SUNDHEDSSTYRELSEN

2026

# Bilag 2 – Sammendrag af evidens og evidensprofiler

## NKA for medicinsk vedligeholdelsesbehandling af mennesker med bipolar lidelse


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# 1. Hvilket peroralt lægemiddel bør man anvende som vedligeholdelsesbehandling til voksne patienter med bipolar lidelse?

## 1.1 Litteratur

Søgningen efter systematiske oversigtsartikler identificerede fire systematiske reviews omhandlende voksne med bipolar lidelse [1-4].

Fra det systematiske review af Nestsiarovich et al. blev der inkluderet 16 randomiserede forsøg [5-20]. Fra det systematiske review af Lindström et al. blev der inkluderet tre randomiserede forsøg [21-23]. Fra det systematiske review af Lui et al. blev der inkluderet syv randomiserede forsøg [24-30]. Fra det systematiske review af Miura et al. blev der inkluderet 13 randomiserede forsøg [9, 17, 31-41].

Fra Sundhedsstyrelsens tidligere nationale kliniske retningslinje for farmakologisk behandling af bipolar lidelse fra 2014 [42] blev der inkluderet et randomiseret forsøg [43]

Vi foretog en opdateret litteratursøgning efter primærstudier baseret på seneste søgedato i de systematiske review af Nestsiarovich et al. og Diaz- Caneja et al. og fandt tre randomiserede forsøg publiceret i fire artikler [44-47].

Der er i 2026 foretaget en opdateret søgning efter primærstudier, hvor der blev identificeret et randomiserede forsøg som var relevant for inklusion [48].

Forsøg, der omfattede en blandet population af personer med bipolar type 1 og 2, samt forsøg, der sammenlignede aktive behandlinger indbyrdes frem for placebo, er beskrevet i evidensgennemgangen. Disse studier indgår imidlertid ikke i beslutningsgrundlaget for anbefalingen, da anbefalingen er baseret på placebo-kontrolleret evidens for den specifikke population.

Evidensgrundlaget for besvarelsen af det fokuserede spørgsmål består således af i alt 31 randomiserede forsøg [5, 6, 8, 10-13, 15, 18-21, 23-27, 29, 31, 35, 36, 39-41, 43, 47-52].

**Tabel 1** over studiekarakteristika kan ses nedenfor.

**Table 1.** Characteristics of included studies in adults.

| Author, year, country | Participants number randomized, mean age, (SD), females (%), bipolar type, index episode, problematic alcohol/substance abuse | Design, pre-randomization phase, tapering (duration), co-interventions and industry sponsorship | Randomization phase Interventions (of interest) and co interventions | Outcomes of interest |
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| Included in the body of evidence | | | | |
| Amsterdam 2005, USA | Number randomized = 12<br>Age in years: 38.0 (14.2)<br>Females: 75%<br>Bipolar type: type 2<br>Index episode: depression<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label fluoxetine 20 mg/day for 8 weeks<br>Tapering of open label fluoxetine: no information<br>Sponsored by industry: yes | Fluoxetine<br>20 mg/day<br>Placebo<br>Identically appearing placebo capsules<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, hypo mania: Number of participants<br>Serious adverse events (SAE): Number of participants |
| Amsterdam 2010, USA | Number randomized = 81<br>Age in years: 37.7<br>Females: 53.3%<br>Bipolar type: type 2<br>Index episode: depression<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label fluoxetine 20-80 mg/day for 12 weeks<br>Tapering of open label fluoxetine: discontinued abruptly.<br>Sponsored by industry: no | Fluoxetine<br>10-40 mg/day<br>Lithium<br>300-1200 mg/day<br>Serum level of 0.5-1.5 mmol/liter<br>Placebo<br>Placebo substitution<br>Duration of the interventions: 50 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, hypo mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Sedation: Number of participants |
| BalanceInvestigators 2010, International | Number randomized = 330<br>Age in years: 43.1 (13)<br>Females:52 %<br>Bipolar type: type 1<br>Index episode: mania<br>Problematic alcohol/substance abuse: 8% | RCT, multicenter, 41 sites in the UK, USA, Italy, and France<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (serum level of 0.4-1.0 mmol/liter)<br>and open label valproate 750-1250 mg/day for 4-8 weeks<br>Tapering of open label lithium: gradually during 4 weeks<br>Sponsored by industry: yes | Lithium<br>Serum level of 0.4-1.0 mmol/liter<br>Valproate<br>750-1250 mg/day<br>Target dose 1250 mg/day or the highest dose tolerated<br>Lithium and valproate<br>Lithium: Serum level of 0.4-1.0 mmol/liter<br>Valproate: 750-1250 mg/day<br>Duration of the interventions: 104 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Psychiatric hospitalization: Number of participants |

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| | | | | Suicidal behavior: Number of participants<br>Quality of life: EQ5D<br>Global functioning: Global assessment of Functioning (GAF) |
| Berwaerts 2012, International | Number randomized = 200 (placebo and paliperidone arms only)<br>Age in years: 40 (12.5)<br>Females: 55%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter, 79 centers in 17 countries<br>Enriched discontinuation design: yes<br>Pre-randomization phase: double blinded paliperidone ER 3-12 mg/day for 15 weeks<br>Tapering of paliperidone ER: no information<br>Sponsored by industry: yes | Paliperidone ER<br>3-12 mg/day<br>Placebo<br>Duration of the interventions: 104 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Bowden 2000, USA | Number randomized = 372<br>Age in years: 39.2<br>Females: 51.2%<br>Bipolar type: type 1<br>Index episode: mania<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label treatment by choice of clinician, except electroconvulsive treatments or depot neuroleptics. 78% received lithium, valproate or both. Duration up to 12 weeks<br>Tapering of open label drug: gradually during 2 weeks<br>Sponsored by industry: yes | Lithium<br>Serum level of 0.8-1.2 mmol/liter<br>Valproate<br>Serum level of 71-125 ug/ml<br>Placebo<br>Duration of the interventions: 52 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Bowden 2003, USA | Number randomized = 175<br>Age in years: 41.1<br>Females: 52.6%<br>Bipolar type: type 1<br>Index episode: mania or hypo mania<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter, 64 centers<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lamotrigine 100-200 mg/day for 8-16 weeks<br>Co-intervention: valproate or carbamazepine were gradually withdrawn | Lamotrigine<br>100-400 mg/day<br>Lithium<br>Serum level of 0.8-1.1 mmol/liter<br>Placebo<br>Duration of the interventions: 78 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants |

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| | | Tapering of open label lamotrigine: no information<br>Sponsored by industry: yes | | Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Bowden 2010, USA | Number randomized = 240<br>Age in years: 38.8<br>Females: 53.7%<br>Bipolar type: type 1<br>Index episode: mania<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label ziprasidone 80-160 mg/day for up to 16 weeks<br>Tapering of open label ziprazidone: gradually during 1 week<br>Co-intervention: Lithium (serum level of 0.6-1.2 mmol/liter) or valproate 50-125 ug/ml<br>Sponsored by industry: yes | Ziprazidone<br>80-160 mg/day<br>Placebo<br>Co-intervention in all arms:<br>Lithium or valproate<br>Lithium: serum level of 0.6-1.2 mmol/liter<br>Valproate: 50-125 ug/ml<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, mixed: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>weight gain over 7%: Number of participants |
| Calabrese 2003, USA | Number randomized = 463<br>Age in years: 43.4<br>Females: 56.6%<br>Bipolar type: type 1<br>Index episode: depression<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter 79 centers in 15 countries<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lamotrigine 100-200 mg/day for 8 -16 weeks<br>Tapering of open label lamotrigine: no information<br>Sponsored by industry: yes | Lamotrigine<br>50-400 mg/day<br>Lithium<br>Serum level of 0.8-1.1 mmol/liter<br>Placebo<br>Duration of the interventions: 78 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>weight gain over 7%: Number of participants |
| Calabrese 2017, International | Number randomized = 496<br>Age in years: 44,4%<br>Females: 56.3%<br>Bipolar type: type 1<br>Index episode: depression or mania<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 26 centers in USA, 10 centers in South America, 48 centers in Europa and 10 centers in Asia<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lurasidone 20-80mg/day for 12-20 weeks<br>Tapering of open label lurasidone: no information of tapering of lurasidone | Lurasidone<br>20-80mg/day<br>Placebo<br>Matching placebo<br>Co-intervention in all arms:<br>Lithium (serum level of 0.4-1.2 mmol/liter) mor valproate (serum level of 50-125 ug/ml)<br>Duration of the interventions: 28 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants |

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| | | Co-intervention pre-randomization phase: Lithium or valproate (serum level of 50-125 ug/ml)<br>Sponsored by industry: yes | | weight gain over 7%:<br>Number of participants |
| Carlson 2012, USA | Number randomized = 351<br>Age in years: 39.1<br>Females: 65%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 69 centers in USA and Puerto Rico<br>Enriched discontinuation design: yes<br>Pre-randomization phase: aripiprazole 10-30mg/day for 9-24 weeks (single blind)<br>Tapering: no information of tapering of aripiprazole<br>Co-intervention in pre-randomization phase: open label lamotrigine 100-200 mg/day<br>Sponsored by industry: yes | Aripiprazole<br>10-30mg/day<br>Placebo<br>Co-intervention in all arms: open label lamotrigine 100-200 mg/day<br>Duration of the interventions: 52 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause:<br>Number of participants<br>Weight gain over 7%:<br>Number of participants |
| Dunner 1976, USA | Number randomized = 40<br>Age in years: 50.6<br>Females: 57.5%<br>Bipolar type: Type 2<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, single center<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase<br>Tapering of open label drug: n/a<br>Sponsored by industry: no information | Lithium<br>Serum level of 0.8-1.2 mmol/liter<br>Placebo<br>Duration of the interventions: 64 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, hypo mania:<br>Number of participants<br>Withdrawal, any cause:<br>Number of participants |
| Fieve 1976, USA | Number randomized = 35<br>Age in years: 48,5<br>Females:50.9%<br>Bipolar type: type 1 & 2 (seperate data)<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, single center<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase<br>Tapering of open label drug: n/a<br>Sponsored by industry: no information | Lithium<br>Serum level of 0.7-1.3 mmol/liter<br>Placebo<br>Matching placebo<br>Duration of the interventions: 210 weeks | New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>Withdrawal, any cause:<br>Number of participants |
| Kane 1981/Quintin 1981, USA | Number randomized = 75<br>Age in years: 36.8 (13.1)<br>Females: 52%<br>Bipolar type: Type 1<br>Index episode: not specified<br>Inclusion of participants with problematic | RCT, single center<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase, but<br>All patients were stabile on lithium for at least 6 weeks before inclusion | Imipramine<br>100-150 mg/day<br>Placebo<br>Identical-appearing placebo tablets<br>Duration of the interventions: 77 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants |

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| | alcohol/substance abuse: no information | Tapering of open label drug: n/a<br>Sponsored by industry: no information | Co-intervention in all arms:<br>Lithium (serum level of 0.6-1.0 mmol/liter) | |
| Kane 1982, USA | Number randomized = 22<br>Age in years: 48.7<br>Females: 77.3 %<br>Bipolar type: type 2<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, single center<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label imipramine of maximum150 mg/day for 6 weeks<br>Tapering of open label imipramine: no information<br>Sponsored by industry: no | Lithium and imipramine<br>Lithium: serum level of 0.8-1.2 mmol/liter<br>Imipramine: 100-150 mg/day<br>Lithium<br>Serum level of 0.8-1.2 mmol/liter<br>Imipramine<br>100-150 mg/day<br>Placebo<br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>New episode, hypo mania:<br>Number of participants |
| Keck 2006, Argentina, Mexico and USA | Number randomized = 161<br>Age in years: 39.6 (013.9)<br>Females: 67%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 76 centers in Argentina, Mexico and USA<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label aripiprazole 15-30 mg for 6-18 weeks<br>Tapering of open label aripriprazole: abruptly<br>Sponsored by industry: yes | Aripiprazole<br>15-30 mg<br>Placebo<br>Duration of the interventions: 26 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>New episode, mixed:<br>Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause:<br>Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%:<br>Number of participants |
| Marcus 2011, International | Number randomized = 337<br>Age in years: 39.0<br>Females: 54.9%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 88 centers in 8 countries worldewide<br>Enriched discontinuation design: yes<br>Pre-randomization phase: single blind aripiprazole 10-30 mg/day for 13-24 weeks<br>Tapering: no information of tapering of aripiprazole<br>Co-intervention in pre-randomization phase: lithium (serum level of 0.6-1.0) mmol/liter | Aripiprazole<br>Aripiprazole 10-30 mg/day<br>Placebo<br>Identically appearing placebo tablets<br>Co-intervention in all arms:<br>Lithium (serum level of 0.6-1.0 mmol/liter) or valproate (serum level of 50-125 ug/ml)<br>Duration of the interventions: 52 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>New episode, mixed:<br>Number of participants<br>Serious adverse events (SAE): Number of participants |

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| | | or valproate (serum level of 50-125 ug/ml)<br>Sponsored by industry: yes | | Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants |
| McIntyre 2024, Canada | Number randomized =<br>Age in years: 42.0<br>Females: 60.1 %<br>Bipolar type: Type 1<br>Index episode: mania or depression<br>Problematic alcohol/substance abuse:<br>Exclusion: Positive result at Visit 1 from the urine drug screen (UDS). Patients with a positive UDS at Visit 1 for opiates, cannabinoids, amphetamines, barbiturates, or benzodiazepines may be enrolled if all of the following are satisfied:<br>The drug was used for a legitimate medical purpose<br>The drug can be discontinued prior to participation in the study (except for benzodiazepines which may be continued if the patient has been taking a stable dose [ie, lorazepam up to 2 mg/d or its benzodiazepine equivalent] for at least 1 month prior to Visit 1 or if used as rescue during washout)<br>A repeat UDS must be performed prior to Visit 2 and must be negative, except benzodiazepine use as described above.<br><br>Blood alcohol concentration ≥0.02 mg/dL at Visit 1 as measured by breathalyzer. | RCT, double blind, multicenter, 10 countries (Bulgaria, South Korea, Malaysia, Poland, Russia, Serbia, Thailand, Taiwan, Ukraine, and the United States)<br>Enriched discontinuation design: yes<br>Pre-randomization phase:<br>open label cariårazine 3.0mg/day during 16 weeks<br>Tapering of open label drug: No; Patients underwent a screening and washout period of up to 7 days; prior medications were gradually withdrawn so that the washout was completed by Visit 2/Baseline<br><br>Sponsored by industry: yes | Cariprazine<br>1.5 or 3.0 mg/day<br>Placebo<br>Identically appearing placebo tablets<br>Co-intervention in all arms:<br>Rescue medication<br>Duration of the interventions: up to 39 weeks; safety FU up to 4 weeks post intervention | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Weight gain over 7%: Number of participants<br>Psychiatric hospitalization: Number of participants<br>Global funtioning: Personal and Social Performance |

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| Melia 1970, Ireland | Number randomized = 18<br>Age in years: 51.3<br>Females: 88.9%<br>Bipolar type: Type 1<br>Index episode: not specified<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, single center<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium for at least 36 weeks<br>Tapering of open label lithium: no information<br>Sponsored by industry: yes | Lithium<br>Tablets of 250 mg, dose between 1,500-500 mgs/day 6 days a week.<br>Placebo<br>Matching placebo<br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants |
| Prien 1973a, USA | Number randomized = 205<br>Age in years: 44<br>Females: 35.1 %<br>Bipolar type: Type 1<br>Index episode: mania<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter, 12 veterans administrations and six public or private hospitals<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (serum level of 0.5-1.4 mmol/liter), duration of open label phase not described<br>Tapering of open label lithium: no information<br>Sponsored by industry: yes | Lithium<br>Serum level of 0.5-1.4 mmol/liter<br>Placebo<br>Identically appearing placebo capsules<br><br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>New episode, mixed:<br>Number of participants<br>Withdrawal, any cause:<br>Number of participants<br>Suicidal behavior: Number of participants |
| Prien 1973b, USA | Number randomized = 44<br>Age in years: 43.3 (11.9)<br>Females: 23 %<br>Bipolar type: Type 1<br>Index episode: depression<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: lithium (serum level of 0.5-1.4 mmol/liter), or imipramine 50-200 mg/day, duration of open label phase not described<br>Tapering of open label drug: no information<br>Sponsored by industry: no | Lithium<br>Serum level of 0.5-1.4 mmol/liter<br>Imipramine<br>50-200 mg/day<br>Placebo<br>Identically appearing placebo capsules<br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants<br>Withdrawal, any cause:<br>Number of participants |
| Prien 1984, USA | Number randomized = 117<br>Age in years: 38.1 (12.4)<br>Females: 58%<br>Bipolar type: Type 1<br>Index episode: depression or mania<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: lithium (targeted serum level of 0.6-0.9 mmol/liter), or imipramine (75-150 mg/day) by choise of clinician in acute fase, here after lithium and imipramine for up to 8 weeks<br>Tapering of open label drug: no information<br>Sponsored by industry: yes | Lithium and imipramine<br>Lithium: targeted serum level of 0.6-0.9 mmol/liter<br>Imipramine: 75-150 mg/day<br>Lithium<br>Targeted serum level of 0.6-0.9 mmol/liter<br>Imipramine<br>75-150 mg/day<br><br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants |

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| Suppes 2009, USA | Number randomized = 623<br>Age in years: 40.1 (11.7)<br>Females: 52.5%<br>Bipolar type: type 1<br>Index episode: any episode<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 127 sites in USA and Canada<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label quetiapine 400-800 mg for up to 36 weeks<br>Tapering of open label quetiapine: gradually tapering of quetiapine during 6-14 days<br>Co-intervention in pre-randomization phase:<br>Lithium (targeted serum level of 0.5-1.2<br>mmol/liter) or valproate (targeted serum level of 50-125 ug/ml)<br><br>Sponsored by industry: yes | Quetiapine<br>400-800 mg, target dose 600 mg<br>Placebo<br>Blinded investigational product<br>Co-intervention in all arms:<br>Lithium (targeted serum level of 0.5-1.2 mmol/liter or valproate targeted serum level of 50-125 ug/ml)<br>Duration of the interventions: 104 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, mixed: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Szegedi 2018, USA | Number randomized = 253<br>Age in years: 41.8<br>Females: 54.8%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label asenapine 5-10 mg/b.i.d for 12-16 weeks and placebo tablet. Knew the received asenapine but were blinded to which tablet was active or placebo<br>Tapering of open label asenapine: abruptly<br>Sponsored by industry: yes | Asenapine<br>5-10 mg/b.i.d, targeted dose 10 mg/b.i.d.<br>Placebo tablet was removed<br>Placebo<br>Asenapine tablet was removed<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, mixed: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Tohen 2004, USA | Number randomized = 99<br>Age in years: 41.3<br>Females: 51.5 %<br>Bipolar type: type 1 | RCT<br>Enriched discontinuation design: yes | Olanzapine<br>5-20 mg/day<br>Placebo<br>Co-intervention in all arms<br>Lithium (serum level of 0.6-1.2 | New episode, any type: Number of participants<br>Withdrawal, any cause: Number of participants |

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| | Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | Pre-randomization phase: double-masked olanzapine 5-20 mg/day for 6 weeks<br>Tapering: no information of tapering of olanzapine<br>Co-intervention in pre-randomization phase:<br>open label lithium (serum level of 0.6-1.2<br>mmol/liter) or valproate (serum level of<br>50-125 ug/ml)<br>Sponsored by industry: yes | mmol/liter) or valproate (serum level of<br>50-125 ug/ml)<br>Duration of the interventions: 78 weeks | Weight gain over 7%:<br>Number of participants<br>Sedation: Number of participants |
| Tohen 2006, International | Number randomized = 361<br>Age in years: 40.6<br>Females:61.2%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter 44 sites I USA and 5 sites in Rumania<br>Enriched discontinuation design:yes<br>Pre-randomization phase: open label olanzapine 5-20 mg/day for 6-12 weeks<br>Tapering of open label olanzapine: no information<br>Sponsored by industry: yes | Olanzapine<br>5-20 mg/day<br>Placebo<br>Duration of the interventions: 48 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>New episode, mixed:<br>Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause:<br>Number of participants<br>Weight gain over 7%:<br>Number of participants<br>Sedation: Number of participants |
| Vieta 2008b, International | Number randomized = 706<br>Age in years: 41.1 (12.7)<br>Females: 55%<br>Bipolar type: type 1<br>Index episode: any episode<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter, 177 centers (37 in USA and 140 in other countries including Australia, Europe and South Africa)<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label quetiapine 400-800 mg/day for 12- 36 weeks<br>Tapering: quetiapine was tapered gradually during 6-14 days<br>Co-intervention in pre-randomization phase:lithium (targeted serum level of 0.5- | Quetiapine<br>400-800 mg/day<br>Placebo<br>Blinded investigational product<br>Co-intervention in all arms:<br>Lithium (targeted serum level of 0.5-1.2<br>mmol/liter) Valproate (targeted serum level of<br>50-125 ug/ml)<br>Duration of the interventions: 104 weeks | New episode, any type:<br>Number of participants<br>New episode, depression:<br>Number of participants<br>New episode, mania:<br>Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause:<br>Number of participants<br>Weight gain over 7%:<br>Number of participants<br>Sedation: Number of participants |

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| | | 1.2mmol/liter) or valproate (targeted serum level of 50-125 ug/ml) for at least 12 weeks<br>Sponsored by industry: yes | | |
| Vieta 2012, International | Number randomized = 266 (olanzapine and placebo arms only)<br>Age in years:<br>Females<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label long-acting injections of risperidone 25-50 mg/every 2 weeks for 12 weeks<br>Tapering of open label risperidon: no information<br>Sponsored by industry: yes | Olanzapine<br>10 mg/day and injectable placebo<br>Placebo<br>Oral and injectable placebo<br>Duration of the interventions: 78 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, hypo mania: Number of participants<br>New episode, mixed: Number of participants<br>Withdrawal, any cause: Number of participants<br>Weight gain over 7%: Number of participants<br>Sedation: Number of participants |
| Weisler 2011, international | Number randomized = 1226<br>Age in years: 36.6<br>Females: 48.7%<br>Bipolar type: type 1<br>Index episode: any episode<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter 128 centers in 15 countries in Asia, Europe, central and South Africa and USA<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label quetiapine 300-800 mg/day for 4-24 weeks<br>Tapering of open label quetiapine: gradually for 2 weeks<br>Sponsored by industry: yes | Quetiapine<br>300-800 mg/day<br>And identically appearing placebo tablets<br>Lithium<br>Serum level of 0.6-1.2 mmol/liter<br>And identically appearing placebo tablets<br>Placebo<br>Identically appearing placebo tablets<br>Duration of the interventions: 104 weeks | New episode, any type: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants<br>Global functioning: Sheeran Disability Scale<br>Global cognitive functioning: Medical Outcomes Study Cognitive Scale |
| Woo 2011, South Korea | Number randomized = 83<br>Age in years: 38.3<br>Females: 61.4%<br>Bipolar type: type 1<br>Index episode: mania or mixed | RCT, multicenter, 23 centers in Korea<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label aripiprazole 10-30 mg/day | Aripiprazole<br>10-30 mg/day<br>Placebo<br>Co-intervention in all arms: valproate serum level of 50-125 ug/ml | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants |

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| | Problematic alcohol/substance abuse: stated as exclusion criteria | and valproate (serum level of 50 125 ug/ml) for 6 weeks<br>Tapering of open label aripiprazoel: no information of tapering of aripiprazole<br>Co-intervention in pre-randomization phase: valproate<br>Sponsored by industry: yes | Duration of the interventions: 24 weeks | Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants |
| Zarate 2004, USA | Number randomized = 37<br>Age in years: 35.8<br>Females: 75.7%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Inclusion of participants with problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label perphenzine 4-64 mg/day for 1-10 weeks<br>Tapering of open label perphenzine: gradually tapered during 1 week<br>Co-intervention in pre-randomization phase: open label mood stabilizer, one or more Lithium (serum level of 0.6-1.2 mmol/liter), carbamazepine (serum level of 4-12 mg/ml) or valproate (serum level of 50-125 ug/ml)<br>Sponsored by industry: no information | Perphenazine<br>4-64 mg/day<br>Placebo<br>Co-intervention in all arms: mood stabilizer, one or more Lithium (serum level of 0.6-1.2 mmol/liter) Carbamazepine (serum level of 4-12 mg/ml) Valproate (serum level of 50-125 ug/ml)<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants |
| Zhang 2022, China | Number randomized = 264<br>Age in years: 36.1<br>Females: 51.9%<br>Bipolar type: type 1<br>Index episode: not specified<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lamotrigine 200 mg/day for 6-16 weeks<br>Tapering of open label lamotrigine: no information<br>Sponsored by industry: yes | Lamotrigine<br>200 mg/day<br>Placebo<br>Matching placebo<br>Duration of the interventions: 36 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants |
| Not included in the evidence to decision | | | | |

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| Berk 2016, Australia | Number randomized = 61<br>Age in years: 21.4 (2.2)<br>Females: 11.5 %<br>Bipolar type: type 1<br>Index episode: mania<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, to sites in Melbourne Australia<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (serum level of 0.8-1.0 mmol/liter) and open label quetiapine (dose determined by treating clinician) for 8-12 weeks<br>Tapering of open label drugs: gradually during weeks or months<br>Sponsored by industry: yes | Quetiapine<br>Dose determined by treating clinician<br>Lithium<br>Serum level of 0.6-0.8 mmol/liter<br>Duration of the interventions: 52 weeks | Withdrawal, any cause: Number of participants<br>Quality of life: Quality of Life Scale<br>Global functioning: Global assessment of Functioning (GAF) |
| Bowden 2012, USA | Number randomized = 86<br>Age in years: 40.7 (12.4)<br>Females: 57.4%<br>Bipolar type: type 1 and 2<br>Index episode: depression<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, two sites in USA<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label valproate (serum level of 45-120 ug/ml) for up to 8 weeks<br><br>Tapering of open valproate: abruptly<br>Co-intervention: lamotrigine 50-200 mg/day<br>Sponsored by industry: yes | Valproate<br>Serum level of 45-120 ug/day, maximum dose 2500 mg/ml<br>Placebo<br>Co-intervention in all arms: lamotrigine 50- 200 mg/day<br><br>Duration of the interventions: 32 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants |
| Calabrese 2000, USA | Number randomized = 182<br>Age in years: 38.0<br>Females: 57.2 %<br>Bipolar type: type 1 and 2<br>Index episode: Any episode<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multicenter<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lamotrigine for 100-300 mg/day for 8 weeks<br>Tapering of open label lamotrigine: abruptly<br>Sponsored by industry: yes | Lamotrigine<br>100-500 mg/day<br>Placebo<br>Matching placebo<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants |
| Calabrese 2005, USA | Number randomized = 60<br>Age in years: 37.1<br>Females: 51.6%<br>Bipolar type: type 1 and 2<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, single center<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (serum level of minimum 0.8 mmol/liter) and valproate (serum level of minimum 50 ug/ml, for 16-24 weeks<br>Tapering of open label drug: gradually during on average 6 weeks | Lithium:<br>Serum level of minimum 0.8 mmol/liter<br>Placebo matching valproate<br>Valproate:<br>Serum level of minimum 50 ug/ml<br>Placebo matching lithium<br>Duration of the interventions: 80 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, hypo mania: Number of participants<br>New episode, hypo mixed: Number of participants<br>Withdrawal, any cause: Number of participants |

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| | | Sponsored by industry: yes | | Sedation: Number of participants<br>Weight gain over 7%: Number of participants |
| Coxhead 1992, United Kingdom | Number randomized = 31<br>Age in years: 48.0<br>Females: 67.7 %<br>Bipolar type: not specified<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: n/a<br>No open label phase, but all patients were stabile on lithium for at least 4 weeks before inclusion<br>No information of tapering of lithium<br>Tapering of open label drug: n/a<br>Sponsored by industry: yes | Carbamazepine<br>Serum level of 38-51 mmol/liter<br>Placebo matching lithium<br>Lithium<br>Serum level of 0.6-1.0 mmol/liter<br>Placebo matching carbamazepine<br>Duration of the interventions: 52 weeks | New episode, any type: Number of participants<br>Withdrawal, any cause: Number of participants |
| Cundall 1972, Scotland | Number randomized = 18<br>Age in years: 53.6<br>Females: 66.6 %<br>Bipolar type: not specified<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: n/a<br>No open label phase, but all patients were stabilized on lithium for 1- 3 years before inclusion<br>No information of tapering of lithium<br>Tapering of open label drug: n/a.<br>Sponsored by industry: no information | Lithium<br>Serum level of 0.5-1.2 mmol/liter<br>Placebo<br>Matching placebo<br>Duration of the interventions: 26 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants |
| Hartong 2003, Netherlands | Number randomized = 94<br>Age in years: 41.89 (13.92)<br>Females: 54.3 %<br>Bipolar type: Type 1 and 2<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase<br>Treatment naive patients<br>Tapering of open label drug: n/a<br>Sponsored by industry: yes | Carbamazepine<br>Serum level of 6-10 mg/liter<br>Lithium<br>Serum level of 0.6-1.0 mmol/liter<br>Duration of the interventions: 104 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>Withdrawal, any cause: Number of participants |
| Kaur SanktAnna 2019, Canada | Number randomized = 69<br>Age in years: 42.8<br>Females: 81.2%<br>Bipolar type: type 1 and 2<br>Index episode: depression | RCT, multicenter, three cemters in Canada<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label tianeptine 37.5 mg/day for 8 weeks | Tianeptine<br>37.5 mg/day<br>Placebo<br>Duration of the interventions: 24 weeks | New episode, any type: Number of participants<br>Withdrawal, any cause: Number of participants |

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| | Problematic alcohol/substance abuse: stated as exclusion criteria | Tapering of open label tianrptine: abruptly<br>Sponsored by industry: no | | |
| Klenidienst 2000, Germany | Number randomized = 171<br>Age in years: 40.0<br>Females: 56.7%<br>Bipolar type: type 1 and 2<br>Index episode: not specified<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, multiventer, 9 sites in Germany<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase<br>Tapering of open label drug: n/a<br>Sponsored by industry: no | Carbamazepine<br>Serum level of 4-12 ug/lml<br>Lithium<br>Serum level of 0.6-0.8 mmol/liter<br>Duration of the interventions: 130 weeks | New episode, any type: Number of participants<br>Withdrawal, any cause: Number of participants<br>Psychiatric hospitalization: Number of participants<br>Suicidal behavior: Number of participants |
| Tamayo 2009; Colombia | Number randomized = 114<br>Age in years: 43.0<br>Females: 62.7%<br>Bipolar type: Type 1 and 2<br>Index episode: depression<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: olanxzapine + fluoxetine (combinded tablet) 6/25 mg/day-12/50 mg/day for 7 weeks<br>Tapering of open label olanzapine+fluoxetine: no information<br>Sponsored by industry: yes | Olanzapine + fluoxetine (combinded tablet)<br>6/25 mg/day-12/50 mg/day<br>Olanzapine<br>5-20 mg/day<br>Duration of the interventions: 12 weeks | New episode, any type: Number of participants<br>New episode, mania: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Quality of life: SF-12 total |
| Tohen 2005, International | Number randomized = 431<br>Age in years: 42.4<br>Females: 52.9%<br>Bipolar type: type 1<br>Index episode: mania or mixed<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter, 87 inpatient and outpatient settings across Europe, Canada, South Africa, Israel, Australia and New Zeeland<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open labe olanzapine 5-20 mg/day and lithium (targeted serum level of 0.6-1.2 mmol/liter) for 6-12 weeks<br>Tapering of open label drug: gradually during 4 weeks<br>Sponsored by industry: yes | Olanzapine<br>5-20 mg/day<br>Lithium<br>Targeted serum level of 0.6-1.2 mmol/liter<br>Duration of the interventions: 52 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, mixed: Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Weight gain over 7%: Number of participants |
| Vieta 2008a, Spain | Number randomized = 55<br>Age in years: 43.52 (11.88)<br>Females: 65.5%<br>Bipolar type: type 1 and 2<br>Index episode: not specified | RCT<br>Enriched discontinuation design: no<br>Pre-randomization phase: n/a<br>No open label phase,<br>All patients were on lithium for at least 6 months before inclusion | Oxcarbazepine<br>300-1200 mg/day<br>Placebo<br>Co-intervention in all arms:<br>Lithium<br>Duration of the interventions: 52 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants |

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| | Problematic alcohol/substance abuse: stated as exclusion criteria | Tapering of open label drug: n/a<br>Sponsored by industry: yes | | New episode, mixed: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Weight gain over 7%: Number of participants |
| Young 2014, International | Number randomized = 585<br>Age in years: 40.1<br>Females: 59.6%<br>Bipolar type: type 1 and 2<br>Index episode: depression<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT, multicenter 110 centers across Europe, Canada and Asia and 83 centers in USA, Europe, turkey, Central and South America, South Africa and Australia<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label quetiapine 300 or 600 mg/day for 8 weeks<br>Tapering of open label quetiapine: no information<br>Sponsored by industry: yes | Quetiapine<br>300 mg/day<br>Quetiapine<br>600 mg/day<br>The two active groups have been merged into one group.<br>Placebo<br>Identically appearing tablets<br>Duration of the interventions: 52 weeks | New episode, any type: Number of participants<br>Serious adverse events (SAE): Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal behavior: Number of participants<br>Sedation: Number of participants<br>Weight gain over 7%: Number of participants |

## 1.2 Gennemgang af evidensen

**Studiedesign**
De inkluderede forsøg var overvejende vedligeholdelsesstudier med et beriget diskontinuationsdesign eller omfattede deltagere, som allerede var stabiliseret på farmakologisk behandling ved randomisering. I de placebokontrollerede forsøg blev deltagerne typisk randomiseret til fortsat behandling eller seponering af eller skift fra den undersøgte behandling til placebo efter en forudgående behandlings- eller stabiliseringsfase. Forsøgene belyser således effekten af fortsat vedligeholdelsesbehandling hos patienter, der havde responderet på og tolereret behandlingen, eller skift til anden behandling. Ingen forsøg belyste effekten af at påbegynde vedligeholdelsesbehandling hos patienter i remission uden igangværende farmakologisk behandling. Yderligere oplysninger om studiedesign, behandlingsfaser, opfølgningstid og finansiering fremgår af karakteristikatabellen (**Tabel 1**).

Størstedelen af de inkluderede forsøg havde angivet industrifinansiering (**Tabel 1**)

**Studiepopulationen**
I 27 af de inkluderede forsøg indgik udelukkende deltagere med bipolar lidelse type 1 [5, 6, 8, 10-13, 15, 18-21, 23, 27, 29, 31, 36, 39-41, 43, 47-52] og i tre forsøg indgik udelukkende deltagere med bipolar lidelse type 2 [25, 26, 35]. I ét forsøg var der angivet en population af deltagere med bipolar lidelse type 2 og NOS, hvor deltagere med NOS udgjorde mindre en 10% og forsøget er i herværende arbejde derfor er klassificeret som bipolar lidelse type 2 [24]. Evidensgrundet for bipolar 2 omfatter således fire forsøg i alt [24-26, 35]. Alle forsøgene inkluderede både mænd og kvinder og langt hovedparten inkluderede voksne over 18 år. I et forsøg vare deltagere over 16 år [31] og i et forsøg deltagere over 21 år [29].

Deltagerne i alle de inkluderede forsøg var i hel eller delvis remission (stabil fase) ved forsøgets begyndelse.

I fire af forsøgene blev der inkluderet deltagere hvor indeksepisoden forud for den stabile fase var depression [24, 25, 27, 49]. I 5 af forsøgene var indeksepisoden mani eller hypomani [6, 8, 21, 40, 48], og i 11 af forsøgene mani eller blandingstilstand. I ét af forsøgene kunne indeksepisoden være både depression eller mani [29], og i seks af forsøgene enhver affektiv episode [10, 18, 20, 26, 28, 52]. I fem af forsøgene var indeksepisoden ikke specificeret [17, 35, 36, 39, 47].
I 16 af de inkluderede forsøg var et aktuelt problematisk rusmiddelbrug defineret som et eksklusionskriterie [6, 10-13, 18-20, 23-25, 39, 43, 47, 48, 51], og 12 forsøg var det ikke angivet direkte at personer med et aktuelt problematisk rusmiddelbrug blev ekskluderet [5, 8, 15, 27-29, 35, 36, 40, 41, 49, 52]. Der var dog samtidig heller ingen oplysninger om hvorvidt personer med et aktuelt rusmiddelbrug var inkluderet, fx med angivelse af hvor mange der havde et aktuelt misbrug i en tabel over deltagere karakteristika. Det er i disse forsøg derfor vanskeligt at vurdere om personer med et samtidigt rusmiddelbrug reelt kunne inkluderes. Kun i et enkelt forsøg var der oplysninger om andelen af inkluderede personer med et aktuelt problematisk rusmiddelbrug [31]. I forsøget havde 8% at de inkluderede deltagere et aktuelt problematisk rusmiddelbrug.

**Interventioner og sammenligning**
De undersøgte interventioner i de inkluderede forsøg omfattede behandling med lithium [6, 8, 18, 26, 29, 31, 35, 36, 39, 40, 49], antipsykotika (paleperidonER, ziprazidon, quetiapin, lurasidon, aripriprazol, asenapin, olanzapin, perphenzine og cariprazine) [5, 10-13, 15, 18-21, 23, 41, 43, 51, 52], antidepressiva (Imipramine) [24-26, 29] og antikonvulsiva (valproat og lamotrigin) [6, 8, 31, 47, 49]. Varigheden af den

forudgående open label fase eller stabiliserende behandlingsfase af en akut episode var ikke oplyst i fem af forsøgene [27, 28, 35, 36, 40]. I de øvrige forsøg varede den forudgående akutte behandlingsfase mellem 4 og 36 uger. De inkluderede forsøg havde en interventionsvarighed på mellem 12 uger og 210 uge (**Tabel 1**).

I tre forsøg indgik studiearme med kombinationsbehandling bestående af lithium + valproat overfor henholdsvis lithum eller valproat [31], lithium + imipramin overfor henholdsvis lithium eller imipramine [26, 29].

Yderligere ti forsøg undersøgte interventioner givet i tillæg til co-medicinering (som alle studiearme modtog) med lithium [28], valproat [19], lithium eller valproat [10, 13, 20, 21, 23, 52], lamotrigin [11], eller lithium, carbamazepin eller valproat [43]

I 29 af forsøgene var der inkluderet en kontrolgruppe der modtog placebo [5, 6, 8, 10-13, 15, 18-21, 23-28, 34-36, 39-41, 43, 47, 49, 51, 52]

## 1.3 Resultater fra parvise metaanalyser, aktive interventioner sammenlignet med placebo

### Lithium vs placebo

Der blev identificeret 14 randomiseret placebokontrolleret forsøg, der bidrog med evidens til belysning af effekten af lithium sammenlignet med placebo til voksne med bipolar lidelse type I og II. Ti forsøg inkluderede udelukkende patienter med bipolar 1 lidelse [6, 8, 18, 27, 29, 31, 36, 39, 40, 49]. Tre forsøg inkluderede udelukkende deltagere med bipolar 2 lidelse [25, 26, 35]. Ét forsøg inkluderede en blandingspopulation af deltagere med bipolar lidelse 1 eller 2. Forsøgene er beskrevet i afsnit 1.1, og resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 1, 2 & 3**).

Alle forsøgene benyttede et seponeringsdesign, idet alle deltagere forinden randomisering til lithium eller placebo var i en aktiv behandling. Ingen forsøg undersøgte påbegyndelse af lithium sammenlignet med ingen behandling (placebo) blandt patienter, der ikke allerede var i behandling. Desuden var der betydelig variation mellem de inkluderede forsøg med hensyn til deltagernes sygdomsfase, varigheden af stabilisering forud for randomisering og den behandling, som deltagerne modtog inden studiestart. I flere forsøg havde deltagerne været eksponeret for lithium umiddelbart inden randomisering, mens deltagere i andre forsøg blev randomiseret efter forudgående behandling med andre lægemidler. Disse forskelle kan have betydning for overførbarheden og fortolkningen af de samlede resultater.

*Bipolar type 1*

Evidensgrundlaget viste, at lithium muligvis reducerer risikoen for nye sygdomsepisoder hos patienter med bipolar lidelse type I sammenlignet med ingen behandling (placebo).

For det kritiske outcome *ny episode, enhver type* var risikoen 36,9 % i lithiumgruppen sammenlignet med 58,6 % i placebogruppen. Den relative risiko blev beregnet til 0.63 (95% CI: 0.54, 0.74), hvilket svarer til, at 217 færre oplever en ny episode per 1000 der behandles med lithium end ved ingen farmakologisk behandling (placebo) (95% CI: 269 til 152 færre) [6, 8, 18, 27, 29, 31, 39, 40, 49]. Tiltroen til evidensen er lav grundet alvorlig risiko for bias og alvorlig manglende overførbarhed.

Tilsvarende viste resultaterne, at lithium muligvis reducerer risikoen for en *ny manisk episode* (kritisk), med 219 hændelser per 1.000 patienter i lithiumgruppen mod 385 per 1.000 i placebogruppen, svarende til 166 færre tilfælde per 1.000 behandlede (RR 0,57; 95 % CI 0,48 til 0,69). Tiltroen til evidensen var ligeledes lav, grundet alvorlig risiko for bias og alvorlig manglende overførbarhed.

For *nye depressive episoder* (kritisk) var der 253 hændelser per 1.000 patienter behandlet med lithium sammenlignet med 312 per 1.000 patienter behandlet med placebo, svarende til 59 færre tilfælde per 1.000 behandlede (RR 0,81; 95 % CI 0,67 til 0,97). Tiltroen til evidensen var meget lav, og resultaterne er derfor forbundet med betydelig usikkerhed. For *ny blandingsepisode* (kritisk) var evidensen også meget usikker. Her var der 10 hændelser per 1.000 patienter i lithiumgruppen mod 29 per 1.000 i placebogruppen (RR 0,34; 95 % CI 0,04 til 3,25), svarende til 19 færre tilfælde per 1.000 behandlede, men konfidensintervallet omfattede både en mulig reduktion og stigning i risikoen. Der blev ikke rapporteret data for *nye episode, hypomani*.

Lithium påvirker muligvis ikke forekomsten af *alvorlige hændelser* i væsentlig grad, med 29 hændelser per 1.000 patienter i lithiumgruppen mod 35 per 1.000 patienter i placebogruppen (RR 0,84; 95 % CI 0,42 til 1,67). Tiltroen til evidensen var ligeledes lav, grundet alvorlig risiko for bias og alvorlig manglende overførbarhed.

Det var meget usikkert, om lithium påvirker risikoen for *frafald af alle årsager*, idet 257 per 1.000 patienter i lithiumgruppen og 209 per 1.000 patienter i placebogruppen afbrød behandlingen (RR 1,23; 95 % CI 0,95 til 1,59; meget lav tiltro til evidensen). Det var ligeledes usikkert, om lithium reducerer risikoen for *selvmordsadfærd*. Der blev observeret 5 hændelser per 1.000 patienter behandlet med lithium mod 12 per 1.000 patienter behandlet med placebo, svarende til 8 færre tilfælde per 1.000 behandlede (Peto OR 0,37; 95 % CI 0,12 til 1,10; lav tiltro til evidensen).

For de vigtige outcomes var det meget usikkert, om lithium påvirker *sedation, psykiatriske indlæggelser eller globalt funktionsniveau*. Derimod tyder resultaterne på, at lithium muligvis øger forekomsten af klinisk relevant *vægtøgning*. Risikoen for *vægtøgning på mere end 7 %* var 74 per 1.000 patienter behandlet med lithium sammenlignet med 38 per 1.000 patienter i gruppen der modtog placebo, svarende til 36 flere tilfælde per 1.000 behandlede (RR 1,95; 95 % CI 1,23 til 3,09). Tiltroen til evidensen var ligeledes lav, grundet alvorlig risiko for bias og alvorlig manglende overførbarhed.

*Livskvalitet* og *nyrepåvirkning* blev ikke rapporteret i de inkluderede forsøg. (**Evidensprofil 1**)

### *Bipolar type 2*

Evidensgrundlaget for lithium sammenlignet med ingen behandling (placebo) hos patienter med bipolar lidelse type II var begrænset og præget af meget lav tiltro til evidensen for samtlige rapporterede outcomes.

For det kritiske outcome *ny episode, enhver type* omfattede evidensen 115 deltagere fra tre randomiserede forsøg [25, 35, 50]. Lithium kan muligvis reducere risikoen for en ny episode sammenlignet med ingen behandling (placebo), men effekten er meget usikker. Risikoen for en ny episode var 60,7 % i lithiumgruppen sammenlignet med 71,4 % i placebogruppen, svarende

til 107 færre tilfælde per 1.000 behandlede (RR 0,85; 95 % CI 0,64 til 1,12). Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias, overførbarhed og alvorlig upræcist effektestimat.

For *ny depressiv episode* omfattede evidensen ligeledes 115 deltagere fra tre forsøg [25, 35, 50]. Resultaterne viste, at det er muligt, at lithium ikke har nogen væsentlig effekt sammenlignet med placebo. Risikoen var 52,8 % i lithiumgruppen mod 50,8 % i placebogruppen, svarende til 20 flere tilfælde per 1.000 behandlede (RR 1,04; 95 % CI 0,73 til 1,50). Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias, overførbarhed og alvorlig upræcist effektestimat.

For *ny manisk episode* blev der rapporteret data fra ét studie med 22 deltagere [26]. Det er meget usikket om lithium øger eller nedsætter antallet af patienter med ny mani. Risikoen var 2,4 % i lithiumgruppen sammenlignet med 8,3 % i placebogruppen, svarende til 59 færre tilfælde per 1.000 behandlede (RR 0,29; 95 % CI 0,01 til 5,79). Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias samt meget alvorlig upræcist effektestimat (kun ét forsøg).

Resultaterne indikerede, at lithium muligvis reducerer risikoen for *nye episode, hypomani*. Risikoen var 7,0 % blandt patienter behandlet med lithium mod 19,0 % blandt patienter behandlet med placebo, svarende til 120 færre tilfælde per 1.000 behandlede (RR 0,37; 95 % KI 0,12 til 1,14). Tiltroen til evidensen var meget lav. Outcome ny blandingsepisode blev ikke rapporteret.

For det kritiske outcome *frafald af alle årsager* omfattede evidensen 93 deltagere fra to forsøg [25, 35]. Behandling med lithium kan muligvis reducere antallet af patienter, der udgår af forsøget, men resultaterne er meget usikre. Risikoen for frafald var 28,5 % i lithiumgruppen sammenlignet med 43,1 % i placebogruppen, svarende til 147 færre frafald per 1.000 behandlede (RR 0,66; 95 % CI 0,30 til 1,42). Tiltroen til evidensen var meget lav.

For *alvorlige hændelser* blev der ikke registreret hændelser i nogen af grupperne i det ene inkluderede forsøg med 53 deltagere [25]. Det er derfor meget usikkert, om lithium påvirker risikoen for *alvorlige hændelser*. Tiltroen til evidensen var meget lav.

For det vigtige outcome *sedation* omfattede evidensen 53 deltagere fra ét studie [25]. Resultaterne viste, at det er meget usikkert, om lithium reducerer eller øger risikoen for sedation. Risikoen var 30,7 % i lithiumgruppen sammenlignet med 22,2 % i placebogruppen, svarende til 84 flere tilfælde per 1.000 behandlede (RR 1,38; 95 % CI 0,56 til 3,44). Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias samt meget alvorlig upræcist effektestimat (kun ét forsøg).

Der blev ikke rapporteret data for *selvmordsadfærd, psykiatriske indlæggelser, nyrepåvirkning, globalt funktionsniveau, vægtøgning eller livskvalitet*. (**Evidensprofil 2**)

*Bipolar type 1 & 2*

Ét forsøg sammenlignede effekten af lithium overfor placebo [34]. Se **tabel 1** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 3**).

**Evidence profile 1: Lithium compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Lithium | Difference | | |
| New episode, any type<br>№ of participants: 1851<br>(8 RCTs) | **RR 0.63**<br>(0.54 to 0.74) | 58.6% | **36.9%**<br>(-- to --) | **21.7% fewer**<br>(26.9% fewer to 15.2% fewer) | ⊕⊕◯◯<br>Low[a,b] | Litium reducerer muligvis antallet af patienter med ny episode af enhver type i væsentlig grad |
| New episode, depression<br>№ of participants: 1087<br>(7 RCTs) | **RR 0.81**<br>(0.67 to 0.97) | 31.2% | **25.3%**<br>(-- to --) | **5.9% fewer**<br>(10.3% fewer to 0.9% fewer) | ⊕◯◯◯<br>Very low[a,b,c] | Der er meget usikkert om lithium øeger eller nedsætter antallet af patienter med ny |
| New episode, mania<br>№ of participants: 1087<br>(7 RCTs) | **RR 0.57**<br>(0.48 to 0.69) | 38.5% | **21.9%**<br>(-- to --) | **16.6% fewer**<br>(20.0% fewer to 11.9% fewer) | ⊕⊕◯◯<br>Low[a,b] | Litium reducerer muligvis antallet af patienter med ny mani i væsentlig grad |
| New episode, mixed<br>№ of participants: 205<br>(1 RCT) | **RR 0.34**<br>(0.04 to 3.25) | 2.9% | **1.0%**<br>(-- to --) | **1.9% fewer**<br>(2.8% fewer to 6.5% more) | ⊕◯◯◯<br>Very low[a,d] | Der er meget usikkert om lithium øeger eller nedsætter antallet af patienter med ny blandingsepisode |
| New episode, hypomania - not reported | - | - | - | - | - | |
| Withdrawal, any cause<br>№ of participants: 1635<br>(7 RCTs) | **RR 1.23**<br>(0.95 to 1.59) | 20.9% | **25.7%**<br>(-- to --) | **4.8% more**<br>(1.0% fewer to 12.3% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om lithium øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Serious adverse events (SAE)<br>№ of participants: 988<br>(2 RCTs) | **RR 0.84**<br>(0.42 to 1.67) | 3.5% | **2.9%**<br>(-- to --) | **0.6% fewer**<br>(2.0% fewer to 2.3% more) | ⊕⊕◯◯<br>Low[a,b] | Lithium påvirker muligvis ikke antallet af patienter med alvorlige hændelser i betydelig grad |
| Suicidal behaviour<br>№ of participants: 1547<br>(5 RCTs) | **OR 0.37**<br>(0.12 to 1.10) | 1.2% | **0.5%**<br>(-- to --) | **0.8% fewer**<br>(1.1% fewer to 0.1% more) | ⊕⊕◯◯<br>Low[a,b] | Det er usikkert om lithium øger eller nedsætter antallet af patienter med selvmordsadfærd |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sedation<br>№ of participants: 1366<br>(4 RCTs) | **RR 0.99**<br>(0.62 to 1.57) | 16.7% | **16.5%**<br>(-- to --) | **0.2% fewer**<br>(6.4% fewer to 9.5% more) | ⊕◯◯◯<br>Very low[a,b,c,e] | Det er muligt at lithium ikke har nogen betydelig effekt på antallet af patienter med sedation, men evidensen er meget usikker |
| Psychiatric hospitalization<br>№ of participants: 220<br>(1 RCT) | **RR 0.64**<br>(0.36 to 1.13) | 22.7% | **14.5%**<br>(-- to --) | **8.2% fewer**<br>(14.5% fewer to 3.0% more) | ⊕◯◯◯<br>Very low[a,d] | Det er meget usikker om lithium øger eller nedsætter antallet af patienter med psykiatrisk indlæggelse |
| Global functioning<br>№ of participants: 220<br>(1 RCT) | - | - | - | MD **1 higher**<br>(3.16 lower to 5.16 higher) | ⊕◯◯◯<br>Very low[a,d] | Det er meget usikkert om lithium forbedrer eller forværrer globalt funktionsniveau |
| Weigt gain, over 7%<br>№ of participants: 1364<br>(4 RCTs) | **RR 1.95**<br>(1.23 to 3.09) | 3.8% | **7.4%**<br>(-- to --) | **3.6% more**<br>(0.9% more to 7.9% more) | ⊕⊕◯◯<br>Low[a,b] | Lithium øger muligvis antallet af patienter med vægtøgning over 7% i nogen grad |
| Quality of life - not reported | - | - | - | - | - | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio
Explanations:a. High risk of bias; b. Variation in intervention: dose and length of intervention, c. Wide confidence intervals, d. Only one study;e. Wide variance in effect estimates

**Evidence profile 2: Lithium compared to Placebo for Bipolar 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **Lithium** | **Difference** | | |
| New episode, any type<br>№ of participants: 115<br>(3 RCTs) | **RR 0.85**<br>(0.64 to 1.12) | 71.4% | **60.7%**<br>(-- to --) | **10.7% fewer**<br>(25.7% fewer to 8.6% more) | ⊕◯◯◯<br>Very low[a,b,c] | Lithium kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er meget usikker |
| New episode, depression<br>№ of participants: 115<br>(3 RCTs) | **RR 1.04**<br>(0.73 to 1.50) | 50.8% | **52.8%**<br>(-- to --) | **2.0% more**<br>(13.7% fewer to 25.4% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er muligt at lithium ikke har nogen betydelig effekt på antallet af patienter med ny depression, men evidensen er meget usikker |

| | | | | | | |
|---|---|---|---|---|---|---|
| New episode, mania<br>№ of participants: 22<br>(1 RCT) | **RR 0.29**<br>(0.01 to 5.79) | 8.3% | **2.4%**<br>(-- to --) | **5.9% fewer**<br>(8.2% fewer to 39.9% more) | ⊕◯◯◯<br>Very low[a,d] | Det er meget usikkert om lithium øger eller nedsætter antallet af patienter med ny mani |
| New episode, mixed - not reported | - | - | - | - | - | |
| New episode, hypomania<br>№ of participants: 115<br>(3 RCTs) | **RR 0.37**<br>(0.12 to 1.14) | 19.0% | **7.0%**<br>(-- to --) | **12.0% fewer**<br>(16.8% fewer to 2.7% more) | ⊕◯◯◯<br>Very low[a,b,c] | Lithium kan muligvis reducere antallet af patienter med ny hypomani, men evidensen er meget usikker |
| Withdrawal, any cause<br>№ of participants: 93<br>(2 RCTs) | **RR 0.66**<br>(0.30 to 1.42) | 43.1% | **28.5%**<br>(-- to --) | **14.7% fewer**<br>(30.2% fewer to 18.1% more) | ⊕◯◯◯<br>Very low[a,b,c] | Lithium kan muligvis reducere antallet af patienter med frafald af alle årsager, men evidensen er meget usikker |
| Serious adverse events (SAE<br>№ of participants: 53<br>(1 RCT) | not estimable | 0.0% | **0.0%**<br>(-7 to 7) | **0.0% fewer**<br>(7.0% fewer to 7.0% more) | ⊕◯◯◯<br>Very low[a,d] | Det er meget usikkert om lithium øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Suicidal behaviour - not reported | - | - | - | - | - | |
| Sedation<br>№ of participants: 53<br>(1 RCT) | **RR 1.38**<br>(0.56 to 3.44) | 22.2% | **30.7%**<br>(-- to --) | **8.4% more**<br>(9.8% fewer to 54.2% more) | ⊕◯◯◯<br>Very low[a,d] | Det er meget usikker om lithium reducerer eller øger antallet af patienter med sedation |
| Psychiatric hospitalization - not reported | - | - | - | - | - | |
| Global functioning - not reported | - | - | - | - | - | |
| Weigt gain, over 7% - not reported | - | - | - | - | - | |
| Quality of life - not reported | - | - | - | - | - | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio
Explanations:a. High risk of bias; b. Variation in intervention: dose and length of intervention, c. Wide confidence intervals, d. Only one study

**Evidence profile 3: Lithium compared to Placebo for Bipolar 1 & 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Placebo** | **Lithium** | **Difference** |
| New episode, any type<br>№ of participants: 13<br>(1 study) | **RR 0.42**<br>(0.18 to 1.00) | 100.0% | **42.0%**<br>(-- to --) | **58.0% fewer**<br>(82.0% fewer to 0.0% fewer) |
| New episode, depression<br>№ of participants: 13<br>(1 study) | **RR 0.31**<br>(0.04 to 2.62) | 40.0% | **12.4%**<br>(-- to --) | **27.6% fewer**<br>(38.4% fewer to 64.8% more) |
| New episode, mania<br>№ of participants: 13<br>(1 study) | **RR 0.31**<br>(0.09 to 1.12) | 80.0% | **24.8%**<br>(-- to --) | **55.2% fewer**<br>(72.8% fewer to 9.6% more) |
| New episode, mixed<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, hypomania<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause<br>№ of participants: 13<br>(1 study) | **RR 2.00**<br>(0.10 to 41.37) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Withdrawal, any cause - Bipolar type not specified<br>№ of participants: 13<br>(1 study) | **RR 2.00**<br>(0.10 to 41.37) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Serious adverse events (SAE)<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour - Bipolar type not specified<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

| | | | | |
|---|---|---|---|---|
| Psychiatric hospitalization<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Global functioning<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| weight gain, over 7%<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

## Antipsykotika vs. placebo

Der blev identificeret 17 randomiseret placebokontrolleret forsøg, der bidrog med evidens til belysning af effekten af antipsykotika sammenlignet med placebo til voksne med bipolar lidelse type 1 og 2 [5, 10-13, 15, 17-21, 23, 43, 48, 51, 52]. I alt inkluderede 16 forsøg udelukkende patienter med bipolar 1 lidelse og ét forsøg inkluderede en blandingspopulation af deltagere med bipolar 1 eller 2, Forsøgene er beskrevet i afsnit 1.1, og resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor **(Evidensprofil 4 og 5)**.

Alle forsøgene benyttede et seponeringsdesign, idet alle deltagerne forinden randomisering til antipsykotika eller placebo var i en aktiv behandling, de havde modtaget i en forudgående eller netop overstået akut sygdomsepisode. Ingen forsøg undersøgte påbegyndelse af antipsykotika sammenlignede med ingen behandling (placebo) blandt patienter, der ikke allerede var i behandling. Desuden var der variation mellem de inkluderede forsøg med hensyn til varigheden af stabilisering forud for randomisering og den behandling, som deltagerne modtog inden studiestart. I 16 af forsøgene havde deltagerne responderet på det antipsykotikum, der blev undersøgt i den randomiserede fase [5, 10-13, 15, 16, 18-21, 23, 43, 48, 51, 52], mens deltagerne i ét forsøg af olanzapin alle havde responderet på risperidon depot i den forudgående akutte fase [41]. Disse forskelle kan have betydning for overførbarheden og fortolkningen af de samlede resultater.

### *Bipolar type 1*

For det kritiske outcome *ny episode af enhver type* viste den samlede analyse, at antipsykotika muligvis reducerer risikoen for tilbagefald sammenlignet med placebo (RR 0,55; 95% CI 0,46 til 0,65). Dette svarer til omkring 204 færre patienter pr. 1.000 i lithiumgruppen, der oplever en ny episode sammenlignet med placebogruppen (fra 245 færre til 159 færre). Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias, overførbarhed, heterogenitet og upræcist effektestimat.

For *ny depressiv episode* var resultaterne mere usikre. Antipsykotika var associeret med 6,3 % færre depressive episoder sammenlignet med placebo (RR 0,67; 95% CI 0,51 til 0,87), men det er meget usikkert, om antipsykotika øger eller nedsætter antallet af patienter med *ny depression*. Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias, overførbarhed og heterogenitet.

For *ny manisk episode* tydede resultaterne på, at antipsykotika muligvis reducerer antallet af patienter med *ny mani* i mindre grad (RR 0,43; 95% CI 0,36 til 0,51), svarende til 115 færre tilfælde per 1.000 patienter (fra 129 færre til 99 færre). Tiltroen til evidensen var lav, grundet alvorlig risiko og overførbarhed.

For *ny blandingsepisode* viste resultaterne at antipsykotika muligvis ikke reducerer antallet af patienter med *ny blandingsepisode* i betydelig grad (RR 0,46; 95% CI 0,34 til 0,62), svarende til 59 færre tilfælde per 1000 patienter (fra 72 færre til 41 færre). Tiltroen til evidensen var lav, grundet alvorlig risiko og overførbarhed.

For *ny episode, hypomani* var evidensen meget usikker. Der sås 0,7 % færre episoder blandt patienter behandlet med antipsykotika (RR 0,77; 95% CI 0,18 til 3,36), men det er meget usikkert, om antipsykotika øger eller nedsætter antallet af patienter med *ny episode, hypomani*. Tiltroen til evidensen var meget lav.

For det kritiske outcome *alvorlige hændelser* er det meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med alvorlige hændelser (RD -0,01; 95% CI -0,03 til 0,00), svarende til 10 færre tilfælde per 1000 patienter (fra 30 færre til 0 færre). Tiltroen til evidensen var meget lav.

For *frafald af alle årsager* var der 2,7 % flere patienter, som afbrød behandlingen i antipsykotikagruppen (RR 1,12; 95% CI 0,93 til 1,34), men det er meget usikkert, om antipsykotika øger eller nedsætter antallet af patienter med frafald af alle årsager. Tiltroen til evidensen var meget lav, grundet alvorlig risiko for bias, overførbarhed og heterogenitet.

For *vægtøgning over 7 %* af kropsvægten var der 8 % flere tilfælde blandt patienter behandlet med antipsykotika (RR 2,38; 95% CI 1,76 til 3,21). Det er dog meget usikkert, om antipsykotika øger eller nedsætter antallet af patienter med vægtøgning over 7 %, og tiltroen til evidensen var meget lav.

For *sedation* var der ligeledes stor usikkerhed. Resultaterne viste 4,2 % flere tilfælde blandt patienter behandlet med antipsykotika (RR 1,91; 95% CI 0,68 til 5,36), men det er meget usikkert, om antipsykotika reducerer eller øger antallet af patienter med sedation. Tiltroen til evidensen var meget lav.

For *selvmordsadfærd* øger antipsykotika muligvis ikke antallet af patienter i væsentlig grad (RR 0,75; 95% CI 0,31 til 1,84), svarende til 2 færre tilfælde per 1.000 patienter. Tiltroen til evidensen var lav.

Det er meget usikkert om antipsykotika forbedrer eller forværrer *globalt funktionsniveau.*

Der blev ikke rapporteret data for *nyrepåvirkning* eller *livskvalitet* (**Evidensprofil 4**).

Evidensgrundlaget omfattede flere forskellige antipsykotiske lægemidler og resultaterne var overordnet konsistente på tværs af præparaterne og pegede generelt i retning af en reduceret risiko for tilbagefald sammenlignet med placebo. Evidensgrundlaget var dog ikke tilrettelagt til direkte sammenligning mellem de enkelte antipsykotika, og der kan derfor ikke drages sikre konklusioner om eventuelle forskelle i effekt eller bivirkninger mellem præparaterne (**Evidensprofil 4**).

*Bipolar type 2*

Der blev ikke identificeret evidens til at vurdere effekten af antipsykotika sammenlignet med placebo til voksne med bipolar type II. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antipsykotikas gavnlige eller skadelige effekter hos voksne med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

*Bipolar type 1 & 2*

Ét forsøg sammenlignede effekten af antipsykotika overfor placebo [16]. Se **tabel 1** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 5**).

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| New episode, any type (all antipsychotics)<br>№ of participants: 5532<br>(16 RCTs) | **RR 0.55**<br>(0.46 to 0.65) | 45.4% | **24.9%**<br>(-- to --) | **20.4% fewer**<br>(24.5% fewer to 15.9% fewer) | ⊕◯◯◯<br>Very low[a,b,c,d] | Antipsykotika kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Paliperidon<br>№ of participants: 290<br>(1 RCT) | **RR 0.85**<br>(0.67 to 1.07) | 53.5% | **45.5%**<br>(-- to --) | **8.0% fewer**<br>(17.6% fewer to 3.7% more) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om paliperidon øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, any type - Ziprasidone<br>№ of participants: 239<br>(1 RCT) | **RR 0.61**<br>(0.39 to 0.95) | 32.1% | **19.6%**<br>(-- to --) | **12.5% fewer**<br>(19.6% fewer to 1.6% fewer) | ⊕◯◯◯<br>Very low[a,e] | Ziprasidone kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Lurasidone<br>№ of participants: 496<br>(1 RCT) | **RR 0.40**<br>(0.31 to 0.53) | 51.6% | **20.6%**<br>(-- to --) | **31.0% fewer**<br>(35.6% fewer to 24.3% fewer) | ⊕◯◯◯<br>Very low[a,e] | Lurasidone kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Aripiprazole<br>№ of participants: 931<br>(4 RCTs) | **RR 0.61**<br>(0.49 to 0.77) | 31.8% | **19.4%**<br>(-- to --) | **12.4% fewer**<br>(16.2% fewer to 7.3% fewer) | ⊕◯◯◯<br>Very low[a,c,d] | Aripiprazole kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Quetiapine<br>№ of participants: 2134<br>(3 RCTs) | **RR 0.40**<br>(0.35 to 0.46) | 50.3% | **20.1%**<br>(-- to --) | **30.2% fewer**<br>(32.7% fewer to 27.1% fewer) | ⊕⊕⊕◯<br>Moderate[a] | Quetiapin reducerer sandsynligvis antallet af patienter med ny episode af enhver type i væsentlig grad |
| New episode, any type - Olanzapine<br>№ of participants: 723<br>(3 RCTs) | **RR 0.57**<br>(0.41 to 0.79) | 62.8% | **35.8%**<br>(-- to --) | **27.0% fewer**<br>(37.0% fewer to 13.2% fewer) | ⊕◯◯◯<br>Very low[a,d,f,g] | Olanzapine kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.26**<br>(0.14 to 0.49) | 33.3% | **8.7%**<br>(-- to --) | **24.7% fewer**<br>(28.7% fewer to 17.0% fewer) | ⊕◯◯◯<br>Very low[a,e] | Asenapine kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Cariprazine<br>№ of participants: 430<br>(1 RCT) | **RR 0.88**<br>(0.58 to 1.34) | 19.7% | **17.4%**<br>(-- to --) | **2.4% fewer**<br>(8.3% fewer to 6.7% fewer) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om cariprazine øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, any type - Perphenazine<br>№ of participants: 37<br>(1 RCT) | **RR 2.37**<br>(0.52 to 10.70) | 11.1% | **26.3%**<br>(-- to --) | **15.2% more**<br>(5.3% fewer to 107.8% more) | ⊕◯◯◯<br>Very low[a,d,e] | Perphenazine kan muligvis øge antallet af patienter med ny episode af enhver type, men evidensen er usikker |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| New episode, depression (all antipsychotics)<br>№ of participants: 4625<br>(13 RCTs) | **RR 0.67**<br>(0.51 to 0.87) | 19.0% | **12.7%**<br>(-- to --) | **6.3% fewer**<br>(9.3% fewer to 2.5% fewer) | ⊕◯◯◯<br>Very low[a,c,h] | Det er meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Paliperidone<br>№ of participants: 290<br>(1 RCT) | **RR 1.33**<br>(0.84 to 2.09) | 18.1% | **24.0%**<br>(-- to --) | **6.0% more**<br>(2.9% fewer to 19.7% more) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om paliperidone øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Ziprasidone<br>№ of participants: 239<br>(1 RCT) | **RR 0.88**<br>(0.46 to 1.68) | 14.3% | **12.6%**<br>(-- to --) | **1.7% fewer**<br>(7.7% fewer to 9.7% more) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om ziprazone øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Lurasidone<br>№ of participants: 496<br>(1 RCT) | **RR 0.42**<br>(0.29 to 0.60) | 31.2% | **13.1%**<br>(-- to --) | **18.1% fewer**<br>(22.2% fewer to 12.5% fewer) | ⊕◯◯◯<br>Very low[a,e] | Lurasidone kan muligvis reducere antallet af patienter med ny depression, men evidensen er usikker |
| New episode, depression - Aripiprazole<br>№ of participants: 931<br>(4 RCTs) | **RR 0.75**<br>(0.53 to 1.06) | 14.5% | **10.9%**<br>(-- to --) | **3.6% fewer**<br>(6.8% fewer to 0.9% more) | ⊕⊕◯◯<br>Low[a,c] | Det er meget usikkert om aripriprazole øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Quetiapine<br>№ of participants: 1326<br>(2 RCTs) | **RR 0.37**<br>(0.27 to 0.51) | 18.7% | **6.9%**<br>(-- to --) | **11.8% fewer**<br>(13.6% fewer to 9.2% fewer) | ⊕⊕◯◯<br>Low[a,d] | Quetiapin reducerer muligvis antallet af patienter med ny depression i mindre grad |
| New episode, depression - Olanzapine<br>№ of participants: 624<br>(2 RCTs) | **RR 0.73**<br>(0.55 to 0.96) | 28.3% | **20.6%**<br>(-- to --) | **7.6% fewer**<br>(12.7% fewer to 1.1% fewer) | ⊕◯◯◯<br>Very low[a,d,g] | Det er meget usikkert om olanzapine øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.38**<br>(0.14 to 1.05) | 10.3% | **3.9%**<br>(-- to --) | **6.4% fewer**<br>(8.9% fewer to 0.5% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om asenapine øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - cariprazine<br>№ of participants: 430<br>(1 RCT) | **RR 1.05**<br>(0.59 to 1.88) | 10.6% | **11.1%**<br>(-- to --) | **0.5% more**<br>(4.3% fewer to 9.3% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om cariprazine øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Perphenazine<br>№ of participants: 37<br>(1 RCT) | **RR 8.55**<br>(0.49 to 148.33) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om perphenazine øger eller nedsætter antallet af patienter med ny episode, depression |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| New episode, mania (all antipsychotics)<br>№ of participants: 4129<br>(13 RCTs) | **RR 0.43**<br>(0.36 to 0.51) | 20.1% | **8.6%**<br>(-- to --) | **11.5% fewer**<br>(12.9% fewer to 9.9% fewer) | ⨁⨁◯◯<br>Low[a,c] | Antipsykotika reducerer muligvis antallet af patienter med ny mani i mindre grad |
| New episode, mania - Paliperidone<br>№ of participants: 290<br>(1 RCT) | **RR 0.60**<br>(0.41 to 0.88) | 35.4% | **21.3%**<br>(-- to --) | **14.2% fewer**<br>(20.9% fewer to 4.3% fewer) | ⨁◯◯◯<br>Very low[a,d,e] | Paliperidone kan muligvis reducere antallet af patienter med ny mani, men evidensen er usikker |
| New episode, mania - Ziprasidone<br>№ of participants: 239<br>(1 RCT) | **RR 0.44**<br>(0.18 to 1.05) | 12.5% | **5.5%**<br>(-- to --) | **7.0% fewer**<br>(10.3% fewer to 0.6% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om ziprasidone øger eller nedsætter antallet af patienter med ny episode, mani |
| New episode, mania - Aripiprazole<br>№ of participants: 931<br>(4 RCTs) | **RR 0.48**<br>(0.32 to 0.71) | 14.7% | **7.1%**<br>(-- to --) | **7.7% fewer**<br>(10.0% fewer to 4.3% fewer) | ⨁⨁◯◯<br>Low[a,c] | Aripiprazol påvirker muligvis ikke forekomsten af patienter med ny mani i betydelig grad |
| New episode, mania - Quetiapine<br>№ of participants: 1326<br>(2 RCTs) | **RR 0.37**<br>(0.26 to 0.52) | 20.6% | **7.6%**<br>(-- to --) | **13.0% fewer**<br>(15.2% fewer to 9.9% fewer) | ⨁⨁◯◯<br>Low[a,d] | Quetiapin reducerer muligvis antallet af patienter med ny mani i mindre grad |
| New episode, mania - Olanzapine<br>№ of participants: 624<br>(2 RCTs) | **RR 0.35**<br>(0.25 to 0.50) | 31.6% | **11.1%**<br>(-- to --) | **20.5% fewer**<br>(23.7% fewer to 15.8% fewer) | ⨁⨁◯◯<br>Low[a,g] | Olanzapine reducerer muligvis reducere antallet af patienter med ny mani, i væsenligt grad |
| New episode, mania - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.21**<br>(0.08 to 0.53) | 19.0% | **4.0%**<br>(-- to --) | **15.0% fewer**<br>(17.5% fewer to 9.0% fewer) | ⨁◯◯◯<br>Very low[a,d,e] | Asenapine kan muligvis reducere antallet af patienter med ny mani, men evidensen er usikker |
| New episode, mania - Perphenazine<br>№ of participants: 37<br>(1 RCT) | **RR 0.47**<br>(0.05 to 4.78) | 11.1% | **5.2%**<br>(-- to --) | **5.9% fewer**<br>(10.6% fewer to 42.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om perphenazine øger eller nedsætter antallet af patienter med ny episode, mani |
| New episode, mania - Cariprazine<br>№ of participants: 430<br>(1 RCT) | **RR 0.82**<br>(0.37 to 1.83) | 6.3% | **5.2%**<br>(-- to --) | **1.1% fewer**<br>(4.0% fewer to 5.3% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om cariprazine øger eller nedsætter antallet af patienter med ny episode, mani |
| New episode, mixed (all antipsychotics)<br>№ of participants: 2235<br>(7 RCTs) | **RR 0.46**<br>(0.34 to 0.62) | 10.9% | **5.0%**<br>(-- to --) | **5.9% fewer**<br>(7.2% fewer to 4.1% fewer) | ⨁⨁◯◯<br>Low[a,c] | Antipsykotika reducerer muligvis ikke antallet af patienter med ny blandingsepisode i betydelig grad |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| New episode, mixed - Ziprasidone<br>№ of participants: 239<br>(1 RCT) | **RR 0.29**<br>(0.06 to 1.43) | 5.4% | **1.6%**<br>(-- to --) | **3.8% fewer**<br>(5.0% fewer to 2.3% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om ziprasidone øger eller nedsætter antallet af patienter med ny blandingsepisode |
| New episode, mixed - Aripiprazole<br>№ of participants: 497<br>(2 RCTs) | **RR 0.76**<br>(0.31 to 1.85) | 4.4% | **3.3%**<br>(-- to --) | **1.0% fewer**<br>(3.0% fewer to 3.7% more) | ⊕⊕◯◯<br>Low[a,c] | Aripiprazole reducerer muligvis ikke antallet af patienter med ny blandingsepisode |
| New episode, mixed - Olanzapine<br>№ of participants: 624<br>(2 RCTs) | **RR 0.49**<br>(0.24 to 0.97) | 7.1% | **3.5%**<br>(-- to --) | **3.6% fewer**<br>(5.4% fewer to 0.2% fewer) | ⊕⊕◯◯<br>Low[a,g] | Olanzapine reducerer muligvis ikke antallet af patienter med ny blandingsepisode |
| New episode, mixed - Quetiapine<br>№ of participants: 623<br>(1 RCT) | **RR 0.44**<br>(0.30 to 0.64) | 24.3% | **10.7%**<br>(-- to --) | **13.6% fewer**<br>(17.0% fewer to 8.7% fewer) | ⊕◯◯◯<br>Very low[a,e] | Quetiapin kan muligvis reducere antallet af patienter med ny blandingsepisode, men evidensen er usikker |
| New episode, mixed - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.20**<br>(0.02 to 1.69) | 4.0% | **0.8%**<br>(-- to --) | **3.2% fewer**<br>(3.9% fewer to 2.7% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om asenapine øger eller nedsætter antallet af patienter med ny blandingsepisode |
| New episode, hypomania (all antipsychotics)<br>№ of participants: 263<br>(1 RCT) | **RR 0.77**<br>(0.18 to 3.36) | 3.0% | **2.3%**<br>(-- to --) | **0.7% fewer**<br>(2.5% fewer to 7.1% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med ny episode, hypomani |
| New episode, hypomania - Olanzapine<br>№ of participants: 263<br>(1 RCT) | **RR 0.77**<br>(0.18 to 3.36) | 3.0% | **2.3%**<br>(-- to --) | **0.7% fewer**<br>(2.5% fewer to 7.1% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om olanzapine øger eller nedsætter antallet af patienter med ny episode, hypomani |
| Withdrawal, any cause (all antipsychotics)<br>№ of participants: 5553<br>(16 RCTs) | **RR 1.12**<br>(0.93 to 1.34) | 22.9% | **25.7%**<br>(-- to --) | **2.7% more**<br>(1.6% fewer to 7.8% more) | ⊕◯◯◯<br>Very low[a,c,i] | Det er meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Paliperidon<br>№ of participants: 300<br>(1 RCT) | **RR 1.05**<br>(0.78 to 1.42) | 35.1% | **36.9%**<br>(-- to --) | **1.8% more**<br>(7.7% fewer to 14.8% more) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om paliperidon øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Ziprasidone<br>№ of participants: 240<br>(1 RCT) | **RR 0.84**<br>(0.57 to 1.25) | 31.9% | **26.8%**<br>(-- to --) | **5.1% fewer**<br>(13.7% fewer to 8.0% more) | ⊕◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om ziprazone øger eller nedsætter antallet af patienter med frafald af alle årsager |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| Withdrawal, any cause - Lurasidone<br>№ of participants: 496<br>(1 RCT) | **RR 0.90**<br>(0.58 to 1.41) | 14.4% | **13.0%**<br>(-- to --) | **1.4% fewer**<br>(6.0% fewer to 5.9% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om lurasidone øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Aripiprazole<br>№ of participants: 932<br>(4 RCTs) | **RR 0.97**<br>(0.80 to 1.16) | 32.5% | **31.5%**<br>(-- to --) | **1.0% fewer**<br>(6.5% fewer to 5.2% more) | ⨁⨁◯◯<br>Low[a,c] | Aripiprazole reducerer muligvis ikke antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Quetiapine<br>№ of participants: 2134<br>(3 RCTs) | **RR 1.21**<br>(0.81 to 1.79) | 19.6% | **23.7%**<br>(-- to --) | **4.1% more**<br>(3.7% fewer to 15.5% more) | ⨁◯◯◯<br>Very low[a,d,j] | Det er meget usikkert om quetiapine øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Olanzapine<br>№ of participants: 726<br>(3 RCTs) | **RR 1.27**<br>(0.65 to 2.50) | 20.7% | **26.3%**<br>(-- to --) | **5.6% more**<br>(7.2% fewer to 31.0% more) | ⨁◯◯◯<br>Very low[a,d,g,k] | Det er meget usikkert olanzapine øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.55**<br>(0.34 to 0.89) | 30.2% | **16.6%**<br>(-- to --) | **13.6% fewer**<br>(19.9% fewer to 3.3% fewer) | ⨁◯◯◯<br>Very low[a,d,e] | Asenapine reducerer muligvis antallet af patienter med frafald af alle årsager, men evidensen er usikker |
| Withdrawal, any cause - Cariprazine<br>№ of participants: 436<br>(1 RCT) | **RR 2.04**<br>(1.29 to 3.23) | 13.1% | **26.7%**<br>(-- to --) | **13.6% more**<br>(3.8% more to 29.2% more) | ⨁◯◯◯<br>Very low[a,e] | Cariprazine øger muligvis antallet af patienter med frafald af alle årsager, men evidensen er usikker |
| Withdrawal, any cause - Perphenazine<br>№ of participants: 37<br>(1 RCT) | **RR 4.74**<br>(0.61 to 36.72) | 5.6% | **26.3%**<br>(-- to --) | **20.8% more**<br>(2.2% fewer to 198.4% more) | ⨁◯◯◯<br>Very low[a,d,e] | Perphenazine øger muligvis antallet af patienter med frafald af alle årsager, men evidensen er usikker |
| Serious adverse events (SAE) (all antipsychotics)<br>№ of participants: 5146<br>(13 RCTs) | **RR 0.74**<br>(0.51 to 1.06) | 6.0% | **5.0%**<br>(3 to 6)[l] | **1.0% fewer**<br>(3.0% fewer to 0.0% fewer) | ⨁◯◯◯<br>Very low[a,c,m] | Det er meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE) - Paliperidone<br>№ of participants: 296<br>(1 RCT) | not estimable | 22.4% | **34.4%**<br>(25.4 to 42.4) | **12.0% more**<br>(3.0% more to 20.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Paliperidone øger muligvis antallet af patienter med alvorlige hændelser, men evidensen er usikker |
| Serious adverse events (SAE) - Ziprasidone<br>№ of participants: 239<br>(1 RCT) | not estimable | 5.4% | **2.4%**<br>(-4.6 to 8.4) | **3.0% fewer**<br>(10.0% fewer to 3.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om ziprasidone øger eller nedsætter antallet af patienter med alvorlige hændelser |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| Serious adverse events (SAE) - Lurasidone<br>№ of participants: 496<br>(1 RCT) | not estimable | 4.4% | **3.4%**<br>(-0.6 to 7.4) | **1.0% fewer**<br>(5.0% fewer to 3.0% more) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om lurasidon øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE) - Aripiprazole<br>№ of participants: 932<br>(4 RCTs) | not estimable | 7.1% | **9.1%**<br>(6.1 to 12.1) | **2.0% more**<br>(1.0% fewer to 5.0% more) | ⨁⨁◯◯<br>Low[a,c] | Aripiprazone påvirker muligvis ikke antallet af patienter med alvorlige hændelser i betydelig grad |
| Serious adverse events (SAE) - Quetiapine<br>№ of participants: 2134<br>(3 RCTs) | not estimable | 3.5% | **4.5%**<br>(0.5 to 7.5) | **1.0% more**<br>(3.0% fewer to 4.0% more) | ⨁⨁◯◯<br>Low[a,n] | Quetiapine påvirker muligvis ikke antallet af patienter med alvorlige hændelser i betydelig grad |
| Serious adverse events (SAE) - Olanzapine<br>№ of participants: 361<br>(1 RCT) | not estimable | 7.4% | **11.4%**<br>(6.4 to 16.4) | **4.0% more**<br>(1.0% fewer to 9.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om olanzapine øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE) - Asenapine<br>№ of participants: 252<br>(1 RCT) | not estimable | 8.7% | **12.7%**<br>(6.7 to 18.7) | **4.0% more**<br>(2.0% fewer to 10.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om asenapine øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE) - cariprazine<br>№ of participants: 436<br>(1 RCT) | not estimable | 3.4% | **3.4%**<br>(-0.6 to 7.4)[o] | **0.0% fewer**<br>(4.0% fewer to 4.0% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om cariprazine øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Weight gain, over 7% (all antipsychotics)<br>№ of participants: 5465<br>(15 RCTs) | **RR 2.38**<br>(1.76 to 3.21) | 5.8% | **13.8%**<br>(-- to --) | **8.0% more**<br>(4.4% more to 12.8% more) | ⨁◯◯◯<br>Very low[a,c,d] | Det er meget usikkert om antipsykotika øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Weight gain, over 7% - Paliperidone<br>№ of participants: 300<br>(1 RCT) | **RR 1.38**<br>(0.91 to 2.09) | 19.6% | **27.0%**<br>(-- to --) | **7.4% more**<br>(1.8% fewer to 21.4% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om paliperidone øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Weight gain, over 7% - Ziprazidone<br>№ of participants: 239<br>(1 RCT) | **RR 1.03**<br>(0.36 to 2.97) | 5.4% | **5.5%**<br>(-- to --) | **0.2% more**<br>(3.4% fewer to 10.6% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om ziprazidone øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Weight gain, over 7% - Lurasidone<br>№ of participants: 496<br>(1 RCT) | **RR 1.88**<br>(0.98 to 3.60) | 5.2% | **9.8%**<br>(-- to --) | **4.6% more**<br>(0.1% fewer to 13.5% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om lurasidone øger eller nedsætter antallet af patienter med vægtøgning over 7% |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| Weight gain, over 7% - Aripiprazole<br>№ of participants: 883<br>(4 RCTs) | **RR 1.97**<br>(0.98 to 3.95) | 5.7% | **11.1%**<br>(-- to --) | **5.5% more**<br>(0.1% fewer to 16.7% more) | ⨁◯◯◯<br>Very low[a,c,d] | Det er meget usikkert om ariprazole øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Weight gain, over 7% - Quetiapine<br>№ of participants: 2133<br>(3 RCTs) | **RR 3.49**<br>(2.27 to 5.36) | 2.4% | **8.4%**<br>(-- to --) | **6.0% more**<br>(3.0% more to 10.5% more) | ⨁⨁◯◯<br>Low[a,d] | Quetiapine påvirker muligvis ikke antallet af patienter med en vægtøgning over 7% i betydelig grad |
| Weight gain, over 7% - Olanzazepine<br>№ of participants: 726<br>(3 RCTs) | **RR 3.47**<br>(2.09 to 5.76) | 5.3% | **18.5%**<br>(-- to --) | **13.2% more**<br>(5.8% more to 25.4% more) | ⨁◯◯◯<br>Very low[a,d,g] | Olanzapine øger muligvis antallet af patienter med en vægtøgning over 7% men evidensen er usikker |
| Weight gain, over 7% - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 6.00**<br>(0.73 to 49.12) | 0.8% | **4.8%**<br>(-- to --) | **4.0% more**<br>(0.2% fewer to 38.2% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om asenapine øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Weight gain, over 7% - cariprazine<br>№ of participants: 436<br>(1 RCT) | **RR 1.20**<br>(0.85 to 1.68) | 24.1% | **29.0%**<br>(-- to --) | **4.8% more**<br>(3.6% fewer to 16.4% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om cariprazine øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Sedation (all antipsychotics)<br>№ of participants: 4153<br>(9 RCTs) | **RR 1.91**<br>(0.68 to 5.36) | 4.6% | **8.7%**<br>(-- to --) | **4.2% more**<br>(1.5% fewer to 20.0% more) | ⨁◯◯◯<br>Very low[a,c,d,p] | Det er meget usikkert om antipsykotika reducerer eller øger antallet af patienter med sedation |
| Sedation - Paliperidone<br>№ of participants: 296<br>(1 RCT) | not estimable | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om paliperidone reducerer eller øger antallet af patienter med sedation |
| Sedation - Aripiprazole<br>№ of participants: 160<br>(1 RCT) | **RR 0.72**<br>(0.21 to 2.45) | 7.2% | **5.2%**<br>(-- to --) | **2.0% fewer**<br>(5.7% fewer to 10.5% more) | ⨁◯◯◯<br>Very low[a,d,e] | Det er meget usikkert om aripiprazole reducerer eller øger antallet af patienter med sedation |
| Sedation - Quetiapine<br>№ of participants: 2134<br>(3 RCTs) | **RR 1.82**<br>(0.30 to 11.04) | 7.4% | **13.4%**<br>(-- to --) | **6.1% more**<br>(5.2% fewer to 74.1% more) | ⨁◯◯◯<br>Very low[a,d,q] | Det er meget usikkert om quetiapine reducerer eller øger antallet af patienter med sedation |
| Sedation - Olanzapine<br>№ of participants: 726<br>(3 RCTs) | **RR 3.13**<br>(1.49 to 6.55) | 2.5% | **7.8%**<br>(-- to --) | **5.3% more**<br>(1.2% more to 13.9% more) | ⨁◯◯◯<br>Very low[a,d,g] | Det er meget usikkert om olanzapine reducerer eller øger antallet af patienter med sedation |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antipsychotics | Difference | | |
| Sedation - Asenapine<br>№ of participants: 252<br>(1 RCT) | not pooled | 0.0% | not pooled | not pooled | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om asenapine reducerer eller øger antallet af patienter med sedation |
| Suicidal behaviour (all antipsychotics)<br>№ of participants: 3328<br>(8 RCTs) | **RR 0.75**<br>(0.31 to 1.84) | 0.7% | **0.5%**<br>(-- to --) | **0.2% fewer**<br>(0.5% fewer to 0.6% more) | ⨁⨁◯◯<br>Low[a,c] | Antipsykotika øger muligvis ikke antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Paliperidone<br>№ of participants: 300<br>(1 RCT) | **RR 2.92**<br>(0.12 to 71.15) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om paliperidone øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Lurasidone<br>№ of participants: 496<br>(1 RCT) | **RR 3.05**<br>(0.12 to 74.47) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om lurasidone øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Asenapine<br>№ of participants: 252<br>(1 RCT) | **RR 0.50**<br>(0.05 to 5.44) | 1.6% | **0.8%**<br>(-- to --) | **0.8% fewer**<br>(1.5% fewer to 7.0% more) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om asenapine øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Aripiprazole<br>№ of participants: 849<br>(3 RCTs) | **RR 1.03**<br>(0.11 to 9.84) | 0.2% | **0.2%**<br>(-- to --) | **0.0% fewer**<br>(0.2% fewer to 2.1% more) | ⨁⨁◯◯<br>Low[a,g] | Det er usikkert om aripiprazole øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Quetiapine<br>№ of participants: 1431<br>(2 RCTs) | **RR 0.63**<br>(0.11 to 3.68) | 1.1% | **0.7%**<br>(-- to --) | **0.4% fewer**<br>(1.0% fewer to 3.0% more) | ⨁⨁◯◯<br>Low[a,g] | Det er usikkert om quetiapine øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Global functioning (all antipsychotics)<br>№ of participants: 425<br>(1 RCT) | - | 0 | - | MD **0.15 lower**<br>(2.53 lower to 2.23 higher) | ⨁◯◯◯<br>Very low[a,e] | Det er meget usikkert om antipsykotika forbedrer eller forværrer globalt funktionsniveau |
| Psychiatric hospitalization<br>№ of participants: 430<br>(1 RCT) | **RR 1.48**<br>(0.30 to 7.24) | 1.4% | **2.1%**<br>(-- to --) | **0.7% more**<br>(1.0% fewer to 8.8% more) | ⨁◯◯◯<br>Very low[a,d] | Det er meget usikkert om antipsykotika reducerer eller øger antallet af patienter med psykiatrisk indlæggelse |
| Quality of life - not reported | - | - | - | - | - | |

**Evidence profile 4: Antipsychotics compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **Antipsychotics** | **Difference** | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; RR: risk ratio
Explanations: a. High risk of bias; b. I2=84,4%; c. Variation in intervention: Dose, length of intervention and medication; d. Wide confidence intervals; e. Only one study; f. I2=65%; g. Variation in intervention length, dose;h. I2=67%; i. I2=68%; j. I2=83%;k. I2=84%;l. RD: -0.01, 95%CI (-0.03; 0.00)

**Evidence profile 5: Antipsychotics compared to Placebo for Bipolar 1 & 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Placebo** | **Antipsychotics** | **Difference** |
| New episode, any type<br>№ of participants: 585<br>(1 study) | **RR 0.60**<br>(0.46 to 0.76) | 39.8% | **23.9%**<br>(-- to --) | **15.9% fewer**<br>(21.5% fewer to 9.6% fewer) |
| New episode, any type - Quetiapine<br>№ of participants: 585<br>(1 study) | **RR 0.60**<br>(0.46 to 0.76) | 39.8% | **23.9%**<br>(-- to --) | **15.9% fewer**<br>(21.5% fewer to 9.6% fewer) |
| New episode, depression<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

| | | | | |
|---|---|---|---|---|
| New episode, mixed<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, hypomania<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause<br>№ of participants: 585<br>(1 study) | **RR 1.14**<br>(0.85 to 1.53) | 21.4% | **24.4%**<br>(-- to --) | **3.0% more**<br>(3.2% fewer to 11.4% more) |
| Withdrawal, any cause - Quetiapine<br>№ of participants: 585<br>(1 study) | **RR 1.14**<br>(0.85 to 1.53) | 21.4% | **24.4%**<br>(-- to --) | **3.0% more**<br>(3.2% fewer to 11.4% more) |
| Serious adverse events (SAE)<br>№ of participants: 585<br>(1 study) | not estimable | 5.4% | **8.4%**<br>(4.4 to 11.4) | **3.0% more**<br>(1.0% fewer to 6.0% more) |
| Serious adverse events (SAE) - Quetiapine<br>№ of participants: 585<br>(1 study) | not estimable | 5.4% | **8.4%**<br>(4.4 to 11.4) | **3.0% more**<br>(1.0% fewer to 6.0% more) |
| Weight gain, over 7%<br>№ of participants: 584<br>(1 study) | **RR 1.94**<br>(0.99 to 3.83) | 4.1% | **7.9%**<br>(-- to --) | **3.8% more**<br>(0.0% fewer to 11.6% more) |
| Weight gain, over 7% - Quetiapine<br>№ of participants: 584<br>(1 study) | **RR 1.94**<br>(0.99 to 3.83) | 4.1% | **7.9%**<br>(-- to --) | **3.8% more**<br>(0.0% fewer to 11.6% more) |
| Sedation<br>№ of participants: 585<br>(1 study) | **RR 5.05**<br>(0.24 to 104.76) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Sedation - Quetiapine<br>№ of participants: 585<br>(1 study) | **RR 5.05**<br>(0.24 to 104.76) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Suicidal behaviour<br>№ of participants: 585<br>(1 study) | **RR 0.67**<br>(0.11 to 4.00) | 1.0% | **0.7%**<br>(-- to --) | **0.3% fewer**<br>(0.9% fewer to 3.1% more) |
| Suicidal behaviour - Quetiapine<br>№ of participants: 585<br>(1 study) | **RR 0.67**<br>(0.11 to 4.00) | 1.0% | **0.7%**<br>(-- to --) | **0.3% fewer**<br>(0.9% fewer to 3.1% more) |

| | | | | |
|---|---|---|---|---|
| Global functioning<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |
| Psychiatric hospitalization<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Quality of life<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |

## Antidepressive vs. placebo

Otte forsøg i alt sammenlignede behandling med et antidepressivum med placebo. Tre forsøg undersøgte fluoxetin [24, 25], fire forsøg undersøgte imipramin[26-29, 50] og ét forsøg undersøgte tianepine [46]. Tre af forsøgene inkluderede udelukkende patienter med bipolar 1 lidelse [27-29, 50], tre forsøg inkluderede patienter med bipolar lidelse 2 [24-26] og to forsøg inkluderede en blandingspopulation af deltagere med bipolar lidelse 1 og 2 [30, 46]. Forsøgene er beskrevet i afsnit 1.1, og resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 6, 7 & 8**).

I alle forsøgene indgik en forudgående open-label fase, hvor deltagere modtog en given behandling. Seks af forsøgene benyttede et beriget seponeringsdesign, mens deltagerne i to forsøg blev stabiliseret på behandling med lithium, som derefter fortsat blev givet som co-medicinering til interventionen med imipramin eller placebo.

*Bipolar type 1*

Tre forsøg med i alt 179 deltagere undersøgte risikoen for *ny episode af enhver type* (kritisk outcome) [27-29]. Resultaterne viste det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med *ny episode af enhver type s*ammenlignet med ingen behandling (placebo) (RR 0,96; 95% CI 0,76 til 1,20). Dette svarer til 18 færre tilfælde pr. 1.000 behandlede (fra 111 færre til 92 flere), idet risikoen var 46,2 % i placebogruppen og 44,4 % i antidepressivagruppen. Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias, indirekte evidens samt upræcist effektestimat.

For det kritiske outcome *ny depressiv episode* viste resultaterne at det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med *ny depressiv episode* sammenlignet med placebo (RR 0,78; 95% CI 0,39 til 1,53) [28, 29, 50]. Absolut svarer det til 44 færre tilfælde pr. 1.000 behandlede (fra 122 færre til 106 flere). Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias, indirekte evidens samt upræcist effektestimat.

For det kritiske outcome *ny manisk episode* viste resultaterne, at det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med *ny manisk* episode sammenlignet med placebo (RR 1,41; 95 % CI 0,67 til 2,92) [28, 29, 50]. Absolut svarer det til 77 flere tilfælde pr. 1.000 behandlede (fra 62 færre til 360 flere). Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias, indirekte evidens samt upræcist effektestimat.

For det vigtige outcome *frafald af alle årsager* viste resultaterne, at det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med frafald af alle årsager sammenlignet med placebo (RR 1,00; 95 % CI 0,25 til 4,07) [27]. Absolut svarer det til ingen forskel mellem grupperne (0 færre pr. 1.000 behandlede; 95 % CI 173 færre til 708 flere).
Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias samt meget alvorlig upræcist effektestimat.

Der blev ikke rapporteret data for *ny hypomani episode, ny blandingsepisode, sedation, nyrepåvirkning, selvmordsadfærd, psykiatriske indlæggelser, globalt funktionsniveau, vægtøgning,*

*livskvalitet* eller *alvorlige uønskede hændelser (SAE)*. Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias samt meget alvorlig upræcist effektestimat. (**Evidensprofil 6**)

*Bipolar type 2*

For det kritiske outcome *ny episode af enhver type* viste resultaterne, at antidepressiva muligvis reducerer antallet af patienter med *ny episode, enhver type* sammenlignet med placebo (RR 0,61; 95 % CI 0,42 til 0,89), men evidensen er meget usikker. Absolut svarer det til 269 færre tilfælde pr. 1.000 behandlede (fra 400 færre til 76 færre). Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias, indirekte evidens samt upræcist effektestimat.

For det kritiske outcome *ny depressiv episode* viste resultaterne, at antidepressiva muligvis reducerer antallet af patienter med ny depressiv episode sammenlignet med placebo, men evidensen er meget usikker (RR 0,57; 95 % CI 0,35 til 0,91). Absolut svarer det til 235 færre tilfælde pr. 1.000 behandlede (fra 356 færre til 49 færre). Tiltroen til evidensen var meget lav grundet alvorlig risiko for bias, indirekte evidens samt upræcist effektestimat.

For det kritiske outcome *ny manisk episode* viste resultaterne, at det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med ny manisk episode sammenlignet med placebo (RR 4,00; 95 % CI 0,20 til 82,01). Tiltroen til evidensen var meget lav.

For det kritiske outcome *ny episode, hypomani* viste resultaterne, at det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med *ny episode, hypomani* sammenlignet med placebo (RR 0,55; 95 % CI 0,16 til 1,87). Absolut svarer det til 64 færre tilfælde pr. 1.000 behandlede (fra 120 færre til 124 flere). Tiltroen til evidensen var meget lav.

For det vigtige outcome *frafald af alle årsager* viste resultaterne, at det er meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med frafald af alle årsager sammenlignet med placebo (RR 1,29; 95 % CI 0,51 til 3,22). Absolut svarer det til 64 flere tilfælde pr. 1.000 behandlede (fra 109 færre til 493 flere). Tiltroen til evidensen var meget lav.

For det vigtige outcome *alvorlige hændelser* forekom der ingen hændelser i de inkluderede forsøg. Det er derfor meget usikkert, om antidepressiva øger eller nedsætter antallet af patienter med alvorlige hændelser sammenlignet med placebo. Tiltroen til evidensen var meget lav.

Der blev ikke rapporteret data for *blandingsepisoder, suicidal adfærd, livskvalitet, sedation, psykiatrisk indlæggelse, global funktionsevne, nyrepåvirkning* eller *vægtøgning over 7 %*.

Evidensgrundlaget var utilstrækkeligt til at vurdere, om et antidepressivum er mere effektivt eller sikrere end et andet.

*Bipolar type 1 & 2*

To forsøg sammenlignede effekten af antidepressive overfor placebo [30, 46]. Se **tabel 1** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 8**).

**Evidence profile 6: Antidepressiva compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antidepressiva | Difference | | |
| New episode, any type (any antidepressant)<br>№ of participants: 179<br>(3 RCTs) | **RR 0.96**<br>(0.76 to 1.20) | 46.2% | **44.4%**<br>(-- to --) | **1.8% fewer**<br>(11.1% fewer to 9.2% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, any type - Imipramin<br>№ of participants: 179<br>(3 RCTs) | **RR 0.96**<br>(0.76 to 1.20) | 46.2% | **44.4%**<br>(-- to --) | **1.8% fewer**<br>(11.1% fewer to 9.2% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, depression (any antidepressant)<br>№ of participants: 153<br>(2 RCTs) | **RR 0.78**<br>(0.39 to 1.53) | 20.0% | **15.6%**<br>(-- to --) | **4.4% fewer**<br>(12.2% fewer to 10.6% more) | ⊕◯◯◯<br>Very low[a,b,c,d] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Imipramin<br>№ of participants: 153<br>(2 RCTs) | **RR 0.78**<br>(0.39 to 1.53) | 20.0% | **15.6%**<br>(-- to --) | **4.4% fewer**<br>(12.2% fewer to 10.6% more) | ⊕◯◯◯<br>Very low[a,b,c,d] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, hypomania - not reported | - | - | - | - | - | |
| New episode, mania (any antidepressant)<br>№ of participants: 153<br>(2 RCTs) | **RR 1.41**<br>(0.67 to 2.92) | 18.8% | **26.4%**<br>(-- to --) | **7.7% more**<br>(6.2% fewer to 36.0% more) | ⊕◯◯◯<br>Very low[a,b,c,d] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med ny episode, mani |
| New episode, mania - Imipramin<br>№ of participants: 153<br>(2 RCTs) | **RR 1.41**<br>(0.67 to 2.92) | 18.8% | **26.4%**<br>(-- to --) | **7.7% more**<br>(6.2% fewer to 36.0% more) | ⊕◯◯◯<br>Very low[a,b,c,d] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med ny episode, mani |
| New episode, mixed - not reported | - | - | - | - | - | |
| Withdrawal, any cause (any antidepressant)<br>№ of participants: 26<br>(1 RCT) | **RR 1.00**<br>(0.25 to 4.07) | 23.1% | **23.1%**<br>(-- to --) | **0.0% fewer**<br>(17.3% fewer to 70.8% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Imipramin<br>№ of participants: 26<br>(1 RCT) | **RR 1.00**<br>(0.25 to 4.07) | 23.1% | **23.1%**<br>(-- to --) | **0.0% fewer**<br>(17.3% fewer to 70.8% more) | ⊕◯◯◯<br>Very low[a,e] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Serious adverse events (SAE) - not reported | - | - | - | - | - | |
| Quality of life - not reported | - | - | - | - | - | |
| Sedation - not reported | - | - | - | - | - | |

**Evidence profile 6: Antidepressiva compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antidepressiva | Difference | | |
| Suicidal behaviour - not reported | - | - | - | - | - | |
| Psychiatric hospitalization - not reported | - | - | - | - | - | |
| Global functioning - not reported | - | - | - | - | - | |
| Weight gain, over 7% - not reported | - | - | - | - | - | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio
*Explanations: a. High risk of bias; b. Intervention: variation in duration; c. Few events <100, few participants; d. Wide confidence intervals;e. Only one study*

**Evidence profile 7: Antidepressiva compared to Placebo for Bipolar 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antidepressiva | Difference | | |
| New episode, any type (any antidepressant)<br>№ of participants: 89<br>(3 RCTs) | **RR 0.61**<br>(0.42 to 0.89) | 69.0% | **42.1%**<br>(-- to --) | **26.9% fewer**<br>(40.0% fewer to 7.6% fewer) | ⊕◯◯◯<br>Very low[a,b,c] | Antidepressiva kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er meget usikker |
| New episode, any type - Fluoxetin<br>№ of participants: 67<br>(2 RCTs) | **RR 0.56**<br>(0.36 to 0.86) | 74.2% | **41.5%**<br>(-- to --) | **32.6% fewer**<br>(47.5% fewer to 10.4% fewer) | ⊕◯◯◯<br>Very low[a,c,d] | Fluoxetin kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er meget usikker |
| New episode, any type - Imipramin<br>№ of participants: 22<br>(1 RCT) | **RR 0.82**<br>(0.37 to 1.84) | 54.5% | **44.7%**<br>(-- to --) | **9.8% fewer**<br>(34.4% fewer to 45.8% more) | ⊕◯◯◯<br>Very low[a,e] | Imipramin kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er meget usikker |
| New episode, depression (any antidepressant)<br>№ of participants: 89<br>(3 RCTs) | **RR 0.57**<br>(0.35 to 0.91) | 54.8% | **31.2%**<br>(-- to --) | **23.5% fewer**<br>(35.6% fewer to 4.9% fewer) | ⊕◯◯◯<br>Very low[a,b,c] | Antidepressiva kan muligvis reducere antallet af patienter med ny depression, men evidensen er meget usikker |

**Evidence profile 7: Antidepressiva compared to Placebo for Bipolar 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Antidepressiva | Difference | | |
| New episode, depression - Imipramin<br>№ of participants: 22<br>(1 RCT) | **RR 0.69**<br>(0.23 to 2.11) | 45.5% | **31.4%**<br>(-- to --) | **14.1% fewer**<br>(35.0% fewer to 50.5% more) | ⊕◯◯◯<br>Very low[a,c] | Imipramin kan muligvis reducere antallet af patienter med ny depression, men evidensen er meget usikker |
| New episode, depression - Fluoxetin<br>№ of participants: 67<br>(2 RCTs) | **RR 0.54**<br>(0.32 to 0.92) | 58.1% | **31.4%**<br>(-- to --) | **26.7% fewer**<br>(39.5% fewer to 4.6% fewer) | ⊕◯◯◯<br>Very low[a,c,d] | Fluoxetin kan muligvis reducere antallet af patienter med ny depression, men evidensen er meget usikker |
| New episode, mania (any antidepressant)<br>№ of participants: 22<br>(1 RCT) | **RR 4.00**<br>(0.20 to 82.01) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⊕◯◯◯<br>Very low[a,c] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med mani |
| New episode, mania - Imipramin<br>№ of participants: 22<br>(1 RCT) | **RR 4.00**<br>(0.20 to 82.01) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) | ⊕◯◯◯<br>Very low[a,c] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med mani |
| New episode, hypomania (any antidepressant)<br>№ of participants: 89<br>(3 RCTs) | **RR 0.55**<br>(0.16 to 1.87) | 14.3% | **7.9%**<br>(-- to --) | **6.4% fewer**<br>(12.0% fewer to 12.4% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med hypomani |
| New episode, hypomania - Imipramin<br>№ of participants: 22<br>(1 RCT) | **RR 0.44**<br>(0.02 to 9.11) | 9.1% | **4.0%**<br>(-- to --) | **5.1% fewer**<br>(8.9% fewer to 73.7% more) | ⊕◯◯◯<br>Very low[a,c] | Det er meget usikkert om imipramin øger eller nedsætter antallet af patienter med hypomani |
| New episode, hypomania - Fluoxetin<br>№ of participants: 67<br>(2 RCTs) | **RR 0.58**<br>(0.15 to 2.19) | 16.1% | **9.4%**<br>(-- to --) | **6.8% fewer**<br>(13.7% fewer to 19.2% more) | ⊕◯◯◯<br>Very low[a,c,d] | Det er meget usikkert om fluoxetin øger eller nedsætter antallet af patienter med hypomani |
| Withdrawal, any cause (any antidepressant)<br>№ of participants: 55<br>(1 RCT) | **RR 1.29**<br>(0.51 to 3.22) | 22.2% | **28.7%**<br>(-- to --) | **6.4% more**<br>(10.9% fewer to 49.3% more) | ⊕◯◯◯<br>Very low[a,c] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Fluoxetin<br>№ of participants: 55<br>(1 RCT) | **RR 1.29**<br>(0.51 to 3.22) | 22.2% | **28.7%**<br>(-- to --) | **6.4% more**<br>(10.9% fewer to 49.3% more) | ⊕◯◯◯<br>Very low[a,c] | Det er meget usikkert om fluoxetin øger eller nedsætter antallet af patienter med frafald af alle årsager |
| New episode, mixed (any antidepressant) - not reported | - | - | - | - | - | |

**Evidence profile 7: Antidepressiva compared to Placebo for Bipolar 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **Antidepressiva** | **Difference** | | |
| Serious adverse events (SAE) (any antidepressant)<br>№ of participants: 67<br>(2 RCTs) | not estimable | 0.0% | **0.0%**<br>(-7 to 7) | **0.0% fewer**<br>(7.0% fewer to 7.0% more) | ⊕◯◯◯<br>Very low[a,d,f] | Det er meget usikkert om antidepressiva øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE), risk diff - Fluoxetin<br>№ of participants: 67<br>(2 RCTs) | not estimable | 0.0% | **0.0%**<br>(-7 to 7) | **0.0% fewer**<br>(7.0% fewer to 7.0% more) | ⊕◯◯◯<br>Very low[a,d,f] | Det er meget usikkert om fluoxetin øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Suicidal behaviour (any antidepressant) - not reported | - | - | - | - | - | |
| Quality of life (any antidepressant) - not reported | - | - | - | - | - | |
| Sedation (any antidepressant) - not reported | - | - | - | - | - | |
| Psychiatric hospitalization (any antidepressant) - not reported | - | - | - | - | - | |
| Global functioning (any antidepressant) - not reported | - | - | - | - | - | |
| weight gain, over 7% (any antidepressant) - not reported | - | - | - | - | - | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio
*Explanations: a. High risk of bias; b. Variation in intervention: dose, length of intervention and type of antidepressant, c. Wide confidence intervals; d. Variation in intervention; Dose and length of intervention; e. Only one study, f. Few participants (n=67) and 0 events*

**Evidence profile 8: Antidepressiva compared to for Bipolar 1 and 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Placebo** | **Antidepressiva** | **Difference** |

| | | | | |
|---|---|---|---|---|
| New episode, any type<br>№ of participants: 179<br>(2 studies) | **RR 0.69**<br>(0.26 to 1.85) | 28.4% | **19.6%**<br>(-- to --) | **8.8% fewer**<br>(21.0% fewer to 24.1% more) |
| New episode, any type - Fluoxetin<br>№ of participants: 110<br>(1 study) | **RR 0.40**<br>(0.17 to 0.95) | 27.3% | **10.9%**<br>(-- to --) | **16.4% fewer**<br>(22.6% fewer to 1.4% fewer) |
| New episode, any type - Tianeptine<br>№ of participants: 69<br>(1 study) | **RR 1.10**<br>(0.55 to 2.20) | 30.3% | **33.3%**<br>(-- to --) | **3.0% more**<br>(13.6% fewer to 36.4% more) |
| New episode, depression<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania<br>№ of participants: 110<br>(1 study) | **RR 3.00**<br>(0.12 to 72.08) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| New episode, hypomania<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mixed<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause<br>№ of participants: 179<br>(2 studies) | **RR 1.00**<br>(0.52 to 1.93) | 26.1% | **26.1%**<br>(-- to --) | **0.0% fewer**<br>(12.5% fewer to 24.3% more) |
| Withdrawal, any cause - Fluxetin<br>№ of participants: 110<br>(1 study) | **RR 0.76**<br>(0.41 to 1.42) | 30.9% | **23.5%**<br>(-- to --) | **7.4% fewer**<br>(18.2% fewer to 13.0% more) |
| Withdrawal, any cause - Tianeptine<br>№ of participants: 69<br>(1 study) | **RR 1.53**<br>(0.62 to 3.74) | 18.2% | **27.8%**<br>(-- to --) | **9.6% more**<br>(6.9% fewer to 49.8% more) |
| Serious adverse events (SAE), risk diff<br>№ of participants: 110<br>(1 study) | not estimable | 0.0% | **-5.0%**<br>(-12 to 1) | **5.0% fewer**<br>(12.0% fewer to 1.0% more) |
| Suicidal behaviour<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

| | | | | |
|---|---|---|---|---|
| Quality of life<br>№ of participants: 84<br>(1 study) | - | - | - | MD **7.2 higher**<br>(0.36 higher to 14.04 higher) |
| Sedation<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Psychiatric hospitalization<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Global functioning<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Weight gain, over 7%<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

## Antikonvulsiva vs. placebo

Otte forsøg i alt sammenlignede behandling med et antidepressivum med placebo [6, 8, 31, 47, 49]. Fire forsøg undersøgte lamotrigin [8, 47, 49], tre forsøg undersøgte valproat [6, 31] og ét forsøg undersøgte oxcarbazepine [17]. Seks af forsøgene inkluderede udelukkende patienter med bipolar lidelse type 1 og tre forsøg inkluderede en blandingspopulation af deltagere med bipolar lidelse 1 og 2. I alle forsøgene blev anvendt et beriget diskontinuationsdesign. Forsøgene er beskrevet i afsnit 1.1, og resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 9 og 10**).

*Bipolar type 1*

For det kritiske outcome *ny episode af enhver type* omfattede evidensen 1.226 deltagere fra fem forsøg [6, 8, 31, 47, 49]. Resultaterne viste at det er meget usikkert, om antikonvulsiva øger eller nedsætter antallet af patienter med ny episode af enhver type sammenlignet med placebo (RR 0,82; 95 % CI 0,70 til 0,96). Absolut svarer dette til 95 færre patienter med ny episode pr. 1.000 behandlede (fra 159 færre til 21 færre). Tiltroen til evidensen var dog meget lav.

For *ny depressiv episode* (kritisk outcome) viste fem forsøg med 1.226 deltagere at det er meget usikkert, om antikonvulsiva øger eller nedsætter antallet af patienter med ny episode, depression (RR 0,76; 95 % CI 0,55 til 1,04) [6, 8, 31, 47, 49]. Dette svarer til 70 færre tilfælde pr. 1.000 behandlede (fra 131 færre til 12 flere). Tiltroen til evidensen var meget lav.

For *ny manisk episode* omfattede evidensen ligeledes 1.226 deltagere fra fem forsøg [6, 8, 31, 47, 49]. Resultaterne tydede på, at antikonvulsiva muligvis ikke reducerer risikoen for *ny manisk episode* (RR: 0,86 (95 % CI 0,70 til 1,05)) i betydelig grad, svarende til 36 færre tilfælde pr. 1.000 behandlede (fra 77 færre til 13 flere). Tiltroen til evidensen var lav.

For *frafald af alle årsager* omfattede evidensen 1.236 deltagere fra fem forsøg [6, 8, 31, 47, 49]. Der sås ingen væsentlig forskel mellem grupperne (RR 1,03; 95 % CI 0,84 til 1,27). Dette svarer til 7 flere patienter med frafald pr. 1.000 behandlede (fra 39 færre til 64 flere). Tiltroen til evidensen var lav. Samlet set er det usikkert, om antikonvulsiva øger eller nedsætter antallet af patienter med frafald af alle årsager.

For *alvorlige uønskede hændelser (SAE)* omfattede evidensen 484 deltagere fra to forsøg [31, 47]. Antikonvulsiva var associeret med RR 0,76 (95 % CI 0,27 til 2,14), svarende til 8 færre tilfælde pr. 1.000 behandlede (fra 24 færre til 37 flere). Tiltroen til evidensen var lav, og resultaterne tydede på, at antikonvulsiva muligvis ikke påvirker antallet af patienter med alvorlige hændelser i betydelig grad.

For *selvmordsadfærd* omfattede evidensen 901 deltagere fra fire forsøg [8, 31, 47, 49]. Estimatet kunne ikke beregnes på grund af meget få hændelser. Tiltroen til evidensen var lav, og det er usikkert, om antikonvulsiva øger eller nedsætter antallet af patienter med selvmordsadfærd.

For *sedation* omfattede evidensen 963 deltagere fra fire forsøg [6, 8, 47, 49]. Resultaterne viste, at antikonvulsiva muligvis ikke påvirker antallet af patienter med sedation i betydelig grad sammenlignet med placebo (RR 1,21 (95 % CI 0,91 til 1,62)), svarende til 23 flere tilfælde pr. 1.000 behandlede (fra 10 færre til 70 flere). Tiltroen til evidensen var lav.

For *psykiatrisk indlæggelse* omfattede evidensen ét forsøg [31], og resultaterne viste, at det er meget usikkert, om antikonvulsiva reducerer eller øger antallet af patienter med psykiatrisk

indlæggelse RR 0,73 (95 % CI 0,40 til 1,31), svarende til 54 færre indlæggelser pr. 1.000 behandlede (fra 120 færre til 62 flere). Tiltroen til evidensen var meget lav.

For *global funktionsevne* omfattede evidensen ét forsøg med 220 deltagere [31] og resultaterne viste at det er meget usikkert, om antikonvulsiva forbedrer eller forværrer globalt funktionsniveau MD 0,9 point lavere (95 % CI 4,65 lavere til 2,85 højere). Tiltroen til evidensen var meget lav, og d

For *vægtøgning over 7 %* viste resultaterne, at antikonvulsiva muligvis øger antallet af patienter med en vægtøgning over 7 %, men evidensen er usikker (RR 2,25; 95 % CI 1,03 til 4,90). Dette svarer til 66 flere patienter med vægtøgning pr. 1.000 behandlede (fra 1 flere til 206 flere), idet risikoen steg fra 53 pr. 1.000 til 119 pr. 1.000. Tiltroen til evidensen var meget lav.

Der blev ikke rapporteret data for *ny episode, hypomani* eller *ny blandingsepisode*.

*Bipolar type 2*
Der blev ikke identificeret evidens til at vurdere effekten af antikonvulsiva sammenlignet med placebo til voksne med bipolar *type II*. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antipsykotikas gavnlige eller skadelige effekter hos voksne med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

*Bipolar type 1 & 2*
Tre forsøg sammenlignede effekten af antikonvulsiva overfor placebo [7]. Se **tabel 1** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 10**).

**Evidence profile 9: Anticonvulsiva compared to Placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Placebo | Anticonvulsiva | Difference | | |
| New episode, any type (Any anticonvulsiva)<br>№ of participants: 1226<br>(5 RCTs) | **RR 0.82**<br>(0.70 to 0.96) | 53.0% | **43.4%**<br>(-- to --) | **9.5% fewer**<br>(15.9% fewer to 2.1% fewer) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om antikonvulsiva øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, any type - Valproate<br>№ of participants: 501<br>(2 RCTs) | **RR 0.78**<br>(0.54 to 1.11) | 49.5% | **38.6%**<br>(-- to --) | **10.9% fewer**<br>(22.8% fewer to 5.4% more) | ⊕◯◯◯<br>Very low[a,c,d] | Valproat kan muligvis reducere antallet af patienter med ny episode af enhver type, men evidensen er usikker |
| New episode, any type - Lamotrigine<br>№ of participants: 725<br>(3 RCTs) | **RR 0.83**<br>(0.68 to 1.02) | 55.1% | **45.8%**<br>(-- to --) | **9.4% fewer**<br>(17.6% fewer to 1.1% more) | ⊕◯◯◯<br>Very low[a,c,e] | Det er meget usikkert om lamotrigin øger eller nedsætter antallet af patienter med ny episode af enhver type |
| New episode, depression (Any anticonvulsiva)<br>№ of participants: 1226<br>(5 RCTs) | **RR 0.76**<br>(0.55 to 1.04) | 29.1% | **22.1%**<br>(-- to --) | **7.0% fewer**<br>(13.1% fewer to 1.2% more) | ⊕◯◯◯<br>Very low[a,b,c,f] | Det er meget usikkert om antikonvulsiva øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Valproate<br>№ of participants: 501<br>(2 RCTs) | **RR 0.70**<br>(0.26 to 1.90) | 24.5% | **17.2%**<br>(-- to --) | **7.4% fewer**<br>(18.1% fewer to 22.1% more) | ⊕◯◯◯<br>Very low[a,b,c,f] | Det er meget usikkert om valproat øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, depression - Lamotrigine<br>№ of participants: 725<br>(3 RCTs) | **RR 0.77**<br>(0.56 to 1.05) | 32.1% | **24.7%**<br>(-- to --) | **7.4% fewer**<br>(14.1% fewer to 1.6% more) | ⊕◯◯◯<br>Very low[a,c,e] | Det er meget usikkert om lamotrigin øger eller nedsætter antallet af patienter med ny episode, depression |
| New episode, mania (Any anticonvulsiva)<br>№ of participants: 1226<br>(5 RCTs) | **RR 0.86**<br>(0.70 to 1.05) | 25.7% | **22.1%**<br>(-- to --) | **3.6% fewer**<br>(7.7% fewer to 1.3% more) | ⊕⊕◯◯<br>Low[a,e] | Antikonvulsiva reducerer muligvis ikke risikoen for ny manisk episode i betydelig grad |
| New episode, mania - Valproate<br>№ of participants: 501<br>(2 RCTs) | **RR 0.77**<br>(0.56 to 1.04) | 29.9% | **23.0%**<br>(-- to --) | **6.9% fewer**<br>(13.2% fewer to 1.2% more) | ⊕◯◯◯<br>Very low[a,b,c] | Det er meget usikkert om valproat øger eller nedsætter antallet af patienter med ny episode, mani |

| | | | | | | |
|---|---|---|---|---|---|---|
| New episode, mania - Lamotrigine<br>№ of participants: 725<br>(3 RCTs) | **RR 0.94**<br>(0.71 to 1.24) | 23.1% | **21.7%**<br>(-- to --) | **1.4% fewer**<br>(6.7% fewer to 5.5% more) | ⊕⊕◯◯<br>Low[a,c] | Lamotrigin reducerer muligvis ikke risikoen for ny manisk episode. |
| New episode, mixed (Any anticonvulsiva) - not reported | - | - | - | - | - | |
| New episode, hypomania (Any anticonvulsiva) - not reported | - | - | - | - | - | |
| Withdrawal, any cause (Any anticonvulsiva)<br>№ of participants: 1236<br>(5 RCTs) | **RR 1.03**<br>(0.84 to 1.27) | 24.1% | **24.8%**<br>(-- to --) | **0.7% more**<br>(3.8% fewer to 6.5% more) | ⊕⊕◯◯<br>Low[a,b] | Det er usikkert om antikonvulssiva øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Valproate<br>№ of participants: 501<br>(2 RCTs) | **RR 0.99**<br>(0.75 to 1.30) | 28.4% | **28.1%**<br>(-- to --) | **0.3% fewer**<br>(7.1% fewer to 8.5% more) | ⊕⊕◯◯<br>Low[a,b] | Det er usikkert om valproat øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Withdrawal, any cause - Lamotrigine<br>№ of participants: 735<br>(3 RCTs) | **RR 1.19**<br>(0.76 to 1.86) | 21.3% | **25.3%**<br>(-- to --) | **4.0% more**<br>(5.1% fewer to 18.3% more) | ⊕◯◯◯<br>Very low[a,c,e,f] | Det er meget usikkert om lamotrigin øger eller nedsætter antallet af patienter med frafald af alle årsager |
| Serious adverse events (SAE) (Any anticonvulsiva)<br>№ of participants: 484<br>(2 RCTs) | **RR 0.76**<br>(0.27 to 2.14) | 3.3% | **2.5%**<br>(-- to --) | **0.8% fewer**<br>(2.4% fewer to 3.8% more) | ⊕⊕◯◯<br>Low[a,b] | Antikonvulsiva påvirker muligvis ikke antallet af patienter med alvorlige hændelser i betydelig grad |
| Serious adverse events (SAE) - Valproate<br>№ of participants: 220<br>(1 RCT) | **RR 0.80**<br>(0.22 to 2.90) | 4.5% | **3.6%**<br>(-- to --) | **0.9% fewer**<br>(3.5% fewer to 8.6% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om valproat øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Serious adverse events (SAE) - Lamotrigine<br>№ of participants: 264<br>(1 RCT) | **RR 0.68**<br>(0.11 to 3.99) | 2.3% | **1.5%**<br>(-- to --) | **0.7% fewer**<br>(2.0% fewer to 6.7% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om lamotrigin øger eller nedsætter antallet af patienter med alvorlige hændelser |
| Suicidal behaviour (Any anticonvulsiva)<br>№ of participants: 901<br>(4 RCTs) | not estimable | 0.2% | **0.2%**<br>(-0.8 to 1.2) | **0.0% fewer**<br>(1.0% fewer to 1.0% more) | ⊕⊕◯◯<br>Low[a,b] | Det er usikkert om antikonvulsiva øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Valproate<br>№ of participants: 220<br>(1 RCT) | not estimable | 0.0% | **0.0%**<br>(-2 to 2) | **0.0% fewer**<br>(2.0% fewer to 2.0% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om valproat øger eller nedsætter antallet af patienter med selvmordsadfærd |
| Suicidal behaviour - Lamotrigine<br>№ of participants: 681<br>(3 RCTs) | not estimable | 0.3% | **0.3%**<br>(-1.7 to 1.3) | **0.0% fewer**<br>(2.0% fewer to 1.0% more) | ⊕⊕◯◯<br>Low[a,e] | Det er usikkert om lamotrigin øger eller nedsætter antallet af patienter med selvmordsadfærd |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sedation (Any anticonvulsiva)<br>№ of participants: 963<br>(4 RCTs) | **RR 1.21**<br>(0.91 to 1.62) | 11.3% | **13.6%**<br>(-- to --) | **2.4% more**<br>(1.0% fewer to 7.0% more) | ⊕⊕◯◯<br>Low[a,b] | Antikonvulsiva påvirker muligvis ikke antallet af patienter med sedation i betydelig grad |
| Sedation - Valproate<br>№ of participants: 281<br>(1 RCT) | **RR 1.19**<br>(0.86 to 1.64) | 35.1% | **41.8%**<br>(-- to --) | **6.7% more**<br>(4.9% fewer to 22.5% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om valproat øger eller nedsætter antallet af patienter med sedation |
| Sedation - Lamotrigine<br>№ of participants: 682<br>(3 RCTs) | **RR 1.33**<br>(0.69 to 2.59) | 4.3% | **5.8%**<br>(-- to --) | **1.4% more**<br>(1.3% fewer to 6.9% more) | ⊕⊕◯◯<br>Low[a,b] | Lamotrigin påvirker muligvis ikke antallet af patienter med sedation i betydelig grad |
| Psychiatric hospitalization (Any anticonvulsiva)<br>№ of participants: 220<br>(1 RCT) | **RR 0.73**<br>(0.40 to 1.31) | 20.0% | **14.6%**<br>(-- to --) | **5.4% fewer**<br>(12.0% fewer to 6.2% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om antikonvulsiva reducerer eller øger antallet af patienter med psykiatrisk indlæggelse |
| Psychiatric hospitalization - Valproate<br>№ of participants: 220<br>(1 RCT) | **RR 0.73**<br>(0.40 to 1.31) | 20.0% | **14.6%**<br>(-- to --) | **5.4% fewer**<br>(12.0% fewer to 6.2% more) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om valproat reducerer eller øger antallet af patienter med psykiatrisk indlæggelse |
| Global functioning (Any anticonvulsiva)<br>№ of participants: 220<br>(1 RCT) | - | - | - | MD **0.9 lower**<br>(4.65 lower to 2.85 higher) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om antikonvulsiva forbedrer eller forværrer globalt funktionsniveau |
| Global functioning - Valproate<br>№ of participants: 220<br>(1 RCT) | - | - | - | MD **0.9 lower**<br>(4.65 lower to 2.85 higher) | ⊕◯◯◯<br>Very low[a,g] | Det er meget usikkert om valproat forbedrer eller forværrer globalt funktionsniveau |
| Weight gain, over 7% (Any anticonvulsiva)<br>№ of participants: 698<br>(3 RCTs) | **RR 2.25**<br>(1.03 to 4.90) | 5.3% | **11.9%**<br>(-- to --) | **6.6% more**<br>(0.2% more to 20.6% more) | ⊕◯◯◯<br>Very low[a,c,e] | Antikonvulsiva øger muligvis antallet af patienter med en vægtøgning over 7% men evidensen er usikker |
| Weight gain, over 7% - Valproate<br>№ of participants: 281<br>(1 RCT) | **RR 2.80**<br>(1.30 to 6.02) | 7.4% | **20.9%**<br>(-- to --) | **13.4% more**<br>(2.2% more to 37.4% more) | ⊕◯◯◯<br>Very low[a,g] | Valproat øger muligvis antallet af patienter med en vægtøgning over 7% men evidensen er usikker |
| Weight gain, over 7% - Lamotrigine<br>№ of participants: 417<br>(2 RCTs) | **RR 2.28**<br>(0.44 to 11.82) | 4.2% | **9.6%**<br>(-- to --) | **5.4% more**<br>(2.4% fewer to 45.6% more) | ⊕◯◯◯<br>Very low[a,c,h] | Det er meget usikkert om lamotrigin øger eller nedsætter antallet af patienter med vægtøgning over 7% |
| Quality of life (Any anticonvulsiva) - not reported | - | - | - | - | - | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations: a. High risk of bias; b. Intervention: variation in medication, dose combination; c. Wide confidence intervals; d. Intervention: Variation in dose and duration; e. Intervention: Variation in duration and dose;f. Variation in point estimates with inconsistent magnitude of effect; g. Only one study; h. I2=57%

**Evidence profile 10: Anticonvulsiva compared to placebo for Bipolar 1 and 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Placebo** | **Anticonvulsiva** | **Difference** |
| New episode, any type<br>№ of participants: 318<br>(3 studies) | **RR 0.75**<br>(0.60 to 0.94) | 65.2% | **48.9%**<br>(-- to --) | **16.3% fewer**<br>(26.1% fewer to 3.9% fewer) |
| New episode, any type - Valproate<br>№ of participants: 86<br>(1 study) | **RR 0.65**<br>(0.48 to 0.87) | 86.7% | **56.3%**<br>(-- to --) | **30.3% fewer**<br>(45.1% fewer to 11.3% fewer) |
| New episode, any type - Lamotrigine<br>№ of participants: 177<br>(1 study) | **RR 0.89**<br>(0.67 to 1.17) | 56.3% | **50.1%**<br>(-- to --) | **6.2% fewer**<br>(18.6% fewer to 9.6% more) |

| | | | | |
|---|---|---|---|---|
| New episode, any type - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 0.66**<br>(0.37 to 1.17) | 58.6% | **38.7%**<br>(-- to --) | **19.9% fewer**<br>(36.9% fewer to 10.0% more) |
| New episode, depression<br>№ of participants: 141<br>(2 studies) | **RR 0.62**<br>(0.42 to 0.91) | 52.7% | **32.7%**<br>(-- to --) | **20.0% fewer**<br>(30.6% fewer to 4.7% fewer) |
| New episode, depression - Valproate<br>№ of participants: 86<br>(1 study) | **RR 0.66**<br>(0.44 to 0.99) | 66.7% | **44.0%**<br>(-- to --) | **22.7% fewer**<br>(37.3% fewer to 0.7% fewer) |
| New episode, depression - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 0.37**<br>(0.11 to 1.23) | 31.0% | **11.5%**<br>(-- to --) | **19.6% fewer**<br>(27.6% fewer to 7.1% more) |
| New episode, mania<br>№ of participants: 141<br>(2 studies) | **RR 0.58**<br>(0.28 to 1.22) | 23.0% | **13.3%**<br>(-- to --) | **9.6% fewer**<br>(16.5% fewer to 5.1% more) |
| New episode, mania - Valproate<br>№ of participants: 86<br>(1 study) | **RR 0.61**<br>(0.22 to 1.67) | 20.0% | **12.2%**<br>(-- to --) | **7.8% fewer**<br>(15.6% fewer to 13.4% more) |
| New episode, mania - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 0.56**<br>(0.19 to 1.64) | 27.6% | **15.4%**<br>(-- to --) | **12.1% fewer**<br>(22.3% fewer to 17.7% more) |
| New episode, mixed<br>№ of participants: 55<br>(1 study) | **RR 1.12**<br>(0.07 to 16.95) | 3.4% | **3.9%**<br>(-- to --) | **0.4% more**<br>(3.2% fewer to 55.0% more) |
| New episode, mixed - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 1.12**<br>(0.07 to 16.95) | 3.4% | **3.9%**<br>(-- to --) | **0.4% more**<br>(3.2% fewer to 55.0% more) |

| | | | | |
|---|---|---|---|---|
| Withdrawal, any cause<br>№ of participants: 323<br>(3 studies) | **RR 1.05**<br>(0.59 to 1.87) | 22.1% | **23.2%**<br>(-- to --) | **1.1% more**<br>(9.1% fewer to 19.2% more) |
| Withdrawal, any cause - Valproate<br>№ of participants: 86<br>(1 study) | **RR 1.71**<br>(0.83 to 3.52) | 20.0% | **34.2%**<br>(-- to --) | **14.2% more**<br>(3.4% fewer to 50.4% more) |
| Withdrawal, any cause - Lamotrigine<br>№ of participants: 182<br>(1 study) | **RR 0.62**<br>(0.31 to 1.25) | 19.1% | **11.8%**<br>(-- to --) | **7.3% fewer**<br>(13.2% fewer to 4.8% more) |
| Withdrawal, any cause - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 1.12**<br>(0.55 to 2.24) | 34.5% | **38.6%**<br>(-- to --) | **4.1% more**<br>(15.5% fewer to 42.8% more) |
| New episode, hypomania<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE)<br>№ of participants: 321<br>(3 studies) | **RR 0.88**<br>(0.24 to 3.13) | 3.1% | **2.7%**<br>(-- to --) | **0.4% fewer**<br>(2.3% fewer to 6.6% more) |
| Serious adverse events (SAE) - Valproate<br>№ of participants: 86<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Serious adverse events (SAE) - Lamotrigine<br>№ of participants: 180<br>(1 study) | **RR 0.48**<br>(0.04 to 5.18) | 2.3% | **1.1%**<br>(-- to --) | **1.2% fewer**<br>(2.2% fewer to 9.5% more) |
| Serious adverse events (SAE) - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 1.12**<br>(0.25 to 5.05) | 10.3% | **11.6%**<br>(-- to --) | **1.2% more**<br>(7.8% fewer to 41.9% more) |

| | | | | |
|---|---|---|---|---|
| Serious adverse events (SAE), risk diff<br>№ of participants: 321<br>(3 studies) | not estimable | 3.1% | **4.1%**<br>(1.1 to 6.1) | **1.0% more**<br>(2.0% fewer to 3.0% more) |
| Serious adverse events (SAE), risk diff - Valproate<br>№ of participants: 86<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-4 to 4) | **0.0% fewer**<br>(4.0% fewer to 4.0% more) |
| Serious adverse events (SAE), risk diff - Lamotrigine<br>№ of participants: 180<br>(1 study) | not estimable | 2.3% | **3.3%**<br>(-0.7 to 7.3) | **1.0% more**<br>(3.0% fewer to 5.0% more) |
| Serious adverse events (SAE), risk diff - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | not estimable | 10.3% | **9.3%**<br>(-7.7 to 25.3) | **1.0% fewer**<br>(18.0% fewer to 15.0% more) |
| Suicidal behaviour<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Psychiatric hospitalization<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Global functioning<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |
| Weigt gain, over 7%<br>№ of participants: 55<br>(1 study) | **RR 2.79**<br>(0.59 to 13.16) | 6.9% | **19.2%**<br>(-- to --) | **12.3% more**<br>(2.8% fewer to 83.9% more) |
| Weigt gain, over 7% - Oxcarbazepine<br>№ of participants: 55<br>(1 study) | **RR 2.79**<br>(0.59 to 13.16) | 6.9% | **19.2%**<br>(-- to --) | **12.3% more**<br>(2.8% fewer to 83.9% more) |

## 1.4 Resultater fra parvise metaanalyser, aktive interventioner

15 forsøg sammenlignngede to aktive interventioner overfor hinanden [6, 8, 9, 14, 18, 25-27, 29, 31, 33, 37, 38, 44, 49]. Se **tabel 1** for karakteristika af de inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 11-13**).

### *Litihium vs. Antikonvulsiva*

*Bipolar type 1*
Fire forsøg sammenlignede effekten af lithium med antikonvulsiva i form af valproat eller lamotrigin [6, 8, 31, 49]. Se **tabel 1** for karakteristika af de inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 11**).

*Bipolar type 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antikonvulsiva.

*Bipolar type 1 & 2*
Fire forsøg sammenlignede effekten af lithium med antikonvulsiva i form af valproat eller carbamazepine [9, 33, 37, 38]. Se **tabel 1** for karakteristika af de inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 11**).

### *Litihium vs. Antipsykotika*

*Bipolar type 1*
Tre forsøg sammenlignede effekten af lithium med antipsykotika i form af quetiapin eller olanzapine [14, 18, 44]. Se **tabel 1** for karakteristika af de inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 12**).

*Bipolar type 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antipsykotika.

*Bipolar type 1 & 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antipsykotika.

### *Litihium vs. Antidepressive*

*Bipolar type 1*
To forsøg sammenlignede effekten af lithium med antidepressiva i form af imipramin. Se **tabel 1** for karakteristika af de inkluderede forsøg [27, 29]. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 13**).

*Bipolar type 2*
To forsøg sammenlignede effekten af lithium med antidepressive i form af imipramin eller fluoxetin. Se **tabel 1** for karakteristika af de inkluderede forsøg [25, 26]. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 13)**.

*Bipolar type 1 & 2*

Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antidepressive.

**Evidence profile 11: Lithium compared to Anticonvulsiva_subgroup bipolar type**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Anticonvulsiva** | **Lithium** | **Difference** |
| New episode, any type - Bipolar 1<br>№ of participants: 935<br>(4 studies) | **RR 0.90**<br>(0.78 to 1.05) | 46.3% | **41.7%**<br>(-- to --) | **4.6% fewer**<br>(10.2% fewer to 2.3% more) |
| New episode, any type - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, any type - Bipolar 1 og 2<br>№ of participants: 315<br>(4 studies) | **RR 0.86**<br>(0.56 to 1.32) | 45.6% | **39.2%**<br>(-- to --) | **6.4% fewer**<br>(20.1% fewer to 14.6% more) |
| New episode, depression - Bipolar 1<br>№ of participants: 935<br>(4 studies) | **RR 1.03**<br>(0.72 to 1.48) | 25.8% | **26.6%**<br>(-- to --) | **0.8% more**<br>(7.2% fewer to 12.4% more) |
| New episode, depression - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, depression - Bipolar 1 og 2<br>№ of participants: 113<br>(2 studies) | **RR 0.68**<br>(0.17 to 2.66) | 29.3% | **19.9%**<br>(-- to --) | **9.4% fewer**<br>(24.3% fewer to 48.7% more) |
| New episode, mania - Bipolar 1<br>№ of participants: 935<br>(4 studies) | **RR 0.75**<br>(0.52 to 1.09) | 24.6% | **18.4%**<br>(-- to --) | **6.1% fewer**<br>(11.8% fewer to 2.2% more) |
| New episode, mania - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania - Bipolar 1 og 2<br>№ of participants: 113<br>(2 studies) | **RR 0.27**<br>(0.06 to 1.25) | 13.8% | **3.7%**<br>(-- to --) | **10.1% fewer**<br>(13.0% fewer to 3.4% more) |
| New episode, hypomania - Bipolar 1<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, hypomania - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

**Evidence profile 11: Lithium compared to Anticonvulsiva_subgroup bipolar type**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Anticonvulsiva** | **Lithium** | **Difference** |
| New episode, hypomania - Bipolar 1 og 2<br>№ of participants: 60<br>(1 study) | **RR 1.46**<br>(0.38 to 5.56) | 10.7% | **15.6%**<br>(-- to --) | **4.9% more**<br>(6.6% fewer to 48.9% more) |
| New episode, mixed<br>№ of participants: 60<br>(1 study) | **RR 2.64**<br>(0.11 to 62.23) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| New episode, mixed - Bipolar 1<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mixed - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mixed - Bipolar 1 og 2<br>№ of participants: 60<br>(1 study) | **RR 2.64**<br>(0.11 to 62.23) | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |
| Withdrawal, any cause - Bipolar 1<br>№ of participants: 945<br>(4 studies) | **RR 1.21**<br>(1.01 to 1.46) | 30.3% | **36.7%**<br>(-- to --) | **6.4% more**<br>(0.3% more to 14.0% more) |
| Withdrawal, any cause - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause - Bipolar 1 og 2<br>№ of participants: 315<br>(4 studies) | **RR 0.95**<br>(0.35 to 2.59) | 26.6% | **25.3%**<br>(-- to --) | **1.3% fewer**<br>(17.3% fewer to 42.3% more) |
| Serious adverse events (SAE) - Bipolar 1<br>№ of participants: 220<br>(1 study) | **RR 0.71**<br>(0.23 to 2.18) | 6.4% | **4.5%**<br>(-- to --) | **1.8% fewer**<br>(4.9% fewer to 7.5% more) |
| Serious adverse events (SAE) - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE) - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

**Evidence profile 11: Lithium compared to Anticonvulsiva_subgroup bipolar type**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Anticonvulsiva** | **Lithium** | **Difference** |
| Suicidal behaviour - Bipolar 1<br>№ of participants: 613<br>(3 studies) | **RR 0.42**<br>(0.02 to 10.04) | 0.3% | **0.1%**<br>(-- to --) | **0.2% fewer**<br>(0.3% fewer to 2.7% more) |
| Suicidal behaviour - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour - Bipolar 1 og 2<br>№ of participants: 171<br>(1 study) | **RR 0.11**<br>(0.01 to 2.01) | 4.7% | **0.5%**<br>(-- to --) | **4.2% fewer**<br>(4.7% fewer to 4.8% more) |
| Suicidal behaviour, risk diff - Bipolar 1<br>№ of participants: 613<br>(3 studies) | not estimable | 0.3% | **0.3%**<br>(-0.7 to 1.3) | **0.0% fewer**<br>(1.0% fewer to 1.0% more) |
| Suicidal behaviour, risk diff - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour, risk diff - Bipolar 1 og 2<br>№ of participants: 171<br>(1 study) | not estimable | 4.7% | **9.7%**<br>(4.7 to 14.7) | **5.0% more**<br>(0.0% fewer to 10.0% more) |
| Sedation - Bipolar 1<br>№ of participants: 675<br>(3 studies) | **RR 0.99**<br>(0.51 to 1.94) | 23.9% | **23.6%**<br>(-- to --) | **0.2% fewer**<br>(11.7% fewer to 22.4% more) |
| Sedation - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation - Bipolar 1 og 2<br>№ of participants: 60<br>(1 study) | **RR 1.75**<br>(0.17 to 18.28) | 3.6% | **6.3%**<br>(-- to --) | **2.7% more**<br>(3.0% fewer to 61.7% more) |
| Psychiatric hospitalization - bipolar 1<br>№ of participants: 220<br>(1 study) | **RR 0.88**<br>(0.53 to 1.46) | 22.7% | **20.0%**<br>(-- to --) | **2.7% fewer**<br>(10.7% fewer to 10.5% more) |
| Psychiatric hospitalization - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

**Evidence profile 11: Lithium compared to Anticonvulsiva_subgroup bipolar type**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Anticonvulsiva** | **Lithium** | **Difference** |
| Psychiatric hospitalization - Bipolar 1 og 2<br>№ of participants: 171<br>(1 study) | **RR 1.15**<br>(0.73 to 1.82) | 28.2% | **32.5%**<br>(-- to --) | **4.2% more**<br>(7.6% fewer to 23.2% more) |
| Weigt gain, over 7% - Bipolar 1<br>№ of participants: 672<br>(3 studies) | **RR 0.87**<br>(0.50 to 1.51) | 13.8% | **12.0%**<br>(-- to --) | **1.8% fewer**<br>(6.9% fewer to 7.0% more) |
| Weigt gain, over 7% - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Weigt gain, over 7% - Bipolar 1 og 2<br>№ of participants: 60<br>(1 study) | **RR 0.88**<br>(0.06 to 13.35) | 3.6% | **3.1%**<br>(-- to --) | **0.4% fewer**<br>(3.4% fewer to 44.1% more) |

**Evidence profile 12: Lithium compared to Antipsychotics_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antipsychotics_subgroup bipolar type** | **Lithium** | **Difference** |
| New episode, any type - Bipolar 1<br>№ of participants: 1199<br>(2 studies) | **RR 1.21**<br>(1.01 to 1.46) | 24.5% | **29.6%**<br>(-- to --) | **5.1% more**<br>(0.2% more to 11.3% more) |
| New episode, any type - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, any type - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, depression - Bipolar 1<br>№ of participants: 431<br>(1 study) | **RR 0.69**<br>(0.42 to 1.12) | 15.7% | **10.8%**<br>(-- to --) | **4.9% fewer**<br>(9.1% fewer to 1.9% more) |

**Evidence profile 12: Lithium compared to Antipsychotics_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antipsychotics_subgroup bipolar type** | **Lithium** | **Difference** |
| New episode, depression - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, depression - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania - Bipolar 1<br>№ of participants: 431<br>(1 study) | **RR 1.69**<br>(1.12 to 2.55) | 13.8% | **23.4%**<br>(-- to --) | **9.5% more**<br>(1.7% more to 21.4% more) |
| New episode, mania - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mixed - Bipolar 1<br>№ of participants: 431<br>(1 study) | **RR 10.14**<br>(1.31 to 78.53) | 0.5% | **4.7%**<br>(-- to --) | **4.2% more**<br>(0.1% more to 35.7% more) |
| New episode, mixed - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mixed - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause - Bipolar 1<br>№ of participants: 1260<br>(3 studies) | **RR 1.35**<br>(1.07 to 1.69) | 25.9% | **35.0%**<br>(-- to --) | **9.1% more**<br>(1.8% more to 17.9% more) |
| Withdrawal, any cause - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE) - Bipolar 1<br>№ of participants: 768<br>(1 study) | **RR 2.22**<br>(0.77 to 6.43) | 1.2% | **2.7%**<br>(-- to --) | **1.5% more**<br>(0.3% fewer to 6.7% more) |

**Evidence profile 12: Lithium compared to Antipsychotics_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antipsychotics_subgroup bipolar type** | **Lithium** | **Difference** |
| Serious adverse events (SAE) - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE) - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour - Bipolar 1<br>№ of participants: 1199<br>(2 studies) | **RR 1.36**<br>(0.33 to 5.65) | 0.5% | **0.7%**<br>(-- to --) | **0.2% more**<br>(0.3% fewer to 2.2% more) |
| Suicidal behaviour - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Suicidal behaviour - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation - Bipolar 1<br>№ of participants: 822<br>(1 study) | **RR 1.93**<br>(1.23 to 3.03) | 6.4% | **12.4%**<br>(-- to --) | **6.0% more**<br>(1.5% more to 13.1% more) |
| Sedation - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Weigt gain, over 7% - Bipolar 1<br>№ of participants: 1253<br>(2 studies) | **RR 0.41**<br>(0.27 to 0.63) | 17.2% | **7.1%**<br>(-- to --) | **10.2% fewer**<br>(12.6% fewer to 6.4% fewer) |
| Weigt gain, over 7% - Bipolar 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Weigt gain, over 7% - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Global functioning - Bipolar 1<br>№ of participants: 40<br>(1 study) | - | - | - | MD **19.6 higher**<br>(8.23 higher to 30.97 higher) |

**Evidence profile 12: Lithium compared to Antipsychotics_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antipsychotics_subgroup bipolar type** | **Lithium** | **Difference** |
| Global functioning - Bipolar 2<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |
| Global functioning - Bipolar 1 og 2<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |
| Quality of life - Bipolar 1<br>№ of participants: 40<br>(1 study) | - | - | - | MD **0.6 lower**<br>(1.15 lower to 0.05 lower) |
| Quality of life - Bipolar 2<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |
| Quality of life - Bipolar 1 og 2<br>№ of participants: (0 studies) | - | not pooled | - | not pooled |

**Evidence profile 13: Lithium compared to Antidepressiva_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antidepressiva_subgroup bipolar type** | **Lithium** | **Difference** |
| New episode, any type - Bipolar 1<br>№ of participants: 109<br>(2 studies) | **RR 0.65**<br>(0.50 to 0.86) | 81.6% | **53.1%**<br>(-- to --) | **28.6% fewer**<br>(40.8% fewer to 11.4% fewer) |
| New episode, any type - Bipolar 2<br>№ of participants: 63<br>(2 studies) | **RR 1.09**<br>(0.36 to 3.32) | 45.5% | **49.5%**<br>(-- to --) | **4.1% more**<br>(29.1% fewer to 105.5% more) |
| New episode, any type - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

**Evidence profile 13: Lithium compared to Antidepressiva_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antidepressiva_subgroup bipolar type** | **Lithium** | **Difference** |
| New episode, depression - Bipolar 1<br>№ of participants: 78<br>(1 study) | **RR 1.03**<br>(0.50 to 2.10) | 27.8% | **28.6%**<br>(-- to --) | **0.8% more**<br>(13.9% fewer to 30.6% more) |
| New episode, depression - Bipolar 2<br>№ of participants: 63<br>(2 studies) | **RR 1.63**<br>(0.89 to 2.98) | 33.3% | **54.3%**<br>(-- to --) | **21.0% more**<br>(3.7% fewer to 66.0% more) |
| New episode, depression - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, mania - Bipolar 1<br>№ of participants: 78<br>(1 study) | **RR 0.50**<br>(0.27 to 0.90) | 52.8% | **26.4%**<br>(-- to --) | **26.4% fewer**<br>(38.5% fewer to 5.3% fewer) |
| New episode, mania - Bipolar 2<br>№ of participants: 9<br>(1 study) | **RR 0.40**<br>(0.02 to 7.82) | 20.0% | **8.0%**<br>(-- to --) | **12.0% fewer**<br>(19.6% fewer to 136.4% more) |
| New episode, mania - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, hypomania - Bipolar 1<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| New episode, hypomania - Bipolar 2<br>№ of participants: 63<br>(2 studies) | not estimable | 9.1% | **12.1%**<br>(-2.9 to 26.1) | **3.0% more**<br>(12.0% fewer to 17.0% more) |
| New episode, hypomania - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Withdrawal, any cause - Bipolar 1<br>№ of participants: 31<br>(1 study) | **RR 0.96**<br>(0.26 to 3.59) | 23.1% | **22.2%**<br>(-- to --) | **0.9% fewer**<br>(17.1% fewer to 59.8% more) |
| Withdrawal, any cause - Bipolar 2<br>№ of participants: 54<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-- to --) | **0.0% fewer**<br>(0.0% fewer to 0.0% fewer) |

**Evidence profile 13: Lithium compared to Antidepressiva_subgroup bipolar type for**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antidepressiva_subgroup bipolar type** | **Lithium** | **Difference** |
| Withdrawal, any cause - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE), risk difference - Bipolar 1<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Serious adverse events (SAE), risk difference - Bipolar 2<br>№ of participants: 54<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-7 to 7) | **0.0% fewer**<br>(7.0% fewer to 7.0% more) |
| Serious adverse events (SAE), risk difference - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation - Bipolar 1<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |
| Sedation - Bipolar 2<br>№ of participants: 54<br>(1 study) | **RR 1.08**<br>(0.47 to 2.45) | 28.6% | **30.9%**<br>(-- to --) | **2.3% more**<br>(15.1% fewer to 41.4% more) |
| Sedation - Bipolar 1 og 2<br>№ of participants: (0 studies) | not pooled | 0.0% | not pooled | not pooled |

# 2. Hvilket peroralt lægemiddel bør man anvende som vedligeholdelsesbehandling til børn og unge med bipolar lidelse

## 2.1 Litteratur

Søgningen efter systematiske oversigter identificerede et systematisk review omhandlende børn og unge med bipolar lidelse [53]. Fra dette reivew blev der inkluderet ét randomiseret forsøg omhandlende børn og unge med bipolar lidelse [54].

Vi foretog en opdaterende litteratursøgning efter primærstudier baseret på den seneste søgedato i det systematiske review af Diaz-Caneja et al. og fandt yderligere ét randomiseret forsøg [55].

På grund af det begrænsede antal forsøg omhandlende børn og unge med bipolar lidelse, valgte arbejdsgruppen at vurdere forsøget af Berk et al. [44], der var identificeret i den opdaterende søgning efter primær litteratur for voksne, med henblik på inklusion i evidensgrundlaget. Populationen i dette studie var unge med bipolar lidelse i alderen 15-25 år.

Forsøgene af Berk et al. (2017) og Findling et al. (2005) indgår i evidensgennemgangen men indgår ikke som grundlag for anbefalingen, da interventionen blev sammenlignet med en aktiv komparator frem for placebo.

Evidensgrundlaget for besvarelsen af det fokuserede spørgsmål består således af i alt ét randomiserede forsøg med i alt 31 inkluderede deltagere [55].

Tabel over studiekarakteristika kan ses nedenfor (**tabel 2**).

**Table 2.** Characteristics of included studies in children and adolescents.

| Author, year, country | Participants number randomized, mean age, (SD), females (%), bipolar type, index episode, problematic alcohol/substance abuse | Design, pre-randomization phase, tapering (duration), co-interventions and industry sponsorship | Randomization phase Interventions (of interest) and co interventions | Outcomes of interest |
|---|---|---|---|---|
| Included in the body of evidence | | | | |
| Findling 2019, USA | Number randomized = 31<br>Age in years: 12.0 (2.5)<br>Females: 32%<br>Bipolar type: type I (100%)<br>Index episode: mania/mixed episode<br>Problematic alcohol/substance abuse: not stated | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (≥ 0.6 mEq/L) for up to 24 weeks<br>Tapering of open label lithium: gradually, duration not described.<br>Sponsored by industry: partly, medicines provided by Abbott industries. | Lithium<br>Serum level of 0.6-1.2 mmol/L, max 1.4 mmol/L<br>Placebo<br>Placebo substitution<br>Duration of the interventions: 28 weeks | New episode, any type: Number of participants<br>SAE: Number of participants<br>Withdrawal, any cause: Number of participants<br>Suicidal related events: Number of participants<br>Weight gain: Mean+SD |
| Not included in the evidence to decision | | | | |
| Berk 2017, Australia | Number randomized = 61<br>Age in years: 21.4 (2.2)<br>Females: 11.5 %<br>Bipolar type: type I<br>Index episode: mania<br>Inclusion of participants with problematic alcohol/substance abuse: no information | RCT, to sites in Melbourne Australia<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label lithium (serum level of 0.8-1.0 mmol/liter) and open label quetiapine (dose determined by treating clinician) for 8-12 weeks<br>Tapering of open label drugs: gradually during weeks or months<br>Sponsored by industry: yes | Quetiapine<br>Dose determined by treating clinician<br>Lithium<br>Serum level of 0.6-0.8 mmol/liter<br>Duration of the interventions: 52 weeks | Withdrawal, any cause: Number of participants<br>Quality of life: Quality of Life Scale<br>Global functioning: Global assessment of Functioning (GAF) |
| Findling 2005, USA | Number randomized = 60<br>Age in years: 10.7 (3.6)<br>Females: 35.03%<br>Bipolar type: type I (91.7%) and type II (8.3%)<br>Index episode: mania/hypomania<br>Problematic alcohol/substance abuse: stated as exclusion criteria | RCT<br>Enriched discontinuation design: yes<br>Pre-randomization phase: open label combination with valproate (up to 20 mg/kg/day) and lithium (up to 30 mg/kg/day) for up to 20 weeks<br>Tapering of open label valproate or lithium: gradually over 8 weeks. | Valproate<br>Dose matching valproate serum concentration of 50-100 ug/mL.<br>Lithium<br>Serum level of 0.6-1.2 mmol/liter<br>Duration of the interventions: 76 weeks | New episode, any type: Number of participants<br>New episode, depression: Number of participants<br>New episode, mania: Number of participants<br>New episode, hypomania: Number of participants |

| | | | | |
|---|---|---|---|---|
| | | Sponsored by industry: partly, medicines provided by Abbott industries. | | Withdrawal, any cause: Number of participants<br>Psychiatric admission: Number of participants<br>Suicidal related events: Number of participants |

## 2.2 Gennemgang af evidensen

**Studiepopulation**
Studiepopulationen i forsøget af Findling et al. (2019) omfattede 31 børn og unge i alderen 7- 17 år med bipolar lidelse type 1 [55]. Heraf indgik 32% piger og 68% drenge, Forsøget inkluderede deltagere, hvor indeksepisoden forud for den stabile fase var mani eller blandingstilstand. Problematisk rusmiddelbrug var et eksklusionskriterie.

**Studiedesign**
Forsøget af Findling et al. (2019) havde et beriget, randomiseret, dobbeltblindet, placebokontrolleret diskontinuationsdesign. Efter en åben behandlingsfase med lithium blev kun deltagere, som opnåede klinisk respons og kunne tolerere behandlingen, randomiseret til fortsat lithiumbehandling eller placebo i vedligeholdelsesfasen. Forsøget angav industrifinansiering.

**Interventioner og sammenligning**
Interventionen bestod af oral lithiumbehandling med fleksibel dosering titreret til terapeutiske serum-lithiumkoncentrationer. Alle deltagere modtog lithium i en åben behandlingsfase, hvorefter deltagere med klinisk respons og stabil sygdomskontrol blev randomiseret til enten fortsat lithiumbehandling eller placebo i den dobbeltblindede vedligeholdelsesfase. Deltagere randomiseret til placebo fik gradvist seponeret lithium under blindede forhold og overgik herefter til placebo. Den randomiserede vedligeholdelsesfase varede op til 28 uger.

## 2.3 Resultater fra parvise metaanalyser, aktive interventioner sammenlignet med placebo

### Lithium vs. placebo

Der blev ikke identificeret evidens til at vurdere effekten af lithium sammenlignet med placebo til børn og unge med bipolar type 2. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antipsykotikas gavnlige eller skadelige effekter hos børn og unge med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

Der blev identificeret ét randomiseret, placebokontrolleret forsøg [55], der bidrog med evidens til belysning af effekten af lithium sammenlignet med placebo til børn og unge med bipolar type 1. Forsøget er beskrevet i afsnit 2.2, og resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor **(Evidensprofil 14)**.

Resultatet viste, at behandling med lithium til børn og unge med bipolar type 1 muligvis kan reducere risikoen for en *ny episode af enhver type*, men evidensen er meget usikker. Den relative risiko blev beregnet til 0.41 (95% CI: 0.18, 0.92). Tiltroen til evidensen er meget lav grundet alvorlig risiko for bias og meget alvorlig upræcist effektestimat (ét forsøg). Det er meget usikkert, om lithium øger eller reducerer antallet af personer med *alvorlige hændelser* (kritisk outcome). Der blev registreret én alvorlig hændelse blandt 17 deltagere i

lithiumgruppen og ingen alvorlige hændelser blandt 14 deltagere i placebogruppen. Tiltroen til evidensen er meget lav grundet alvorlig risiko for bias og meget alvorlig upræcist effektestimat (ét forsøg).

Resultaterne viste, at det er meget usikkert, om behandling med lithium påvirker *frafald af alle årsager*, antallet af patienter med selvmordsadfærd eller vægtøgning mere end 7% sammenlignet med placebo. Tiltroen til evidensen var meget lav for alle tre outcomes på grund af alvorlig risiko for bias og meget alvorlig upræcist effektestimat.

De vigtige outcomes *psykiatrisk indlæggelse, livskvalitet, global kognitiv funktion, sedation* og *nyrepåvirkning* blev ikke belyst i de inkluderede forsøg. **(Evidensprofil 14)**

**Evidence profile 14: Lithium compared to placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **Lithium** | **Difference** | | |
| New episode any type<br>№ of participants: 31<br>(1 RCT) | **RR 0.41**<br>(0.18 to 0.92) | 71.4% | **29.3%**<br>(-- to --) | **42.1% fewer**<br>(58.6% fewer to 5.7% fewer) | ⊕◯◯◯<br>Very low[a,b] | Lithium kan muligvis reducere antallet af patienter med ny episode, enhver type, men evidensen er meget usikker |
| Serious adverse events (SAE) - Risk Diff<br>№ of participants: 31<br>(1 RCT) | not estimable | 0.0% | **6.0%**<br>(-22 to 10) | **6.0% more**<br>(22.0% fewer to 10.0% more) | ⊕◯◯◯<br>Very low[a,b] | Det er meget usikkert om lithium øger eller reducerer antallet af personer med alvorlige hændelser |
| Withdrawal, any cause<br>№ of participants: 31<br>(1 RCT) | **RR 0.82**<br>(0.13 to 5.12) | 14.3% | **17.3%**<br>(-6.7 to 40.3) | **3.0% more**<br>(21.0% fewer to 26.0% more) | ⊕◯◯◯<br>Very low[a,b] | Det er meget usikkert om lithium øger eller reducerer antallet af personer med frafald alle årsager |
| Suicidal behaviour - Risk Diff<br>№ of participants: 31<br>(1 RCT) | not estimable | 0.0% | **0.0%**<br>(-12 to 12) | **0.0% fewer**<br>(12.0% fewer to 12.0% more) | ⊕◯◯◯<br>Very low[a,b] | Det er meget usikkert om lithium øger eller reducerer antallet af personer med selvmordsadfærd |
| Weight gain<br>№ of participants: 31<br>(1 RCT) | - | The mean weight gain without Lithium was **1.7** kg | - | MD **0.1 kg higher**<br>(2.62 lower to 2.82 higher) | ⊕◯◯◯<br>Very low[a,b] | Det er meget usikkert om lithium medfører vægtøgning |
| New episode, depression - not reported | - | - | - | - | - | |
| New episode, mania - not reported | - | - | - | - | - | |
| Quality of life - not reported | - | - | - | - | - | |
| New episode, mixed - not reported | - | - | - | - | - | |
| New episode, mania - not reported | - | - | - | - | - | |
| Sedation - not reported | - | - | - | - | - | |
| Global functioning - not reported | - | - | - | - | - | |

**Evidence profile 14: Lithium compared to placebo for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **Lithium** | **Difference** | | |
| Psychiatric hospitalization - not reported | - | - | - | - | - | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio
*Explanations. a. High risk of bias, b. Only one study*

### Antipsykotika vs. placebo
Der blev ikke identificeret evidens til at vurdere effekten af antipsykotika sammenlignet med placebo til børn og unge med henholdsvis bipolar type 1 eller 2. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antipsykotikas gavnlige eller skadelige effekter hos børn og unge med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

### Antikonvulsiva vs. placebo
Der blev ikke identificeret evidens til at vurdere effekten af antikonvulsiva sammenlignet med placebo til børn og unge med henholdsvis bipolar type I eller II. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antikonvulsiva's gavnlige eller skadelige effekter hos børn og unge med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

### Antidepressiva vs. placebo
Der blev ikke identificeret evidens til at vurdere effekten af antidepressiva sammenlignet med placebo til børn og unge med henholdsvis bipolar type I eller II. Der kan derfor ikke drages sikre evidensbaserede konklusioner om antidepressivas gavnlige eller skadelige effekter hos børn og unge med bipolar lidelse. Anbefalingen baseres derfor primært på kliniske overvejelser, herunder en samlet vurdering af potentielle fordele og ulemper ved behandlingen, samt på patientpræferencer.

## 2.4 Resultater fra parvise metaanalyser, aktive interventioner
To forsøg sammenlignede to aktive interventioner overfor hinanden [44, 54]. Se **tabel 2** for karakteristika af de inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 15-16**).

*Litihium vs. Antikonvulsiva*

*Bipolar type 1*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antikonvulsiva.

*Bipolar type 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antikonvulsiva.

*Bipolar type 1 & 2*
Et forsøg sammenlignede effekten af lithium med antikonvulsiva i form af valproat [54]. Se **tabel 2** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 15**).

*Litihium vs. Antipsykotika*

*Bipolar type 1*

Et forsøg sammenlignede effekten af lithium med antipsykotika i form af quetiapin [44]. Se **tabel 2** for karakteristika af det inkluderede forsøg. Resultaterne for de kritiske og vigtige outcomes er sammenfattet i evidensprofilen nedenfor (**Evidensprofil 16**).

*Bipolar type 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antipsykotika.

*Bipolar type 1 & 2*
Der blev ikke fundet nogle forsøg der undersøgte effekten af litium overfor antipsykotika.

**Evidence profile 15: Lithium compared to Anticonvulsants (Valproate) for Bipolar 1 & 2**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Anticonvulsants (Valproate)** | **Børn og unge_Lithium** | **Difference** |
| New episode, any type<br>№ of participants: 60<br>(1 study) | **RR 0.90**<br>(0.61 to 1.32) | 66.7% | **60.0%**<br>(-- to --) | **6.7% fewer**<br>(26.0% fewer to 21.3% more) |
| New episode, depression<br>№ of participants: 60<br>(1 study) | **RR 3.00**<br>(0.33 to 27.23) | 3.3% | **10.0%**<br>(-- to --) | **6.7% more**<br>(2.2% fewer to 87.4% more) |
| New episode, mania<br>№ of participants: 60<br>(1 study) | **RR 0.79**<br>(0.50 to 1.24) | 63.3% | **50.0%**<br>(-- to --) | **13.3% fewer**<br>(31.7% fewer to 15.2% more) |
| Withdrawal, any cause<br>№ of participants: 60<br>(1 study) | **RR 1.40**<br>(0.50 to 3.92) | 16.7% | **23.3%**<br>(-- to --) | **6.7% more**<br>(8.3% fewer to 48.7% more) |
| Suicidal behaviour<br>№ of participants: 60<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-6 to 6) | **0.0% fewer**<br>(6.0% fewer to 6.0% more) |
| Psychiatric hospitalization<br>№ of participants: 60<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-6 to 6) | **0.0% fewer**<br>(6.0% fewer to 6.0% more) |
| Sariuos adverse events<br>№ of participants: 60<br>(1 study) | not estimable | 0.0% | **0.0%**<br>(-6 to 6) | **0.0% fewer**<br>(6.0% fewer to 6.0% more) |

**Evidence profile 16: Lithium compared to Antipsychotics (quetiapin) for Bipolar 1**

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | |
|---|---|---|---|---|
| | | **Antipsychotics (quetiapin)** | **Børn og unge_Lithium** | **Difference** |
| Withdrawal, any cause<br>№ of participants: 61<br>(1 study) | **RR 0.97**<br>(0.59 to 1.59) | 51.6% | **50.1%**<br>(-- to --) | **1.5% fewer**<br>(21.2% fewer to 30.5% more) |
| Quality of life<br>№ of participants: 40<br>(1 study) | - | - | - | MD **0.6 lower**<br>(1.15 lower to 0.05 lower) |
| Global functioning<br>№ of participants: 40<br>(1 study) | - | - | - | MD **19.6 higher**<br>(8.23 higher to 30.97 higher) |

# 3. Generelt vedrørende design af de inkluderede forsøg

Størstedelen af de inkluderede forsøg, og alle forsøg der har sammenlignet et lægemiddel med ingen behandling, har benyttet et såkaldt beriget diskontinuationsdesign. I et sådant design er patienter i en akut sygdomsepisode med f.eks. depression eller mani (indeks episode) eller umiddelbart efter lindring af denne, behandlet open-label med det lægemiddel, der er studiets hovedinteresse. De patienter, der ikke havde effekt af lægemidlet eller fik bivirkninger, er derefter blevet ekskluderet eller set bort fra. Kun deltagere, der ikke har haft væsentlige bivirkninger og har haft effekt af lægemidlet, ved at det har givet lindring af akutte symptomer i den akutte episode eller har kunnet vedblive symptomfri, er således gået videre til næste studiefase. Her er deltagerne randomiseret til at fortsætte behandling med det undersøgte lægemiddel eller behandling med et andet lægemiddel eller placebo. I andre tilfælde har deltagere i en forudgående akut sygdomsfase været behandlet med forskellige lægemidler efter klinisk skøn, således at en del af deltagerne har været behandlet i den akutte sygdomsfase med et af de lægemidler, der var interessen i forsøget og som deltagerne efterfølgende kunne modtage i lodtrækningsfasen. De deltagere der er blevet randomiseret til anden behandling eller placebo skal derfor ophøre med det lægemiddel der er studiets hovedinteresse og som de har været behandlet med i den akutte sygdomsepisode eller umiddelbart derefter. I nogle tilfælde ophøres lægemidlet, der forudgående har været behandlet med brat, mens det i andre tilfælde sker ved en udtrapning. Studiedesignet har en række begrænsninger, der er væsentlige at være opmærksom på, hvoraf nogle hovedpunkter fremhæves her.

## 3.1 Berigelse for tolerabilitet og effekt favoriserer lægemidlet, der er hovedinteresse

I et beriget diskontinuationsdesign er studiepopulationen beriget med patienter, som har haft få eller ingen bivirkninger og opnået en gavnlig effekt i form af lindring af akutte symptomer eller delvis remission eller vedligeholdelse af denne under behandling med det pågældende lægemiddel. Man kan tale om, at populationen på den måde er beriget både hvad angår tolerabilitet og effekt. I nogle tilfælde er der tale om hele studiepopulationen, i andre tilfælde om en betydelig del af studiepopulationen. Studiepopulationen udgør dermed en selekteret gruppe patienter, hvilket begrænser generaliserbarheden af resultaterne [56-58]. Dermed favoriserer designet det undersøgte lægemiddel i forhold til en eventuel aktiv komparator - et andet lægemiddel både i forhold til risikoen for en ny sygdomsepisode og i forhold til forekomst af bivirkninger og designet kan derfor føre til overvurdering af den gavnlige effekt af det undersøgte lægemiddel og en undervurdering af de skadelige virkninger [56, 57]. Eksempelvis ekskluderede tidligere systematiske oversigter af lithium vedligeholdelsesbehandling grundet begrænsningerne i deres design berigede diskontinuationsstudier, bl.a. med henvisning til, at sådanne forsøg har høj risiko for bias relateret til ophørsrelateret tilbagefald og at de ikke adresserer den kliniske problemstilling som vedrører forebyggelse af nye episoder [58, 59].

## 3.2 Seponeringsdesign favoriserer både lægemidlet, der er hovedinteresse og en aktiv komparator overfor placebo

Den ofte abrupte eller hurtige seponering af det lægemiddel der er studiets hovedinteresse, hos de deltagere der er randomiseret til placebo eller anden aktiv behandling, kan i sig selv føre til tidligt tilbagefald og dermed til en højere forekomst af nye episoder i placebo- og komparatorgrupperne i studiet [58, 60]. Idet en aktiv komparator ofte vil have effekter, der i nogen grad ligner dem som lægemidlet der er studiets hovedinteresse har, vil risikoen for en effekt af seponering forventes at være særligt udtalt i placebogruppen og i højere grad en i en aktiv komparator gruppe. Herved kan en eventuel effekt af det undersøgte lægemiddel overestimeres [56, 57], ligesom effekten af en aktiv komparator, hvis den har en vis virkning, sammenlignet med placebo, også overestimeres. For at reducere risikoen for tilbagefald og symptomer som følge af seponering, anbefales i klinisk praksis, at lithium, antipsykotika, antidepressiva og antikonvulsiva seponeres gradvist over 4 uger eller længere, for lithiums vedkommende over 3 måneder eller længere [60] og for antipsykotikas vedkommende over op til et år, afhængig af varigheden af den akuktte behandling [61]. Imidlertid er lægemidlerne i hovedparten af de berigede forsøg enten seponeret umiddelbart eller trappet ud over en kort periode på typisk én til to uger, hvilket hos en del patienter kan medføre seponeringssymptomer, som kan fejltolkes som recidiv eller en ny episode, føre til ophør i studiet, eller som i sig selv kan føre til forværring af tilstanden og udvikling af tilbagefald. I et af de inkluderede forsøg, blev patienter med bipolar lidelse type 1 f.eks. stabiliseret på behandling med quetiapin efter hvilken som helst episode igennem 4-24 uger og respondere blev derefter randomiseret til at fortsætte quetiapin eller skift til lithium eller placebo, med seponering af quetiapin i løbet af mindre end 2 uger [18]. Indenfor 2 måneder havde 30% af deltagerne i placebo-gruppen fået en ny episode, svarende til at alle i placebogruppen ville have fået ny episode indenfor 6 måneder, hvilket er betydeligt flere og hurtigere end forventet ud fra sygdommens naturhistorie. I et andet studie blev patienter, der var i behandling med lithium randomiseret til at fortsætte eller skifte til carbamazepin [33]. Andelen af deltagere der fik en ny episode i løbet af et år, var stort set identisk i de to grupper, men i gruppen der blev skiftet til behandling med carbamazepin forekom næsten alle tilbagefald i løbet af de første 4 uger. Det er påpeget, at forekomsten af nye episoder i moderne kliniske forsøg blandt patienter uden behandling, grundet deres design, muligvis overstiger hvad man ville forvente ud fra kendskab til sygdommens naturhistorie [56, 60]. Det er endvidere fundet, at hyppigheden af episoder muligvis stiger hos patienter efter ophør af lithium i forhold til perioden før behandlingen blev begyndt [62]. Om det samme gør sig gældende for øvrige lægemidler er uklart. En yderligere konsekvens af det berigede design er, at risikoen for bivirkninger og skadevirkninger, herunder alvorlige hændelser, underestimeres, idet udelukkende deltagere, der allerede har tolereret lægemidlet inkluderes og de patienter, der ikke har gjort det, er udelukket. Hvor ikke alle, men en del af deltagerne, har været i behandling med lægemidlet i en forudgående periode, kan det også at påvirke resultaterne i nogen grad, således at risikoen for skadevirkninger også undervurderes i sådanne forsøg.

## 3.3 Studiedesign undersøger risiko for tilbagefald af akut sygdomsepisode, snarere end forebyggelse af ny episode

I hovedparten af forsøgene er deltagerne randomiseret efter observeret bedring af symptomerne under behandling i en relativt kort open-label af en akut sygdomsepisode, typisk 8-12 ugers behandling. Eftersom naturhistorien af en akut sygdomsepisode med mani eller depression ofte er betydeligt længere med en varighed, om end varierende, på 3-9 måneder [63, 64], vil der i mange tilfælde være tale om, at en behandling af en akut

sygdomsepisode ophøres, hvor episoden stadig er aktiv, hvorfor sygdomsepisoder i studieperioden snarere må betragtes som tilbagefald af den akutte sygdomsepisode, snarere end en egentlig ny episode [40, 65]. Sådanne forsøg undersøger således i betydelig grad risikoen for tilbagefald af den akutte sygdomsepisode, snarere end forebyggelse af en ny episode [56, 65]. Dette forhold afspejles bl.a. i at nye episoder i sådanne forsøg typisk forekommer med størst hyppighed kort efter randomisering og i at patienter typisk oplever en ny episode af samme type, som den indeks episode, der blev behandlet i den akutte fase af studiet, hvilket er mindre almindeligt i klinisk praksis [56, 57]. Det har været påpeget, at designet således besvarer spørgsmålet om en patient, der responderer på lægemidlet, fortsat vil respondere på lægemidlet ved længerevarende behandling [56]. Førende forfattere, har i forlængelse heraf anført, at episoder, der indtræder indenfor de første 6 måneder efter en akut episode er velbehandlet, repræsenterer tilbagefald, ikke nye episoder [57]. Kun episoder, der indtræder efter 6 måneder [56, 57, 66] eller endda efter 12 måneder efter ophøret af den akutte episode, anføres af flere at kunne demonstrere en effekt i forhold til vedligeholdelsesbehandling [65]. Forsøg, der har benyttet et beriget diskontinuationsdesign, belyser således snarere risikoen for tilbagefald (af den akutte sygdomsepisode) end risikoen for en ny episode [56-58].

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