Post hoc: worsening psychosis

| Study or Subgroup | non-stimulant | | Placebo | | Total | Weight | Risk Ratio | |
|-----------------------|---------------|-----------|----------|-----------|---------------|-------------|---------------------|---------------------|
| | Events | Total | Events | Total | | | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Freudenreich 2009 (1) | 0 | 19 | 1 | 16 | 32.9% | 0.28 | [0.01, 6.51] | |
| Lehr 2013 (2) | 0 | 12 | 1 | 12 | 33.5% | 0.33 | [0.01, 7.45] | |
| Seyv 2005 (3) | 1 | 13 | 0 | 11 | 33.5% | 2.57 | [0.12, 57.44] | |
| Total (95% CI) | 1 | 44 | 2 | 39 | 100.0% | 0.63 | [0.10, 3.79] | |

Total events: non-stimulant 1, Placebo 2
 Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
 Test for overall effect: Z = 0.51 (P = 0.61)

Footnotes

- (1) Modafinil
- (2) Modafinil
- (3) Modafinil



Risk of bias legend

Intention-to-treat

| <u>Unique ID</u> | <u>Study ID</u> | <u>Experimental</u> | <u>Comparator</u> | <u>Outcome</u> | <u>Weight</u> | <u>D1</u> | <u>D2</u> | <u>D3</u> | <u>D4</u> | <u>D5</u> | <u>Overall</u> | |
|------------------|-------------------|---------------------|-------------------|----------------|---------------|-----------|-----------|-----------|-----------|-----------|----------------|---|
| 1 | Pourshams 2020 | Atomoxetine | Placebo | NA | 1 | + | + | - | + | ! | - | + |
| 2 | ShojaShafti 2016 | Modafinil | Placebo | NA | 1 | + | + | + | + | ! | ! | ! |
| 3 | Kelly 2009 | Modafinil | placebo | NA | 1 | ! | + | - | + | + | - | - |
| 4 | Friedman 2008 | Atomexetin | Placebo | NA | 1 | ! | + | - | + | ! | - | |
| 5 | Ball 2011 | Atomexetin | Placebo | NA | 1 | ! | + | - | + | + | - | D1 Randomisation process |
| 6 | Arbabi 2012 | Modafinil | Placebo | NA | 1 | + | + | + | + | ! | ! | D2 Deviations from the intended interventions |
| 7 | Freudenreich 2009 | Modafinil | Placebo | NA | 1 | ! | + | + | + | + | + | D3 Missing outcome data |
| 8 | Lohr 2013 | Modafinil | Placebo | NA | 1 | ! | + | + | + | + | + | D4 Measurement of the outcome |
| 9 | Martin 2014 | LDX | Placebo | NA | 1 | ! | + | + | + | ! | ! | D5 Selection of the reported result |
| 10 | Peloian 2008 | Modafinil | Placebo | NA | 1 | ! | + | - | + | ! | - | |
| 11 | Pierre 2007 | Modafinil | Placebo | NA | 1 | ! | ! | - | + | ! | - | |
| 12 | Prasuna 2014 | Modafinil | Placebo | NA | 1 | + | - | + | + | ! | - | |
| 13 | Sevy 2005 | Modafinil | Placebo | NA | 1 | ! | + | - | - | ! | - | |

Risk of bias domains

| | D1 | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
|--------------|----|----|----|----|----|----|----|---------|
| Corbeil 2024 | - | + | + | - | ? | + | + | - |
| Rohde 2018 | - | + | + | - | + | + | + | - |
| Burcu 2018 | - | + | + | - | ? | + | + | - |
| Hollis 2019 | + | + | + | - | + | + | + | - |

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

- Moderate

+ Low

? No information

