NKR 55 Demens og medicin

Review information

Authors

Sundhedsstyrelsen[1]

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Citation example: S. NKR 55 Demens og medicin. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Scoralick 2017

Methods	**Study design:** a randomized, double-blind, placebo-controlled trial with a placebo group (87%) consisting of historical controls **Study grouping:** Parallel group
Participants	**Inclusion criteria:** Eligible participants were all community-dwelling patients aged 60 years or over who had a diagnosis of probable AD. Diagnoses were based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition,14 and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association).16 All participants had (formal or informal) caregivers to monitor them during the 21-day protocol. A diagnosis of SD was established based on the caregiver's emotional distress as assessed by the Sleep and Night-time Behaviour item of the Neuropsychiatric Inventory (score ≥ 2) and according to criteria suggested by Yesavage et al.17,18 Eligible patients should have kept their dosing regimen stable for at least 4 weeks prior to enrollment in the study and were not allowed to change medications during the trial. **Exclusion criteria:** Patients were excluded if they had a mean nocturnal total sleep time (NTST) >8 hours as assessed by actigraphy, developed an acute sleep disturbance in the 4 weeks preceding enrolment in the study, or reported previous use of mirtazapine. Because wrist actigraphy was used to monitor sleep–wake patterns, patients with movement disorders or upper limb

	paresis were excluded. Patients with a diagnosis of other types of dementia or meeting the clinical criteria for schizophrenia, schizoaffective disorders, delusional disorders, delirium, or mood disorders with psychotic features were also excluded.
Interventions	**Intervention characteristics:** Intervention 1 ● *Description*: 15-mg mirtazapine once daily at 2100 hours for 14 consecutive days. ● Patients who met the clinical inclusion criteria were subjected to in-home actigraphic measurement ofsleep for 7 consecutive days (baseline period). The actigraphic data for each patient were then analyzed,and patients who had a mean NTST ≤ 8 hours and no acute sleep disturbance (inclusion criteria) wereenrolled in the study. The caregiver of each enrolled participant was provided with the medication required for 14 days. Each enrolled participant received medication use recommendations and was instructed to wear the actigraph for the 14-day intervention period. In addition, caregivers received guidance on sleep hygiene practices and were asked to maintain the patient on a regimen of caffeine abstinence after 1500 hours and limit his/her alcohol intake to a maximum of two drinks per day. ● *Duration (week)*: 2 weeks ● *Length of follow-up after end of intervention*: no FU Control ● *Description*: 15-mg placebo once daily at 2100 hours for 14 consecutive days. ● Patients who met the clinical inclusion criteria were subjected to in-home actigraphic measurement ofsleep for 7 consecutive days (baseline period). The actigraphic data for each patient were then analyzed,and patients who had a mean NTST ≤ 8 hours and no acute sleep disturbance (inclusion criteria) wereenrolled in the study. The caregiver of each enrolled participant was provided with the medication required for 14 days. Each enrolled participant received medication use recommendations and was instructed to wear the actigraph for the 14-day intervention period. In addition, caregivers received guidance on sleep hygiene practices and were asked to maintain the patient on a regimen of caffeine abstinence after 1500 hours and limit his/her alcohol intake to a maximum of two drinks per day. ● *Duration (week)*: 2 weeks ● *Length of follow-up after end of intervention*: no FU
Outcomes	Antal natlige vågenperioder ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported

	● **Scale**: Awekenings (n) ● **Direction**: Lower is better ● **Data value**: Endpoint Længde af nattesøvn ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Scale**: Nocturnal total sleep timee (NTST) (minutes) ● **Direction**: Higher is better ● **Data value**: Endpoint Bivirkninger (antal) ● **Outcome type**: Dichotonomous Outcome ● **Reporting**: Fully reported ● **Scale**: numbers of event ● **Direction**: Lower is better ● **Data value**: Endpoint Sedation i dagtiden ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Scale**: Daytime total sleep time (DTST) (minutes) ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	**Sponsorship source:** This work was supported by a grant (#550315/2008-0) and a fellowship for productivity in research (#310157/2012-9) provided by CNPq to O.T. Nóbrega. This was a non-industry-supported study. **Country:** Brazil **Setting:** Volunteers were recruited among those who responded to advertisements in outpatient clinics **Comments:** **Authors name:** Dr Otávio T. Nóbrega **Institution:** Geriatic Medical Center, HUB, Brasilia University Hospital, **Email:** otavionobrega@unb.br **Address:** SGAN 605 Av. L2 norte, Asa Norte, Brasilia, DF,CEP 70840-901

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization sequence was created by the principal investigator using the True Random Number Service (www.random.org). The random number generator mode was used to produce random alphanumeric, three-digit codes. The inclusion of historical controls is considered a major source of bias.
Allocation concealment (selection bias)	High risk	Randomization sequence was created by the princi- pal investigator using the True Random Number Service (www.random.org). The random number generator mode was used to produce random alphanu- meric, three-digit codes. The codes were handed to an independent pharmacist for medication preparation. The inclusion of historical controls is considered a major source of bias.
Blinding of participants and personnel (performance bias)	Low risk	The mirtazapine and placebo were in standard capsule form and identical in appearance. They were prepacked in bottles, which were individually labelled for each patient with the identifying code and admin- istration time. All individuals involved in the study were blinded to the treatment assignment, and the final randomization list was not accessed until the analysis of all actigraphic sleep data was completed. The randomization ratio was 2:1 (two control participants per each treatment participant). The statistical analysis was performed by external, blinded examiners.
Blinding of outcome assessment (detection bias)	Low risk	All individuals involved in the study were blinded to the treatment assignment, and the final randomization list was not accessed until the analysis of all actigraphic sleep data was completed.
Incomplete outcome data (attrition bias)	Unclear risk	The study did not adress this. In table 3 no missing data are reported
Selective reporting (reporting bias)	High risk	The pre-specified protocol is available at: https://clinicaltrials.gov/ct2/show/NCT01867775. The study did not report all the pre-specified outcomes: Change of Baseline in Behavioral Variables (BAHAVE-AD Scale) [Time Frame: Baseline, 14 days follow-up]]. Change From Baseline in Cognitive Function (Digit Symbol Substitution Test) [Time Frame: Baseline, 14 days follow-up]].
Other bias	High risk	Comments: The inclusion of historical controls is considered a major source of bias. Supporting annotations:

		14 patients with a diagnosis of AD and SD fulfilled the clinical evaluation and actigraphic measurement of sleep (7-day base- line period). Of these, 3 ended up randomized to the placebo group and 11 to mirtazapine group. In the mirtazapine group, one patient discontinued medica- tion due to excessive sedation after the first dose. The data of two patients in the mirtazapine group and one in the placebo group could not be recovered from the actigraph because of device decalibration. The data of 14 historical controls were used to compose the final sample, which consisted of 24 patients (mirtazapine group, n = 8; placebo group, n = 16). The main baseline demographic and clinical characteris- tics of current control subjects were comparable to data from historical controls, according to Fisher's exact test or the Mann–Whitney U-test. Data on the 14 patients assigned to the control group were obtained from the clinical trial NCT01142258, which was also conducted at University General Hospital using the same methodology, so part of the placebo group (87%) consisted of historical controls. The decision to include historical placebo controls was mainly based on ethical grounds, to avoid rendering a larger number of demented patients without intervention for several weeks.

Footnotes

Characteristics of excluded studies

Eeles 2006

Reason for exclusion	Wrong study design

Karlsson 2000

Reason for exclusion	Wrong patient population

Mayer 2011

Reason for exclusion	Wrong intervention

McClam 2015

Reason for exclusion	Wrong study design

Padberg 2005

Reason for exclusion	Wrong intervention

Pahwa 2009

Reason for exclusion	Wrong study design

Poewe 2007

Reason for exclusion	Wrong patient population

Rajima 2001

Reason for exclusion	Wrong study design

Romeo 2013

Reason for exclusion	Wrong patient population

Roose 2003

Reason for exclusion	Wrong patient population

Schroeck 2016

Reason for exclusion	Wrong patient population

Sheikh 2004

Reason for exclusion	Wrong study design

Swanbergand 2002

Reason for exclusion	Wrong patient population

Weintraub 2007

Reason for exclusion	Wrong intervention

Weldemichael 2010

Reason for exclusion	Wrong outcomes

Wishart 2011

Reason for exclusion	Wrong outcomes

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Scoralick 2017

[Empty]

Excluded studies

Eeles 2006

Eeles E.M.; Stephens M.; Benedict C.; Beaverstock J.; Gupta M.; Page, M.. Sleep in dementia assessment may require a multidisciplinary approach [2].. American Journal of Geriatric Psychiatry 2006;14(11):986. [DOI:]

Karlsson 2000

Karlsson, I.; Godderis, J.; Augusto De Mendonca Lima, C.; Nygaard, H.; Simanyi, M.; Taal, M.; Eglin, M.. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia.. International journal of geriatric psychiatry 2000;15(4):295-305. [DOI:]

Mayer 2011

Mayer G.; Jennum P.; Riemann D.; Dauvilliers, Y.. Insomnia in central neurologic diseases - occurrence and management.. Sleep Medicine Reviews 2011;15(6):369-378. [DOI: http://dx.doi.org/10.1016/j.smrv.2011.01.005]

McClam 2015

McClam T.D.; Marano C.M.; Rosenberg P.B.; Lyketsos, C. G.. Interventions for Neuropsychiatric symptoms in Neurocognitive impairment due to Alzheimer's disease: A review of the literature.. Harvard review of psychiatry 2015;23(5):377-393. [DOI: http://dx.doi.org/10.1097/HRP.0000000000000097]

Padberg 2005

Padberg F.; Moller H.J.; Bottlender R.; Hampel, H.. Modern therapy for dementia.. MMW-Fortschritte der Medizin 2005;147(SUPPL. 2):71-77. [DOI:]

Pahwa 2009

Pahwa, R.. Treatment of non-motor symptoms of PD. 2009;(Conference Proceedings). [DOI: http://dx.doi.org/10.1016/S1353-8020%2809%2970092-6]

Poewe 2007

Poewe, W.. Depression in Parkinson's disease. 2007;(Conference Proceedings). [DOI: http://dx.doi.org/10.1007/s00415-007-5008-4]

Rajima 2001

[Empty]

Romeo 2013

[Empty]

Roose 2003

Roose, Steven P.; Nelson, J. Craig; Salzman, Carl; Hollander, Steven B.; Rodrigues, Heidi; Mirtazapine in the Nursing Home Study Group. Open-label study of mirtazapine orally disintegrating tablets in depressed patients in the nursing home.. Current Medical Research & Opinion 2003;19(8):737-746. [DOI:]

Schroeck 2016

Schroeck, Jennifer L.; Ford, James; Conway, Erin L.; Kurtzhalts, Kari E.; Gee, Megan E.; Vollmer, Krista A.; Mergenhagen, Kari A.. Review of Safety and Efficacy of Sleep Medicines in Older Adults. Clinical therapeutics 2016;38(11):2340-2372. [DOI: https://dx.doi.org/10.1016/j.clinthera.2016.09.010]

Sheikh 2004

Sheikh, J. I.. Anxiolytics, sedatives, and older patients.. Primary Psychiatry 2004;11(8):51-54. [DOI:]

Swanbergand 2002

Swanbergand M.M.; Cummings, J. L.. Benefit-risk considerations in the treatment of dementia with Lewy bodies.. Drug Safety 2002;25(7):511-523. [DOI:]

Weintraub 2007

Weintraub D.; Stern, M. B.. Intervening in the neuropsychiatric features of Parkinson's disease.. Expert Review of Neurotherapeutics 2007;7(6):699-710. [DOI: http://dx.doi.org/10.1586/14737175.7.6.699]

Weldemichael 2010

Weldemichael D.A.; Grossberg, G. T.. Circadian rhythm disturbances in patients with Alzheimer's disease: A review.. International Journal of Alzheimer's Disease 2010;(pagination). [DOI: http://dx.doi.org/10.4061/2010/716453]

Wishart 2011

Wishart S.; Macphee, G. J. A.. Evaluation and management of the non-motor features of Parkinson's disease.. Therapeutic Advances in Chronic Disease 2011;2(2):68-95. [DOI: http://dx.doi.org/10.1177/2040622310387847]

Other references

Additional references

Other published versions of this review

Classification pending references

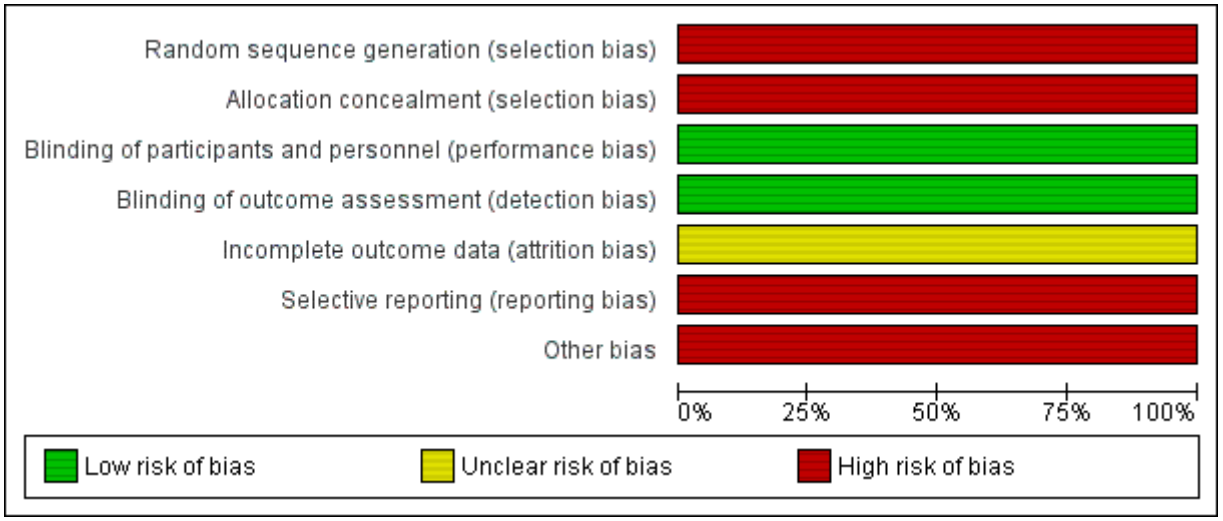
Data and analyses

1 Mirtazapin or mianserin vs non pharmacological

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Antal natlig vågenperioder	1	24	Mean Difference (IV, Fixed, 95% CI)	6.00 [-2.69, 14.69]
1.2 Længde af nattesøvn	1	24	Mean Difference (IV, Random, 95% CI)	-124.20 [-199.30, -49.10]
1.3 Søvnkvalitet vurderet af omsorgsgiver	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 BPSD	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
1.5 Bivirkninger_antal personer	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.06, 2.87]
1.6 Livskvalitet	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
1.7 Sedation i dagtiden_DTST (min)	1	24	Mean Difference (IV, Fixed, 95% CI)	104.90 [21.54, 188.26]
1.8 Antal fald	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

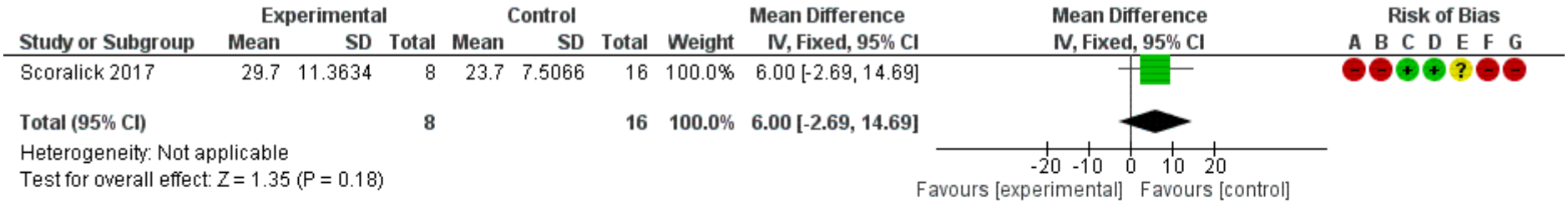
Figures

Figure 1



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

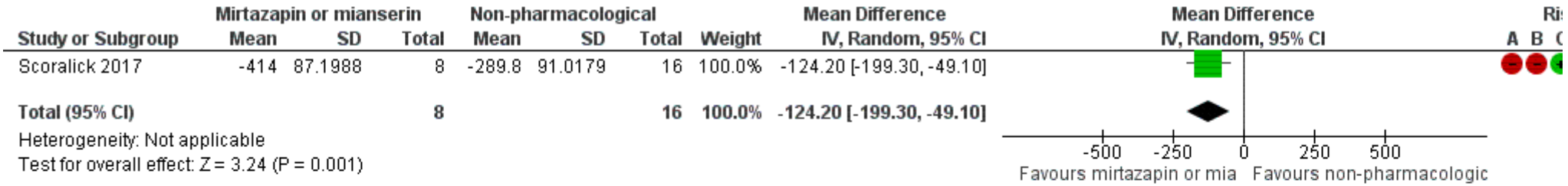
Figure 2 (Analysis 1.1)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Mirtazapin or mianserin vs non pharmacological, outcome: 1.1 Antal natlig vågenperioder.

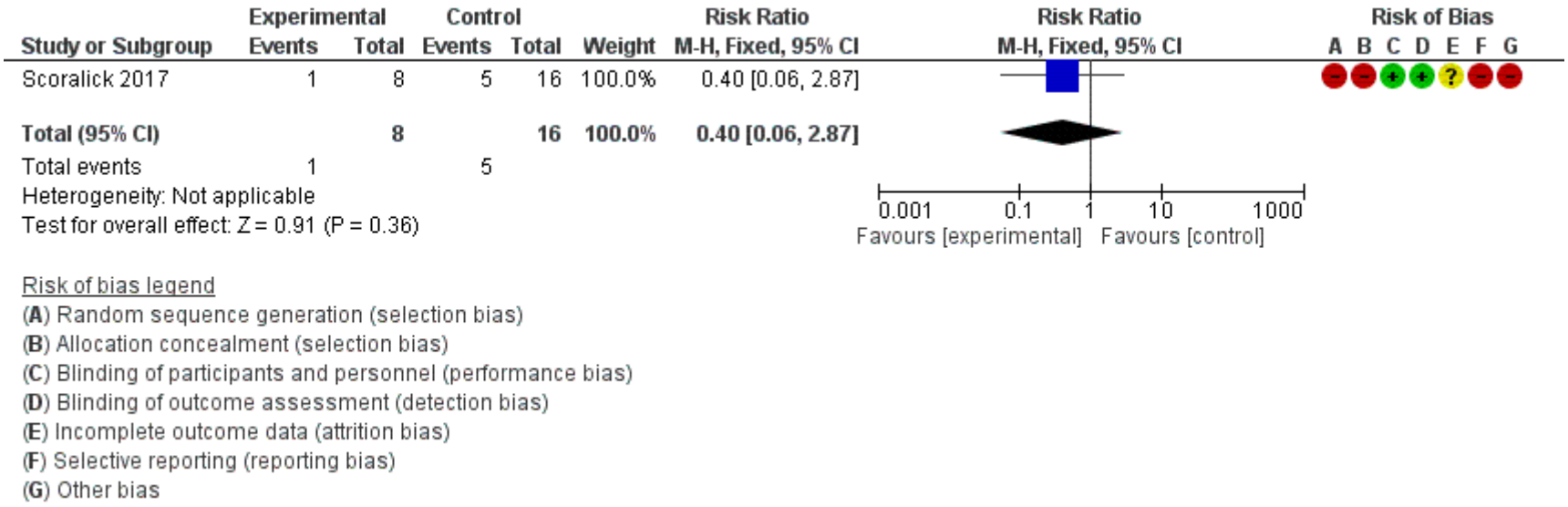
Figure 3 (Analysis 1.2)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

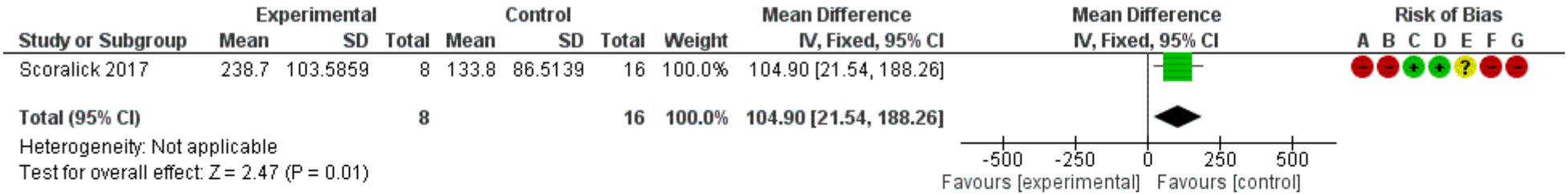
Forest plot of comparison: 1 Mirtazapin or mianserin vs non pharmacological, outcome: 1.2 Længde af nattesøvn.

Figure 4 (Analysis 1.5)



Forest plot of comparison: 1 Mirtazapin or mianserin vs non pharmacological, outcome: 1.5 Bivirkninger_antal personer.

Figure 5 (Analysis 1.7)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Mirtazapin or mianserin vs non pharmacological, outcome: 1.7 Sedation i dagtiden_DTST (min).