NKR opdt. delir PICO 7 Behandling af delir med antiopsykotika

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Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *Age*: 76.5 (8.2) ● D*elir ved studie start*: Delirium symptom score: 2.60 (1.48) Control ● *Age*: 73.8 (10.7) ● D*elir ved studie start*: Delirium symptom score: 2.54 (1.43) Intervention 2 ● *Age*: 74.5 (10.6) ● *Coma*: ● *Mechanical ventilation*: ● *surgery*: ● *Delir ved studie start*: Delirium symptom score: 2.54 (1.23) **Included criteria:** Participants included adult patients receiving hospice or pal-liative care with advanced, progressive disease that was no lon-ger curable who required inpatient care by a specialist pallia-tive care team. Participants needed to meet the following3 criteria: delirium diagnosed via criteria from theDiagnosticand Statistical Manual of Mental Disorders(Fourth Edition, TextRevision), Memorial Delirium Assessment Scale (MDAS) scoreof 7 or more, and presence of the target symptoms of de-lirium associated with distress, defined as a delirium symp-toms score of 1 or more (sum of the scores from items 2 [inap-propriate behavior], 3 [inappropriate communication], and4 [illusions and hallucinations] on the Nursing Delirium Screen-ing Scale [NuDESC] [severity range, 0-6]) **Excluded criteria:** Exclusion criteria included delirium due to substance with-drawal, history of neuroleptic malignant syndrome, regular useof antipsychotic drugs within 48 hours (a single as-needed dosewas allowed if administered more than 24 hours before thestudy for a nondelirium indication), previous adverse reac-tion to antipsychotic drugs, extrapyramidal disorders, pro-longed QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days,and pregnancy or breastfeeding. Participants were required tospeak English and be able to swallow liquids **Pretreatment:** The study reached its preplanned sample size, withcomparable clinicodemographic baseline data between arms

Interventions	**Intervention Characteristics** Intervention ● *Description*: haloperidol (Partici-pants 65 years or younger received a 0.5 mg loading doseadministered with the first dose of 0.5 mg, then 0.5 mg main-tenance doses every 12 hours. Doses could be titrated by 0.25mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4mg/d. For participants older than 65 years, the loading, ini-tial, and maximum doses were halved.) (Doses were increased if the sum of NuDESC scores for items2, 3, and 4 (delirium symptoms score) was 1 or more at the mostrecent assessment, conducted every 8 hours. Dose reductionto the prior dose could occur for adverse effects, resolution ofdelirium (MDAS score of <7 for 48 hours), or resolution of symp-toms (all NuDESC item scores <1 for 48 hours)) ● *Duration of intervention*: 72 hours ● *Evt. rescue medication*: Midazolam use was significantly lower among those in theplacebo arm compared with the risperidone and haloperidolarms combined on each study day (13 of 75 [17.3%] vs 50 of 144[34.7%] on day 1;P= .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%]on day 2;P= .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] onday 3;P= .02). ● *Co-medication*: Patients receiving opioids, N: 31 (38) Control ● *Description*: Placebo. Partici-pants 65 years or younger received a 0.5 mg loading doseadministered with the first dose of 0.5 mg, then 0.5 mg main-tenance doses every 12 hours. Doses could be titrated by 0.25mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4mg/d. For participants older than 65 years, the loading, ini-tial, and maximum doses were halved. The placebo solutionwas titrated similarly using matching volumes of solution foreach dose level. ● *Duration of intervention*: 72 hours ● *Evt. rescue medication*: Midazolam use was significantly lower among those in theplacebo arm compared with the risperidone and haloperidolarms combined on each study day (13 of 75 [17.3%] vs 50 of 144[34.7%] on day 1;P= .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%]on day 2;P= .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] onday 3;P= .02). ● *Co-medication*: Patients receiving opioids, N: 35 (42) Intervention 2 ● *Description*: risperidone (Partici-pants 65 years or younger received a 0.5 mg loading doseadministered with the first dose of 0.5 mg, then 0.5 mg main-tenance doses every 12 hours. Doses could be titrated by 0.25mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4mg/d. For participants older than 65 years, the loading, ini-tial, and maximum doses were halved.) (Doses were increased if the sum of NuDESC scores for items2, 3, and 4 (delirium symptoms score) was 1 or more at the mostrecent assessment, conducted every 8 hours. Dose reductionto the prior dose could occur for adverse effects, resolution ofdelirium (MDAS score of <7 for 48 hours), or resolution of symp-toms (all NuDESC item scores <1 for 48 hours)) ● *Duration of intervention*: 72 hours ● *Evt. rescue medication*: Midazolam use was significantly lower among those in theplacebo arm compared with the risperidone and haloperidolarms combined on each study day (13 of 75 [17.3%] vs 50 of 144[34.7%] on day 1;P= .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%]on day 2;P= .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] onday 3;P= .02). ● *Co-medication*: Patients receiving opioids, N: 39 (48)
Outcomes	*SAE (under indlæggelse)* ● **Outcome type**: DichotomousOutcome *Delirium varighed (Mean CI)* ● **Outcome type**: ContinuousOutcome *Delirium varighed (Mean SD)* ● **Outcome type**: ContinuousOutcome *Kritisk Uro* ● **Outcome type**: ContinuousOutcome *Indlæggelsestid* ● **Outcome type**: ContinuousOutcome *Genindlæggelser Op til 3 mdr. efter udskrivelse* ● **Outcome type**: DichotomousOutcome *Fald* ● **Outcome type**: DichotomousOutcome *Angst*

	● **Outcome type**: ContinuousOutcome *Ekstrapyramidale bivirkninger* ● **Outcome type**: ContinuousOutcome *Ekstrapyramidale bivirkninger* ● **Outcome type**: DichotomousOutcome *Kognitiv funktion* ● **Outcome type**: ContinuousOutcome *Død* ● **Outcome type**: DichotomousOutcome *Delirium severity* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** This study was funded by the Australian Government's Department of Health under the National Palliative Care Strategy.Individual site funding was supplemented by grant NHMRC 480476 from the National Health and Medical Research Council, Australia **Country:** Australia **Setting:** inpatient hospice or hospital palliative care **Comments:** http://www.anzctr.org.au/trial_view.aspx?ACTRN=ACTRN12607000562471 **Authors name:** Meera R. Agar **Institution:** Centre for Cardiovascular and Chronic Care, Faculty of Health,University of Technology Sydney **Email:** meera.agar@uts.edu.au **Address:** Centre for Cardiovascular and Chronic Care, Faculty of Health,University of Technology Sydney, Level 3, 235 Jones St (PO Box 123),Ultimo, New South Wales, Australia
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	rights reserved. Randomization and Masking Site randomization schedules were generated using random number tables at an independent blinded central registry. Par- ticipants were randomized in blocks of 6 by site in a 1:1:1 ratio by arm. Allocation concealment was by sealed opaque enve- lopes. Site clinical trial pharmacists who opened
Allocation concealment	Low risk	Allocation concealment was by sealed opaque enve- lopes.clinical trial pharmacists who opened the treat- ment schedules to prepare the intervention were not other- wise involved in patient care.
Blinding of participants and personnel	Low risk	Site clinical trial pharmacists who opened the treat- ment schedules to prepare the intervention were not other- wise involved in patient care. Study medication was dispensed in opaque screw-top bottles, which were identical in terms of volume, color, and smell and taste of the contents. Treat- ment assignment was double-blinded: both participants and investigators were masked to treatment group for the dura- tion of the study.Study medication was dispensed in opaque screw-top bottles, which were identical in terms of volume, color, and smell and taste of the contents.
Blinding of outcome assessors	Low risk	covariate. Second- ary outcomes included daily MDAS score, lowest delirium symptoms score, daily use of midazolam use, extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale, sedation assessed by the Richmond Agitation-Sedation Scale, National Cancer Institute Common Terminol- ogy Criteria for Adverse Events, and survival.ment assignment was double-blinded: both participants and investigators were masked to treatment group for the dura- tion of the study.
Incomplete outcome data	Low risk	Present results from ITT analyses
Selective outcome reporting	Unclear risk	TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12607000562471.

Other sources of bias	Unclear risk	Interest Disclosures: None reported. Funding/Support: This study was funded by the Australian Government's Department of Health under the National Palliative Care Strategy. Individual site funding was supplemented by grant NHMRC 480476 from the National Health and Medical Research Council, Australia. Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation review, or approval of the manuscript; and decision to submit the manuscript for publication. Additional Contributions: Debbie Marriott, Flinders

Agar 2017 A

Methods	
Participants	
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Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Unclear risk	
Allocation concealment	Unclear risk	
Blinding of participants and personnel	Unclear risk	
Blinding of outcome assessors	Unclear risk	
Incomplete outcome data	Unclear risk	
Selective outcome reporting	Unclear risk	
Other sources of bias	Unclear risk	

Devlin 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age*: 62,4 (14) ● *Antal pt. med delir ved studiestart*: 100% Kontrol ● *Age*: 63,6 (15.3) ● *Antal pt. med delir ved studiestart*: 100% **Included criteria:** April 2006-august 2008 adult patients admitted to the medical and surgical ICU at each institution with delirium diagnosed with the ICDSC, had an order for as-needed haloperidol and were tolerating enteral nutrition. **Excluded criteria:** History of irreversible cognitive dysfunctionAdmitted with a primary neurological condition or injuryHistory of hepatic encephalopathy or end-stage liver failure

	(Childs Pugh B or worse)Actively withdrawing from alcoholTreatment with an antipsychotic agent in the 30 days before ICU-admissionCurrent treatment with dexmedetomidine or neuromuscular blockerCurrent treatment with an agent having either the potential to affect the quetipine concentration or increase the risk of QTc prolongation.Baseline QTc > 500 msPregnancyNon-english speakingPresence of a condition preventing delirium assessmentPrognosis considered hopelessInformed consent could not be obtained from the legally authourized representative. **Pretreatment:** Væsentlig flere intuberede ved start i placebo gruppe og flere udsat for fentanyl og benzo i de sidste 24 timer. Flere kom hjemmefra i interventionsgruppe.
Interventions	**Intervention Characteristics** Intervention ● *Description*: Patients receive Quatipine, dosage 50mg every 12 hours (100mg /day) ● *Duration of intervention*: Pt. deliriumfri, udskrives fra ICU, oplever adverse events eller 10 dage. ● *Evt rescue-medication*: I.v. haloperidol 1-10 mg administered min 2 hours interval as-needed basis Kontrol ● *Description*: Patients receive placebo (50 mg NG twice a day - 12 hours interval) ● *Duration of intervention*: as for the IV group ● *Evt rescue-medication*: as for the IV group
Outcomes	*Død/mortality (Ved udskrivelse)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported *Genindlæggelser/readmissions (3 mdr FU)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported *Fald/falls (Ved udskrivelse)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported *Funktionsevne/physical function (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported *Angst/anxiety (Ved udskrivelse)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported *Ekstrapyramidale bivirkninger/extrapyramidal symptoms (Ved udskrivelse)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported *Uro/restlessness (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Not reported *SAE (Ved udskrivelse)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported *Død/mortality (3 mdr FU)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Not reported *Delirium severity (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome

	● **Reporting**: Partially reported ● **Scale**: DRS-S-98 ● **Range**: 0-46 ● **Direction**: Lower is better
Identification	**Sponsorship source:** Society of Critical Care Medicines; Critical Care Pharmacy research Award; Astra Zeneca Pharmaceuticals; Author grant support from Hospira **Country:** US **Setting:** Intensive care unit /critically ill **Comments:** **Authors name:** J.Devlin **Institution:** Northeastern University School of Pharmacy, Boston MA **Email:** j.devlin@neu.edu **Address:** Northeastern University School of Pharmacy, Boston MA
Notes	*Susanne Stabel Gren* on 07/06/2016 07:59 **Select** Placebokontrolleret RCT på ITA-ptt. Selvom det er en lille gruppe 36 skal det med *Jakob Carlsen* on 07/06/2016 18:51 **Select** Quetiapin med "ad-on" serenase. Lille, men relevant?! *Nkr 42 Delir* on 14/06/2016 22:42 **Outcomes** Indlæggelsestid (Ved udskrivelse) opgjort i median (interquartile range)Intervention: 24 (11-33)Kontrol: 26 (17-49)Delirvarighed (Ved udskrivelse) opgjort i median (interquartile range)Intervention: 36 (12-87) timerKontrol: 120 (60-195) *Henning Keinke Andersen* on 16/06/2016 22:09 **Outcomes** I assume the notified mortality rates (2 resp. 3) are at discharge from the hospital unit!

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Judgement Comment: Computergenerated random number table
Allocation concealment	Unclear risk	Judgement Comment: Not enough details. 'Known to the investigator at each site'
Blinding of participants and personnel	Low risk	Judgement Comment: Patients blinded, no info on personnel
Blinding of outcome assessors	Unclear risk	Judgement Comment: Ej beskrevet hvem der vurderer. Desuden databehandling ej beskrevet om blinding.
Incomplete outcome data	Low risk	Judgement Comment: 36 pts randomised. Data were obtained from all 18 allocated pts in each group.
Selective outcome reporting	Low risk	Judgement Comment: No study protocol available, but the outlined endpoints in the RCT are all reported.
Other sources of bias	Low risk	Judgement Comment: Study seems to be free of other sources of bias

Girard 2018

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *Age*: Median age (IQR) — yr): 61 (51–69) ● *Coma*: ● *Mechanical ventilation*: Invasive: 178 (93); Noninvasive: 7 (4) ● *surgery*: Surgery diagnosis at admission: 13 (7%) ● *Delir ved studie start*: Hyper: 19 (10%); Hypo: 172 (90%) Control ● *Age*: Median age (IQR) — yr): 59 (52–67) ● *Coma*: ● *Mechanical ventilation*: Invasive: 170 (92); Noninvasive: 5 (3) ● *surgery*: Surgery diagnosis at admission: 13 (7%) ● *Delir ved studie start*: Hyper: 22 (12%); Hypo: 161 (88%) Intervention 2 ● *Age*: Median age (IQR) — yr): 61 (50–69) ● *Coma*: ● *Mechanical ventilation*: Invasive: 180 (95); Noninvasive: 5 (3) ● *surgery*: Surgery diagnosis at admission: 23 (12%) ● *Delir ved studie start*: Hyper: 16 (8%); Hypo: 172 (91%) Overall ● *Age*: ● *Coma*: ● *Mechanical ventilation*: ● *surgery*: ● *Delir ved studie start*: **Included criteria:** Patients who had been admitted to the par-ticipating hospitals were eligible for inclusion if they were 18 years of age or older and were re-ceiving treatment in a medical or surgical ICU with invasive or noninvasive positive pressure ventilation, vasopressors, or an intraaortic balloon pump, and they were eligible for random assign-ment to a trial group if they had delirium. **Excluded criteria:** We excluded patients who, at baseline, had severe cognitive impairment, as determined by medical record review and the short form of the Infor-mant Questionnaire on Cognitive Decline in the Elderly (IQCODE; scores range from 1.0 to 5.0, with higher scores indicating more severe cogni-tive impairment [a score of ≥4.5 resulted in exclu-sion because of severe dementia])22; were at high risk for medication side effects because of preg-nancy, breast-feeding, a history of torsades de pointes, QT prolongation, a history of neurolep-tic malignant syndrome, or allergy to haloperidol or ziprasidone; were receiving ongoing treatment with an antipsychotic medication; were in a mori-bund state; had rapidly resolving organ failure; were blind, deaf, or unable to speak or under-stand English; were incarcerated; or were en-rolled in another study or trial that prohibited coenrollment. Details of the inclusion and exclu-sion criteria are provided in the Supplementary Appendix. Noncomatose patients were excluded if informed consent could not be obtained within 72 hours after inclusion criteria had been met, and comatose patients were excluded if informed consent could not be obtained within 120 hours after inclusion criteria had been met. **Pretreatment:** There were no significant differences in baseline characteristics between the trial groups (Table1)
Interventions	**Intervention Characteristics** Intervention ● *Description*: HALOPERIDOL: The trial drugs or placebo were administeredintravenously with the use of colorless preparations delivered in identical bags. Immediatelyafter the trial-group assignment, the first dose of a trial drug or placebo was administered. Patients younger than 70 years of age received 2.5 mg of haloperidol per 0.5 ml, whereas those who were 70 yearsof age or older received 1.25 mg of haloperidol per 0.25 ml. Subsequent doses wereadministered every 12 hours at approximately10 a.m. and 10 p.m. Research personnel doubledthe volume and dose of the trial drug or placeboif a patient had delirium, was not yet receivingthe maximum dose, and had not met criteriathat

	required the trial drug or placebo to bewithheld. Patients in the haloperidol group received a dose of up to 10 mg per administrationand up to 20 mg per day. ● *Duration of intervention*: 14 days or ICU discharge ● *Evt. rescue medication*: In the current trial, approximately 90%of the patients received one or more doses ofsedatives or analgesics, and the doses of sedatives and off-trial antipsychotic medications andthe durations of exposures to those agents weresimilar in all trial groups ● *Co-medication*: Received antipsychotic Between admission and randomization (N (%)): 20 (10) Control ● *Description*: PLACEBO: The trial drugs or placebo were administeredintravenously with the use of colorless preparations delivered in identical bags. Immediatelyafter the trial-group assignment, the first dose of a trial drug or placebo was administered. Patients younger than 70 years of age received 0.5 ml of placebo (0.9% saline) whereas those who were 70 years of age or older received 0.25 ml of placebo. Subsequent doses wereadministered every 12 hours at approximately10 a.m. and 10 p.m. Research personnel doubledthe volume and dose of the trial drug or placeboif a patient had delirium, was not yet receivingthe maximum dose, and had not met criteriathat required the trial drug or placebo to bewithheld. ● *Duration of intervention*: 14 days or ICU discharge ● *Evt. rescue medication*: In the current trial, approximately 90%of the patients received one or more doses ofsedatives or analgesics, and the doses of sedatives and off-trial antipsychotic medications andthe durations of exposures to those agents weresimilar in all trial groups ● *Co-medication*: Received antipsychotic Between admission and randomization (N (%)): 18 (10) Intervention 2 ● *Description*: ZIPRASIDONE: The trial drugs or placebo were administeredintravenously with the use of colorless preparations delivered in identical bags. Immediatelyafter the trial-group assignment, the first dose of a trial drug or placebo was administered. patients younger than 70 years of age received 5 mg of ziprasidone per 0.5 ml, whereas those who were 70 years of age or older received or 2.5 mg ofziprasidone per 0.25 ml. Subsequent doses wereadministered every 12 hours at approximately10 a.m. and 10 p.m. Research personnel doubledthe volume and dose of the trial drug or placeboif a patient had delirium, was not yet receivingthe maximum dose, and had not met criteriathat required the trial drug or placebo to bewithheld. Those in the ziprasidone group received a dose of up to 20 mg peradministration and up to 40 mg per day. ● *Duration of intervention*: 14 days or ICU discharge ● *Evt. rescue medication*: In the current trial, approximately 90%of the patients received one or more doses ofsedatives or analgesics, and the doses of sedatives and off-trial antipsychotic medications andthe durations of exposures to those agents weresimilar in all trial groups ● *Co-medication*: Received antipsychotic Between admission and randomization (N (%)): 22 (12)
Outcomes	*SAE (under indlæggelse)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Delirium varighed (Mean CI)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Delirium varighed (Mean SD)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Kritisk Uro* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Higher is better ● **Data value**: Endpoint *Indlæggelsestid*

	● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Genindlæggelser Op til 3 mdr. efter udskrivelse* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Data value**: Endpoint *Fald* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Angst* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Data value**: Endpoint *Ekstrapyramidale bivirkninger* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Ekstrapyramidale bivirkninger* ● **Outcome type**: DichotomousOutcome ● **Direction**: Lower is better ● **Data value**: Endpoint *Kognitiv funktion* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Data value**: Endpoint *Død* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Delirium severity* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Data value**: Endpoint
Identification	**Sponsorship source:** **Country:** USA **Setting:** **Comments:** The trial was registered at ClinicalTrials.gov on September 29, 2010, before the first patient was enrolled. The statistical analysis plan was regis-tered at Open Science Framework (https://osf.io/mq38r)on March 22, 2018 **Authors name:** T.D. Girard

	Institution: **Email:** wes.ely@vumc.org. **Address:** Dr. Ely at the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center at Vanderbilt University, 2525 West End Ave., Suite 450, Nashville, TN 37203
Notes	*NKR 42 Delir* on 19/08/2020 02:54 **Screen** 3 arme *Helle Svenningsen* on 19/08/2020 22:58 **Select** patienterne er både < og > 65 år, og der skelnes ikke i resultaterne

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	randomized, double-blind, placebo-con- trolled, phasewe randomly assigned the patients, in a 1:1:1 ratio, to receive placebo, haloperidol, or ziprasidone using a computer-generated, permuted- block randomization scheme, with stratification according to trial site.
Allocation concealment	Low risk	The research personnel, managing clinicians, patients, and their families were not aware of the trial-group assignments.
Blinding of participants and personnel	Low risk	patients, and their families were not aware of the trial-group assignments.The research personnel, managing clinicians, patients, and their families were not aware of the trial-group assignments. The trial drugs or placebo were administered intravenously with the use of colorless prepara- tions delivered in identical bags. s
Blinding of outcome assessors	Low risk	Objective measures of relevant outcomes
Incomplete outcome data	Low risk	A total of 300 of 6100 (5%) potential assessments for delirium or coma were missing; we imputed these individual assessments using polytomous logistic regression that included multiple co- variates. After calculating days alive without delirium or coma, we then used complete case analysis for all outcomes (see the Supplementary Appendix).COMMENTSafraporterer på alle der er randomiseret
Selective outcome reporting	Low risk	ClinicalTrials.gov number, NCT01211522.)The trial was registered at ClinicalTrials.gov on September 29, 2010, before the first patient was enrolled. The statistical analysis plan was regis- tered at Open Science Framework (https://osf. io/ mq38r) onWe analyzed all data using an intention-to- treat approach and compared the effects of halo- peridol, ziprasidone, and placebo with respect to the primary end point using the Kruskal–Wallis test in unadjusted analyses and proportional-odds logistic regression in adjusted analyse
Other sources of bias	Unclear risk	it is not stated weather or not the patients had delirium before randomization. And the how do they obtain consent. Also they treat for he full 14 days, but what is the patients did not have delirium throughout the trail period.

Tahir 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Intervention ● *Age*: 84.1 (9.45) ● *Delir ved studiets start*: 100% Kontrol ● *Age*: 84.3 (7.16)

	● *Delir ved studiets start*: 100% **Included criteria:** Screening for delirium was conducted by daily contactwith medical, surgical and orthopedic wards at the UniversityHospital of Wales by a research assistant. An attempt wasmade to recruit those who met theDSM-IVcriteria fordelirium on the same day if they had a DRS-R-98 total scoreof 15 or more. **Excluded criteria:** Individuals with major pre-existing cognitivedeficits, alcohol withdrawal, pre-existing psychosis, sub-stance dependence, inability to comply with the constraints ofthe trial, or who were on medication that interacted withquetiapine were excluded from the study. The nature anddegree of any pre-existing cognitive deficits were determinedby reviewing clinical notes and by obtaining informationfrom a reliable informant. Informed consent was obtainedfrom participants with mental capacity. **Pretreatment:** none stated
Interventions	**Intervention Characteristics** Intervention ● *Description*: flexible dosing regime of 25 mg once daily oralquetiapine with dose titration of 25mg/day to a maximum daily dose of 175 mg in divided doses. ● *Duration of intervention*: Optitrering i max 10 dage. FU i 30 dage i begge grp. ● *Evt. rescue medication*: Tilsyneladende 4 ptt. i interventionsgrp. fået lorazepam Kontrol ● *Description*: Matching placebo dose tablet. ● *Duration of intervention*: ● *Evt. rescue medication*: ingen.
Outcomes	*Død/mortality (3 mdr FU)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Notes**: Kun 30 dages FU *Genindlæggelser/readmissions (3 mdr FU)* ● **Outcome type**: ContinuousOutcome *Fald/falls (Ved udskrivelse)* ● **Outcome type**: ContinuousOutcome *Funktionsevne/physical function (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome *Angst/anxiety (Ved udskrivelse)* ● **Outcome type**: ContinuousOutcome *Ekstrapyramidale bivirkninger/extrapyramidal symptoms (Ved udskrivelse)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported *Uro/restlessness (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome *SAE (Ved udskrivelse)* ● **Outcome type**: DichotomousOutcome *Delirium severity (ved udskrivelse)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Partially reported ● **Scale**: DRS-S-98 severity ● **Range**: 0-39 ● **Unit of measure**: point ● **Direction**: Lower is better ● **Data value**: Endpoint

	● **Notes**: Ingen udskrivelsesværdi, kun værdi på dag 10 for alle patienter.
Identification	**Sponsorship source:** AstraZeneca UKsponsored the study and provided funding for a researchassistant, trial medication,and the randomization codes **Country:** UK **Setting:** Medical , surgical og orthopedic wards **Comments:** **Authors name:** Tayyeb A. Tahir **Institution:** Department of Liaison Psychiatry, University Hospital of Wales, Cardiff and Vale University Health Board, Heath Park, Cardiff, UK **Email:** tayyeb.tahir@wales.nhs.uk **Address:** Corresponding author. Department of Liaison Psychiatry, Room 124,1st Floor, Monmouth House, University Hospital of Wales, CF14 4XNCardiff, UK
Notes	*Jakob Carlsen* on 08/06/2016 05:15 **Select** Seroquel vs. placebo. *Susanne Stabel Gren* on 11/06/2016 18:30 **Included** DB.blindet RCT skal med *Henning Keinke Andersen* on 16/06/2016 23:10 **Outcomes** NB! Død er efter 30 dage og ikke 3 mdrExtrapyramidal symptoms reported as 'abnormal involuntary movements' (tolerability) p 488Why not death at discharge, reported in fig 1 (3 IV; 1 Placebo)?Går udfra ITT analyser

Risk of bias table

Bias	Authors' judgement	Support for judgement
Sequence Generation	Low risk	Quote: "Computer-generated randomization codes"
Allocation concealment	Low risk	Quote: "Computer-generated randomization codes were kept in sealed envelopes at the University Hospital of Wales' Pharmacy. In addition, a set of individual treatment codes was kept by the Scottish Poisons Information Bureau, Royal Infirmary Edin- burgh, for emergency out-of-hours use only."
Blinding of participants and personnel	Unclear risk	Judgement Comment: De beskriver ikke selve blindingsprocessen
Blinding of outcome assessors	Unclear risk	Judgement Comment: Ej beskrevet
Incomplete outcome data	Unclear risk	Quote: "To account for the noncompleters, due to various reasons given below, it was important to take into account missing data and the improvement in delirium with or without medication; we used non-linear, mixed-effects model to estimate differences in recovery trajectories between treatment groups. Initially, we considered models that allowed different starting and long-term mean values in the two treatment groups; however, no significant evidence of such differences was found." Judgement Comment: There is a substantial drop-out rate for each group (5/21 for IV - and 7/21 for placebo). And it is notified that the trial stopped at an early stage (p 489)
Selective outcome reporting	Low risk	Judgement Comment: The outlined outcomes are reported fully of partial. Primary outcome (DRS-R-98) is reported
Other sources of bias	Unclear risk	Judgement Comment: Not quite sure whether the clinicians decision on dosage changes will affect the outcome. Probbably - therefore the 'unclear'

Footnotes

Characteristics of excluded studies

Aizawa 2002

Reason for exclusion	Wrong intervention

Atalan 2013

Reason for exclusion	Wrong comparator

Bayindir 2001

Reason for exclusion	Wrong intervention

Boettger 2011

Reason for exclusion	Wrong comparator

Boettger 2011a

Reason for exclusion	Wrong study design

Boettger 2017

Reason for exclusion	Wrong study design

Breitbart 1996

Reason for exclusion	Wrong patient population

Breitbart 2002

Reason for exclusion	Wrong study design

Douglas 2008

Reason for exclusion	Wrong outcomes

Duprey 2018

Reason for exclusion	Wrong patient population

Duprey 2018a

Reason for exclusion	Wrong study design

Duprey 2020

Reason for exclusion	Wrong intervention

Gill 2005

Reason for exclusion	Wrong study design

Girard 2010

Reason for exclusion	Wrong patient population

Grover 2011

Reason for exclusion	Wrong study design

Hakim 2012

Reason for exclusion	

Han 2001

Reason for exclusion	Wrong study design

Han 2004

Reason for exclusion	Wrong study design

Han 2009

Reason for exclusion	Wrong study design

Herrmann 2004

Reason for exclusion	Wrong study design

Horikawa 2003

Reason for exclusion	Wrong study design

Hui 2017

Reason for exclusion	Wrong intervention

Hui 2017a

Reason for exclusion	Wrong intervention

Hui 2018

Reason for exclusion	Wrong intervention

Hui 2020

Reason for exclusion	Wrong intervention

Jain 2017

Reason for exclusion	Wrong comparator

Kalisvaart 2005

Reason for exclusion	Wrong patient population

Kaneko 1999

Reason for exclusion	Wrong patient population

Khan 2019

Reason for exclusion	Wrong comparator

Kim 2001

Reason for exclusion	Wrong study design

Kim 2003

Reason for exclusion	Wrong comparator

Kim 2005

Reason for exclusion	Wrong study design

Kim 2010

Reason for exclusion	Wrong study design

Kishi 2012

Reason for exclusion	Wrong study design

Lee 2005

Reason for exclusion	Wrong intervention

Lee 2017

Reason for exclusion	Wrong study design

Lin 2004

Reason for exclusion	Wrong setting

Maneeton 2013

Reason for exclusion	Wrong intervention

Matsuoka 2019

Reason for exclusion	Wrong outcomes

Mittal 2004

Reason for exclusion	Wrong comparator

Miyaji 2007

Reason for exclusion	Wrong study design

Omura 2003

Reason for exclusion	Wrong study design

Pae 2004

Reason for exclusion	Wrong study design

Page 2013

Reason for exclusion	Wrong patient population

Pandharipande 2017

Reason for exclusion	Wrong study design

Parellada 2004

Reason for exclusion	Wrong study design

Prakanrattana 2007

Reason for exclusion	Wrong study design

Reade 2009

Reason for exclusion	Wrong study design

Sasaki 2003

Reason for exclusion	Wrong study design

Schrijver 2018

Reason for exclusion	Wrong patient population

Schrijver 2018a

Reason for exclusion	Wrong outcomes

ShrikantKulkarni 2017

Reason for exclusion	Wrong study design

Sipahimalani 1998

Reason for exclusion	Wrong study design

Skrobik 2004

Reason for exclusion	Wrong study design

Straker 2006

Reason for exclusion	Wrong intervention

Tagarakis 2012

Reason for exclusion	Wrong intervention

Takeuchi 2007

Reason for exclusion	Wrong study design

Toda 2005

Reason for exclusion	Wrong study design

vandenBoogaard 2013

Reason for exclusion	Wrong patient population

vandenBoogaard 2018

Reason for exclusion	Wrong patient population

VanDerVorst 2017

Reason for exclusion	Wrong comparator

VanDerVorst 2018

Reason for exclusion	dublicate

vanderVorst 2019

Reason for exclusion	Wrong comparator

vanderVorst 2020

Reason for exclusion	Wrong comparator

vanEijk 2010

Reason for exclusion	Wrong intervention

Yoon 2013

Reason for exclusion	Wrong comparator

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

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Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

Data and analyses

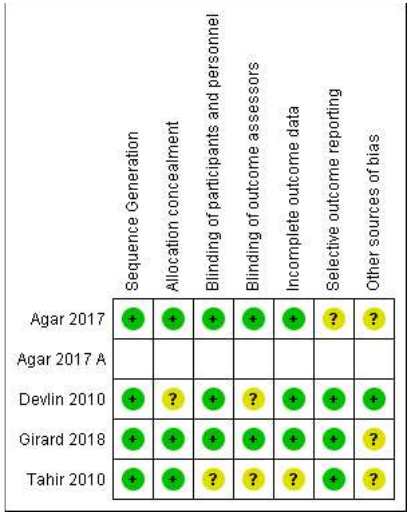
1 Antipsykotika vs ingen antipsykotika

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

1.1 SAE (under indlæggelse))	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 All cause mortality	3	324	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.72, 2.55]
1.1.2 Ophør eller afblænding af behandling	2	607	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.25]
1.1.3 Adverse events	1	41	Risk Ratio (M-H, Random, 95% CI)	2.86 [0.12, 66.44]
1.1.4 Serious adverse events	1	576	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.23, 18.05]
1.2 Delirium varighed (dage)	2	602	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-1.12, 0.24]
1.3 Uro/restlessness (under indlæggelse)	2	247	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.22, 0.03]
1.4 Uro - Antal personer der får det bedre (RASS score på 0)	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.12]
1.5 Duraition of hospitalization, days	2	602	Mean Difference (IV, Random, 95% CI)	-0.53 [-2.40, 1.35]
1.6 Genindlæggelser/readmissions (op til 3 mdr efter udskrivelse)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.7 Fald/falls (under indlæggelse)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.8 Angst/anxiety (Under indlægelse)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.10 Ekstrapyramidale bivirkninger (under indlæggelse)_RR	2	607	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.15, 2.85]
1.12 Kognitiv funktion (min 3-6 mdr. efter udskrivelse)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.13 Død/mortality (Op til 6 mdr. efter udskrivelse)	2	607	Risk Ratio (IV, Random, 95% CI)	1.06 [0.84, 1.34]
1.14 Delirium severity (ved udskrivelse)	3	288	Std. Mean Difference (IV, Random, 95% CI)	0.32 [0.08, 0.57]

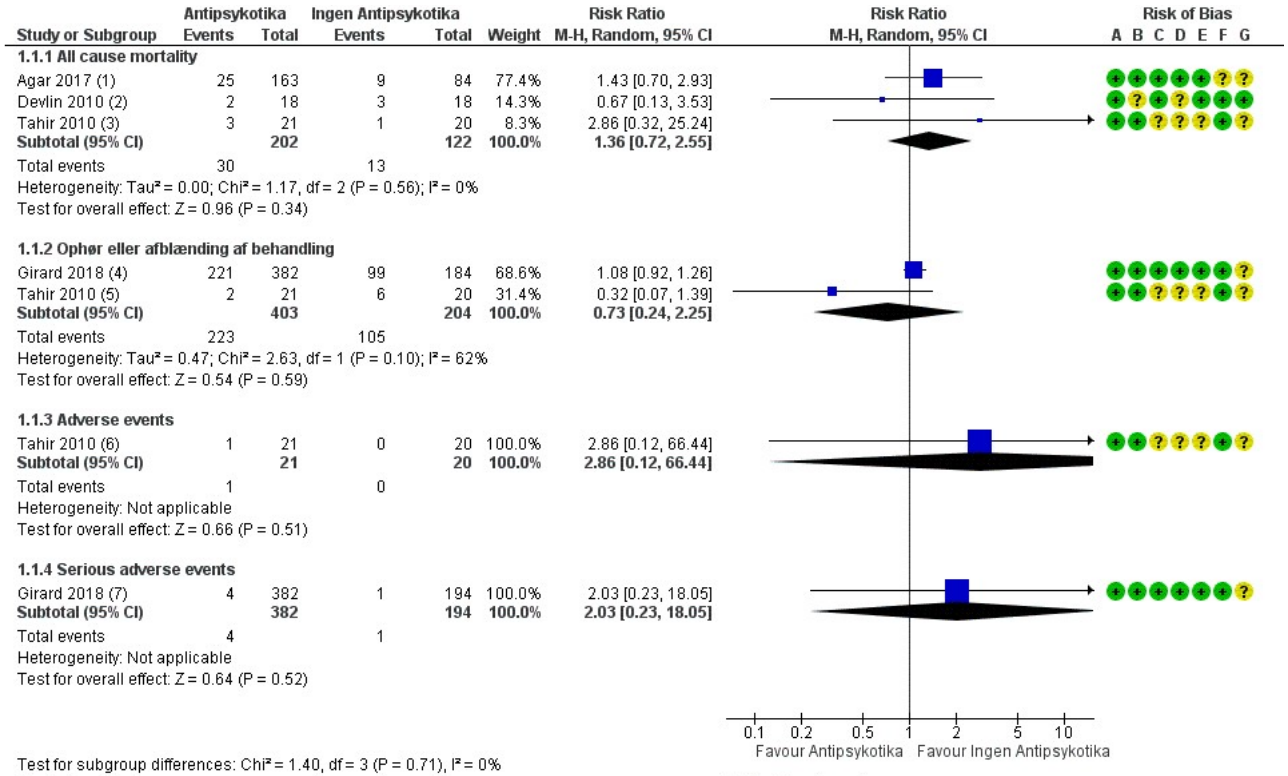
Figures

Figure 1



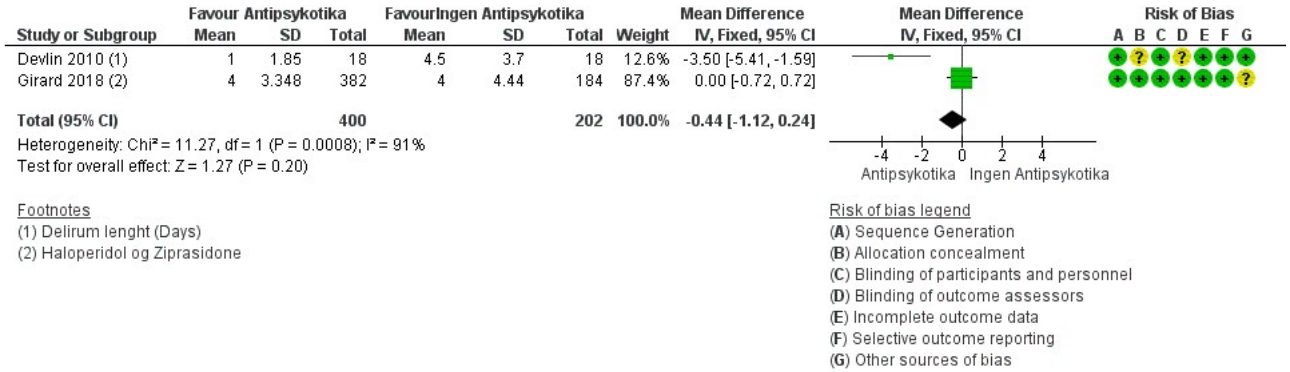
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.1)



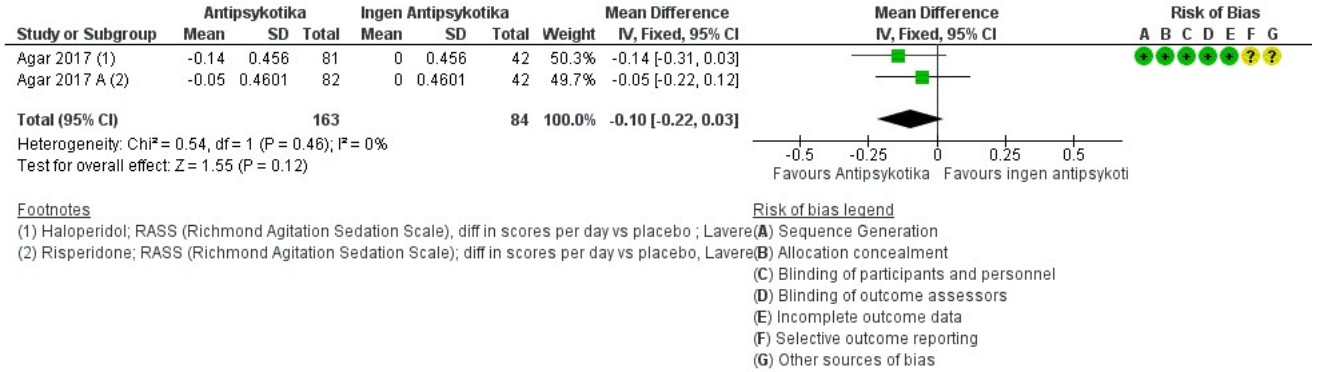
Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.1 SAE (under indlæggelse)).

Figure 3 (Analysis 1.2)



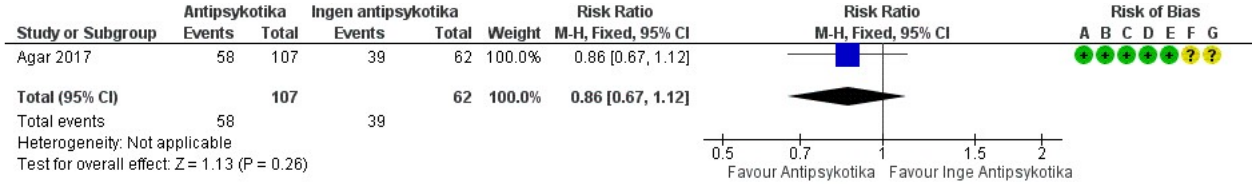
Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.2 Delirium varighed (dage).

Figure 4 (Analysis 1.3)



Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.3 Uro/restlessness (under indlæggelse).

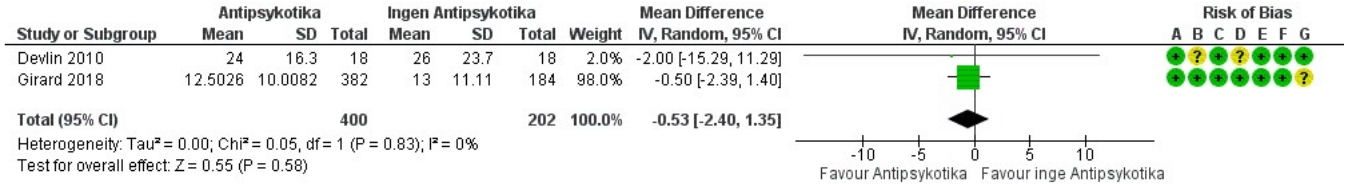
Figure 5 (Analysis 1.4)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.4 Uro - Antal personer der får det bedre (RASS score på 0).

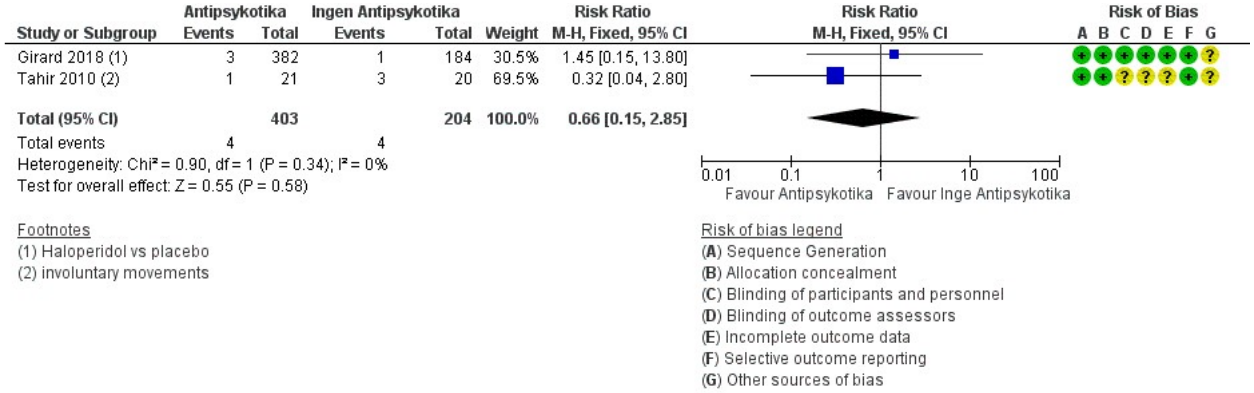
Figure 6 (Analysis 1.5)



Risk of bias legend
(A) Sequence Generation
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Incomplete outcome data
(F) Selective outcome reporting
(G) Other sources of bias

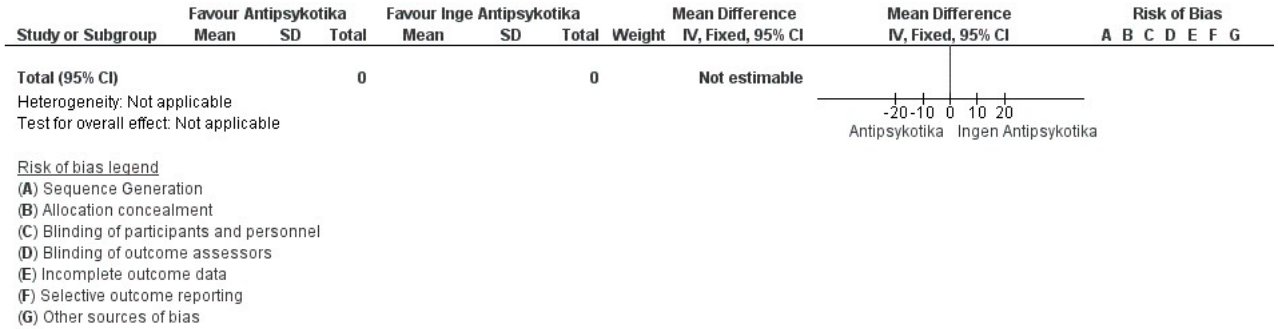
Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.5 Duraition of hospitalization, days.

Figure 8 (Analysis 1.10)



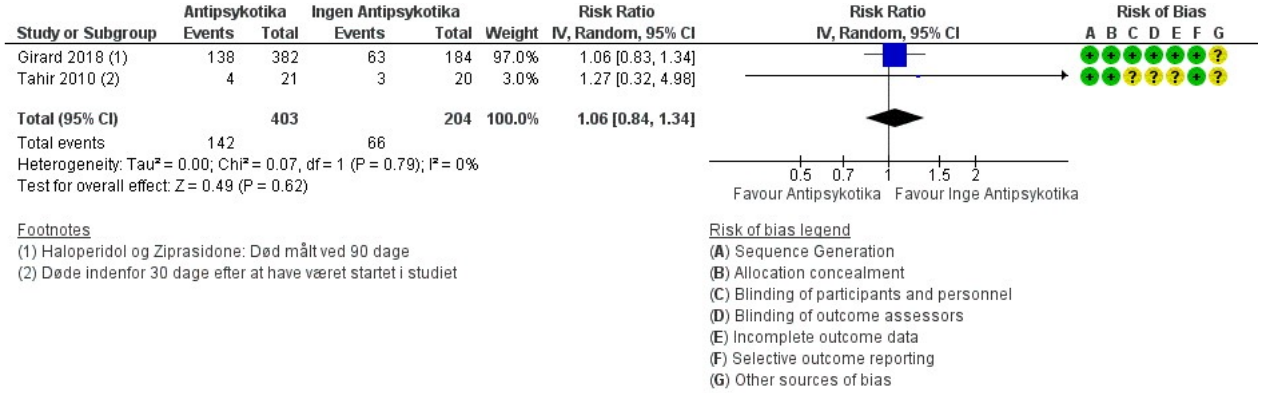
Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.10 Ekstrapyramidale bivirkninger (under indlæggelse)_RR.

Figure 10 (Analysis 1.12)



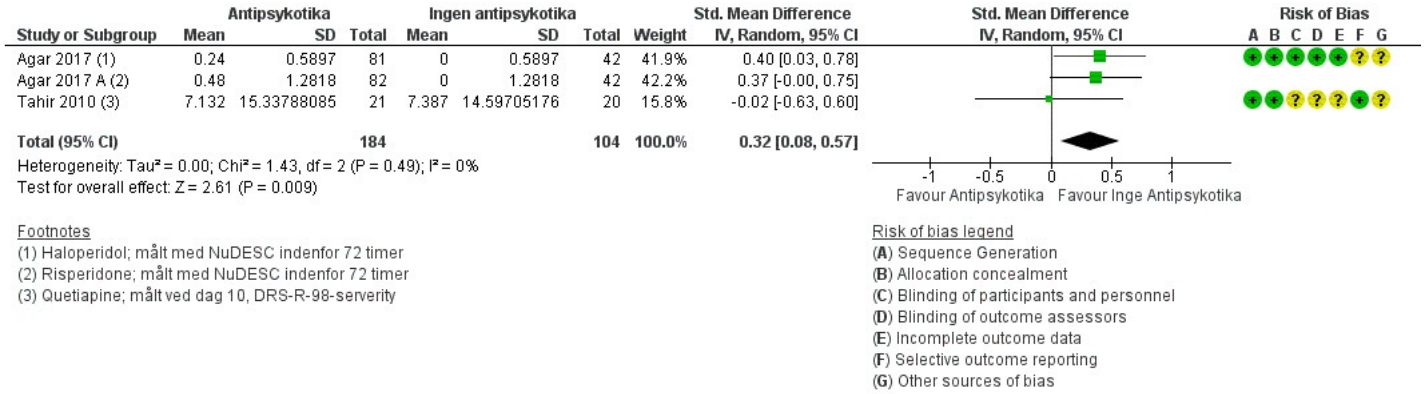
Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.12 Kognitiv funktion (min 3-6 mdr. efter udskrivelse).

Figure 11 (Analysis 1.13)



Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.13 Død/mortality (Op til 6 mdr. efter udskrivelse).

Figure 12 (Analysis 1.14)



Forest plot of comparison: 1 Antipsykotika vs ingen antipsykotika, outcome: 1.14 Delirium severity (ved udskrivelse).