# Data supplement

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**Table DS1**: Examples of systematic reviews on the efficacy of psychiatric drugs versus placebo that were mainly based on older studies

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**Table DS4**: Systematic reviews on the efficacy of psychiatric drugs versus placebo (full version of Table 2 in the print version, with more drugs and meta-analyses, confidence intervals and NNTs)

**Figs DS1–24**: PRISMA diagrams on search process

**Fig. DS25**: Systematic presentation of the effect sizes in Fig. 1 labelled by ‘Disease - Drug – Outcome’

**Figs DS26, DS27**: Summary of the percentage relative risk reductions/response ratios presented in Tables DS3 and DS4

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**Explanation of statistical indices** presented in the text and Tables DS3 and DS4

**References** to supplemental material

## Table DS1 Examples of systematic reviews on the efficacy of psychiatric drugs versus placebo that were mainly based on older studies

| Study (Ref) | Therapy | Outcome | Mean dur. wks (range) | N | n | % PBO | % Drug | ARR/ARD (95%CI) | NNT/NNH (95%CI) | RRR/RR (95%CI) | SMD (95%CI) | WMD (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Schizophrenia** | | | | | | | | | | | | |
| [128] | Haloperidol[1)] | Response | (0-24)[2)] | 8 | 409 | 15.4 | 50.7 | 36% (25-46)*** | 3 (2-4) | 203%(79-414)*** | | |
| [129] | Chlorpromazine[1)] | Response | (0-26)[2)] | 24 | 555 | 24.7 | 39.1 | 26% (17-34)*** | | 78% (48-115)*** | | |
| [130] | Antipsychotics | Relapse | (4-104) | 35 | 3720 | 55.0 | 21.0 | 34 % (n.i.)* | 3 (n.i.) | 62 % (n.i.)* | | |
| [131] | Antipsychotics | Relapse | 26 (2-104) | 66 | 4365 | 53.0 | 16.0 | 37% (n.i.)* | 3 (n.i.) | 70% (n.i.)* | | |
| **Depression**[3)] | | | | | | | | | | | | |
| [132] | Tricyclic ADs | Response | n.i. | 79 | 5159 | 36.0 | 63.0 | 27% (n.i.) *** | 4 (n.i.) | 75% (n.i.)*** | | |
| [132] | MAO-inhibitors | Response | n.i. | 33 | 1944 | 34.0 | 65.0 | 32% (n.i.) *** | 3 (n.i.) | n.i. (n.i.) | | |
| [133] | Phenelzine | Response | 5 (3-6) | 9 | 1108 | n.i. | n.i. | 29.5% (n.i.)* | 3 (n.i.) | n.i. (n.i.) | | |
| [134] | Tricyclic ADs | Var. scales | n.i. | ni | n.i. | | | | | | 0.67 (n.i.) | n.i. |
| [135] | Tricyclic ADs | Var. scales | 8.1 | 54 | n.i. | | | | | | 0.79 SE 0.07* | n.i. |
| **Obsessive compulsive disorder** | | | | | | | | | | | | |
| [136] | Clomipramine | OC sym. | 9 (5-10) | 9 | 668 | | | | | | 1.31 (1.15 to 1.47)*** | n.i. |
| [137] | Any SRI | OC sym. | (6-13) | 12 | n.i. | | | | | | 0.75 (n.i.) | n.i. |
| [138] | Any SRI | OC sym. | 9 (4-13) | 15 | n.i. | | | | | | 1.09 (n.i.)** | n.i. |
| **Panic disorder** | | | | | | | | | | | | |
| [139] | Antidepressants | Var. scales | 16 (6-28) | 13 | 580 | | | | | | 0.66 (0.17-0.82)* | n.i. |
| | Benzodiazepines | Var. scales | 7 (5-8) | 6 | 696 | | | | | | 0.37 (0.24-0.89)* | n.i. |
| [140] | Antidepressants | Var. scales | | 5 | | | | | | | 0.82 (n.i.)* | n.i. |
| | Benzodiazepines | Var. scales | | 4 | | | | | | | 0.29 (n.i.)* | n.i. |
| [141] | Tricyclic ADs | Response | | 7 | 1072 | 51.0 | 72.0 | 21% *** | 5 (n.i.) | 40% (n.i.) | | |
| [141] | SSRIs | Response | | 4 | 148 | 30.0 | 80.0 | 50% *** | 2 (n.i.) | n.i. | | |
| [141] | Alprazolam | Response | | 7 | 1486 | 45.0 | 72.0 | 26% (n.i.) *** | 4 (n.i.) | | 1.60 (n.i.) | |

Ref = reference, N = number of studies, n = number of participants, % PBO = percentage of patients with the outcome in the placebo group, % Drug = percentage of patients with the outcome in the drug group, ARD = absolute response or risk difference, CI = 95% confidence interval, NNT/H = number needed to treat or number needed to harm, RRR/RR: 'Negative outcomes' (mortality, relapse, exacerbation, hospitalization, dropout etc) are presented as relative risk reductions (RRR), while positive outcomes (response to treatment, improvement, remission) are presented as percentage response ratios (RR). Positive values mean superiority of drug, SMD = standardized mean difference, WMD = weighted mean difference, SE = standard error, *** = p<0.001, ** = p<0.01, * = p<0.05, ns= not significant, ni = not indicated, d = days, var.=various, AD = antidepressant, MAO-inhibitors = mono-amino-oxidase inhibitors, OC symptoms = symptoms of obsessive compulsive disorder, SRI = serotonin-reuptake-inhibitor, SSRIs = selective-serotonin-reuptake-inhibitors, SleepOL = sleep onset latency, min = minutes, TST = total sleep time, Benzod. =benzodiazepine; 1) mainly based on studies from the 1960s to 80s, 2) we combined short-term and medium-term results, 3) various forms of depression, not exclusively major depressive disorder

**Table DS2 Calculation of effect sizes for continuous and dichotomous outcomes**

| Index/measure | Formula | Example |
|---|---|---|
| **Effect sizes for continuous data (e.g. weight, rating scale scores*)** | | |
| Difference of means (DM) | Mean group A – Mean group B | 75kg bodyweight at endpoint in drug group and 70kg in placebo, DM = 5kg |
| Standardised difference of means (SDM) | (Mean group A – Mean group B)/pooled standard deviation (SD) | 75kg drug, 70kg placebo, pooled SD 10, SMD = 5/10 = 0.50 |
| **Effect sizes for dichotomous data ("yes/no", e.g. death, relapse)** | | |
| Risk or response rate | Number of participants in a group with an event divided by total number of participants in this group | 1 out of 100 participants died, mortality risk = 1/100 = 1% |
| Absolute risk or response difference (ARD) | Risk or percentage responders in group A – Risk or percentage responders in group B | 1% deaths in drug - 3% deaths in placebo, ARD = \|-2%\|<br>Or 50% drug responders - 31% placebo responders, ARD = 29% |
| Relative risk reduction (RRR) | 1- (Risk or percentage responders in group A – Risk or percentage responders in group B) | 1-(1%/3%) = 67% |
| Percentage response ratio (RR) | Percentage responders group A / percentage responders group B | 50% drug responders / 31% to placebo, RR = 1.61 times or 61% more responders. |
| Number needed to treat (NNT) | 1/absolute risk or response difference | 1 / 2% = 1/0.02, NNT = 50 |

* mean values of psychiatric ratings scales are not really continuous data, but are treated as such in meta-analyses

**Table DS3 Systematic reviews on the efficacy of general medicine drugs versus placebo (full version of Table 1 in the print version with more drugs and meta-analyses, confidence intervals and NNTs)**

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | [1]RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hypertension – effects on blood pressure** | | | | | | | | | | | | |
| [1]/5[1)] | Any antihyp. | RR systolic (mmHg) | 8 | 94 | 17641 | | | | | | 0.56 (0.52-0.58)*** | 9.4 (8.9-9.9)*** |
| | | RR diastolic (mmHg) | 8 | 94 | 17641 | | | | | | 0.54 (0.52-0.58)*** | 5.5 (5.2-5.8)*** |
| [1]/5[1)] | ACE-inhibitors | RR systolic (mmHg) | 8 (2-14) | 39 | 6601 | | | | | | 0.5 (0.4 to 0.5)*** | 9.6 (8.5-10.6)*** |
| | | RR diastolic (mmHg) | 8 (2-14) | 39 | 6601 | | | | | | 0.5 (0.4 to 0.5)*** | 5.4 (4.8-5.9)*** |
| [1]/5[1)] | ARBs | RR systolic (mmHg) | 8 (2-14) | 28 | 11715 | | | | | | 0.5 (0.5 to 0.6)*** | 10.0 (9.2-10.9)*** |
| | | RR diastolic (mmHg) | 8 (2-14) | 28 | 11715 | | | | | | 0.5 (0.4 to 0.5)*** | 5.7 (5.2-6.2)*** |
| [1]/5[1)] | Beta-blockers | RR systolic (mmHg) | 8 (2-14) | 19 | 3018 | | | | | | 0.5 (0.4 to 0.6)*** | 8.4 (7.1-9.7)*** |
| | | RR diastolic (mmHg) | 8 (2-14) | 19 | 3018 | | | | | | 0.5 (0.5 to 0.6)*** | 6.9 (5.9-7.9)*** |
| [1]/5[1)] | Thiazide | RR systolic (mmHg) | 8 (2-14) | 26 | 4094 | | | | | | 0.6 (0.5 to 0.6)*** | 8.7 (7.7-9.7)*** |
| | | RR diastolic (mmHg) | 8 (2-14) | 26 | 4094 | | | | | | 0.6 (0.5 to 0.6)*** | 4.4 (3.8-4.9)*** |
| **Hypertension – long term effects on cardiovascular events and mortality** | | | | | | | | | | | | |
| [2]/5[2)] | ACE- inhibitors | CV events | 3.9y | 5 | 18229 | 18.1 | 14.1 | 4% (ni)ni | 25 (ni) | 22% (17-27)*** | *0.16 (0.12-0.21)* | |
| | | Mortality | 3.9y | 5 | 18229 | 10.4 | 9.2 | 1% (ni)ni | 83 (ni) | 12% (4-19)** | *0.07 (-0.02-0.13)* | |
| [2]/5[2)] | Ca-antagonists | CV events | 2.8y | 3 | 6656 | 10.3 | 8.3 | 2% (ni)ni | 50 (ni) | 18% (5-29)** | *0.13 (0.04-0.22)* | |
| | | Mortality | 2.8y | 4 | 7482 | 7.1 | 6.3 | 1% (ni)ni | 125 (ni) | 11% (-5-25)ns | *0.07 (-0.03-0.17)* | |
| [3]/10[3)] | Beta-Blockers | CV events | 3.9y | 4 | 23613 | 6.5 | 5.7 | 1% (0-2)ns | 100 (ne) | 12% (2-22)* | *0.08 (0.02-0.14)* | |
| | | Mortality | 3.9y | 4 | 23613 | 5.2 | 5.0 | 0% (0-1)ns | ne | 1% (-11-11)ns | *0.02 (-0.04-0.09)* | |
| [4]/8 | Diuretics | CV events | 3.9y | 42 | 192478 | ni | ni | ni | ni | 24% (17-31)*** | *ne* | |
| | | Mortality | 3.9y | 42 | 192478 | ni | ni | ni | ni | 10% (4-16)** | *ne* | |
| **Acute stroke** | | | | | | | | | | | | |
| [5]/9 | Thrombolysis | Death/dependency | 12-26 | 22 | 6283 | 55.8 | 50.9 | 5% (1-9)** | 20 (11-100) | 9% (3-14)** | *0.11 (-0.05-0.16)* | |
| [6]/11 | ASA | Death/dependency | 4-26 | 4 | 41291 | 46.0 | 45.0 | 1%(0-2)* | 100 (ne) | 2%(1- 4) * | *0.02 (0.01-0.04)* | |
| [7]/11 | Anticoagulants | Death/dependency | >4 | 8 | 22152 | 59.9 | 59.4 | 3% (-1-7)ns | 33 (H50-T14) | 5% (-4-14)ns | *0.01 (-0.02-0.04)* | |
| **Prevention of cardiovascular disesase and stroke** | | | | | | | | | | | | |
| [8]/5[4)] | ASA (prim.prev.) | Serious vasc. ev. | 5.8y | 6 | 95000 | 0.57/y | 0.51/y | 0.07%/y (ni)ni | 1429/y (ni)ni | 12%/y (6-18)*** | *0.06 (-0.03-0.16)* | |

| **Study (Ref) AM-STAR score** | **Therapy** | **Outcome** | **Mean weeks** | **N** | **n** | **% PBO** | **% Drug** | **ARD (CI)** | **NNT/H (CI)** | **[1]RRR/ RR (CI)** | **SDM (CI)** | **WMD (CI)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Vascular mort. | 5.8y | 6 | 95000 | 0.19/y | 0.19/y | 0.0%/y (ni)ni | ne/y | 3%/y (-9-13)ns | *0.00 (-0.16-0.16)* | |
| [8]/5 | ASA (sec.prev.) | Serious vasc. ev. | ni | 16 | 17000 | 8.2/y | 6.7/y | 1.5%/y (ni)ni | 67/y (ni)ni | 19%/y (13-25)*** | *0.12 (0.06-0.18)* | |
| | | Vascular mort. | ni | 16 | 17000 | 4.07/y | 3.67/y | 0.29%/y (ni)ni | 358/y (ni)ni | 9%/y (0-18)ns | *0.06 (-0.03-0.15)* | |
| [9]/5 | Statins | LDL-cholesterol (mmol/l) | 2-6 | 164 | ~38000 | | | | | | ni | 1.54(ni)*** |
| [10]/6[5)] | Statins | Maj. CV events | 5.0y | 14 | 90056 | 17.8 | 14.1 | 4% (3-4)*** | 27 (25-33) | 21% (19-23)*** | *0.15 (0.13-0.17)* | |
| | | Mortality | 5.0y | 14 | 90056 | 9.7 | 8.5 | 1.2% (1-2)*** | 83 (50-100) | 12% (9-14)*** | *0.08 (0.05-0.11)* | |
| **Chronic heart failure** | | | | | | | | | | | | |
| [11]/6 | ACE-inhib. short-term | Mortality | > 8 | 32 | 7105 | 21.9 | 15.8 | 6% (4-8)*** | 16 (13-25) | 19% (10-28)*** | *0.22 (0.16-0.29)* | |
| | | Mort. or Hosp. | > 8 | 30 | 6988 | 32.6 | 22.4 | 10% (8-12)*** | 10 (8-13) | 27% (19-34)*** | *0.28 (0.23-0.34)* | |
| [12]/6[6)] | ACE-inhib. long-term | Mortality | 2.9y | 5 | 12763 | 26.8 | 23.0 | 4% (2-5)*** | 26 (20-50) | 15% (12-20)*** | *0.11 (0.07-0.16)* | |
| | | Hospitalization | 2.9y | 5 | 12763 | 18.9 | 13.7 | 5% (ni)*** | 19 (ni) | 29% (22-34)*** | *0.21 (0.16-0.26)* | |
| [13]/9 | ARBs | Mortality | 45 | 9 | 4623 | 17.7 | 10.6 | 7% (5-9)*** | 14 (11-20) | 14% (0.01-27)*** | *0.33 (0.23-0.42)* | |
| | | Hospitalization | 45 | 3 | 2590 | 25.1 | 17.2 | 8% (5-11)*** | 13 (9-20) | 30% (17-40)*** | *0.26 (0.16-0.37)* | |
| [14]/7[7)] | Beta-Blockers (partly add on) | Mortality | 36 | 22 | 10135 | 13.2 | 8.4 | 5% (3-6)*** | 21 (17-33) | 32% (18-44)*** | *0.28 (0.21-0.35)* | |
| | | Hospitalization | 36 | 22 | 10135 | 15.5 | 10.2 | 5% (3-6)*** | 19 (14-25) | 32% (18-43)*** | *0.26 (0.20-0.33)* | |
| [15]/10 | Diuretics | Mortality | 17 | 3 | 202 | 11.9 | 2.9 | 8% (-1-17)ns | 13 (H100-T6) | 72% (12-91)* | *0.83 (0.11-1.55)* | |
| | | Worsening | 17 | 2 | 169 | 14.8 | 0.0 | 15% (1-30)*** | 7 (3-100) | 92% (40-99)** | *1.88 (0.32-3.44)* | |
| [16]/9 | Digitalis | Mortality | 25 | 8 | 7755 | 31.2 | 30.9 | 0% (-1-2)ns | ne | 1% (-6-7)ns | *0.01 (-0.05-0.06)* | |
| | | Hospitalization | 25 | 4 | 7262 | 33.1 | 25.4 | 8% (6-10)*** | 13 (10-17) | 46% (2-70)*** | *0.21 (0.15-0.26)* | |
| **Rheumatoid arthritis** | | | | | | | | | | | | |
| [17]/10 | Methotrexate | No. tend. joints | > 12 | 5 | 218 | | | | | | 0.86 (0.58-1.14)*** | ne |
| | | DO for inefficacy | > 12 | 5 | 313 | 12.8 | 2.5 | 3% (-7-14)ns | 33 (H14-T7) | 0.48% (0.03-8.84)ns | *0.96 (0.35-1.57)* | |
| [18]/10 | Steroids short-term | No. tend. joints | < 4 | 2 | 182 | | | | | | 0.52 (0.03-1.01)* | ne |
| [19]/9 | Steroids mod.-term | No. tend. joints | > 12 | 5 | 304 | | | | | | 0.37 (0.14-0.59)** | ne |
| [20]/9 | Azathioprine | No. tend. joints | > 26 | 3 | 81 | | | | | | 1.12 (0.30-1.93)** | ne |
| [21]/10 | Cyclosporine | Change no. tend. joints | < 52 | 1 | 144 | | | | | | 0.60 (0.27-0.93)*** | ne |
| [22]/9 | Cyclophosphamide | No. tend. joints | > 26 | 2 | 70 | | | | | | 0.57 (0.09-1.05)* | ne |
| | | DO for inefficacy | > 26 | 1 | 88 | 6.3 | 0.0 | 5% (-3-4) ns | 20 (H33-T7) | 81% (-260-99)ns | *1.06 (0.58-2.71)* | |

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | [1]RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [23]/10[8)] | Sulfasalazine | No. tend. joints | > 26 | 6 | 256 | | | | | | 0.49 (0.24-.75)*** | ne |
| | | DO for inefficacy | > 26 | 6 | 468 | 32.0 | 10.3 | 22% (10-4)*** | 5 (3-0) | 67% (39-2)*** | *0.78 (0.50-1.05)* | |
| [24]/8 | Penicillamine | No. tend. joints | > 12 | 5 | 316 | | | | | | 0.48 (0.25-.71)*** | ne |
| | | DO for inefficacy | > 12 | 2 | 317 | 5.7 | 2.8 | 3% (-1-7)ns | 33 (H100-T14) | 56% (-33-85)ns | *0.41 (-0.23-1.04)* | |
| [25]/8 | Auranofin | No. tend. joints | > 26 | 7 | 750 | | | | | | 0.40 (0.19-0.62)*** | ne |
| | | DO for inefficacy | > 26 | 8 | 1049 | 19.6 | 6.5 | 14% (3-5)** | 7 (4-33) | 60% (31-7)*** | *0.69 (0.47-0.92)* | |
| [26]/10 | Leflunomide | No. tend. joints | 52 | 1 | 300 | | | | | | 0.58 (0.35-0.82)*** | ne |
| | | ACR 20 response | 52 | 1 | 300 | 26.3 | 52.2 | 26% (15-37)*** | 4 (4-7) | 50% (36-0)*** | *0.62 (0.35-0.88)* | |
| [27]/9 | Antimalarials | No. tend. joints | > 26 | 4 | 571 | | | | | | 0.33 (0.17-0.50)*** | ne |
| | | DO for inefficacy | > 26 | 3 | 467 | 19.4 | 11.5 | 7% (0.1-14)* | 14 (7-1000) | 40% (6-62)* | *0.34 (0.05-0.62)* | |
| [28]/9 | Celecoxib (200mg) | No. tend. joints | 12 | 1 | 466 | | | | | | 0.34 (0.16-0.52)*** | ne |
| | | ACR20 response | 12 | 1 | 466 | 28.6 | 43.8 | 15% (7-24)*** | 7 (4-14) | 53% (19-97)*** | *0.37 (0.15-0.58)* | |
| | | DO for inefficacy | 12 | 1 | 466 | 45.0 | 21.3 | 24% (15-32)*** | 4 (3-7) | 53% (37-64)*** | *0.61 (0.39-0.83)* | |
| [29]/10 | Adalimumab (40mg) | No. tend. joints | 28 | 1 | 213 | | | | | | 0.39 (0.13-0.66)*** | ne |
| | | ACR 20 response | 28 | 1 | 140 | 10.0 | 57.1 | 47% (34-61)*** | 2 (2-3) | 470% (180-1080)*** | *1.36 (0.86-1.86)* | |
| [30]/11 | Ifx (10mg/kg) (+ Mtx) | No. tend. joints | 26-52 | 2 | 197 | | | | | | 1.33 (-0.29-2.96)ns | ne |
| | | ACR 20 response | 26-52 | 1 | 175 | 20.5 | 52.9 | 32% (19-46)*** | 3 (2-5) | 160% (60-410)*** | *0.81 (0.44-1.17)* | |
| **Migraine - acute treatment** | | | | | | | | | | | | |
| [31]/8[9)] | Sumatriptan | Pain-free | 2 hrs | 8 | 2221 | 8.5 | 29.5 | 20% (15-24)*** | 5 (4-7) | 220% (150-310)*** | *0.41 (0.25-0.56)* | |
| [32]/3 | Aspirin | Pain-free | 2 hrs | 3 | 1246 | 15.1 | 27.1 | 12% (ni)ni | 8 (ni) | 80% (n.i)*** | *0.83 (0.69-0.97)* | |
| **Migraine – prophylaxis** | | | | | | | | | | | | |
| [33]/9 | Propanolol | Response | 13 | 4 | 205 | 30.9 | 52.3 | 35% (5-69)* | 3 (1-20) | 80% (3-210)* | *0.49 (0.18-0.81)* | |
| | | Mig. freq. | 13 | 4 | 172 | | | | | | 0.47 (0.12-0.83)** | 0.90 (0.26-1.54)** |
| [34]/7 | Anticonvulsants | Response | 12.3 | 14 | 1773 | 20.6 | 47.0 | 26% (ni)ni | 4 (ni)ni | 130% (90-180)*** | *0.68 (0.56-0.79)* | |
| | | Mig. freq. | 12.3 | 10 | 902 | | | | | | 0.55 (0.26-0.85)*** | ni |
| **Asthma** (data on short-acting-beta-2 agonists as needed are not presented, because we only found a systematic review compared to continuous treatment[35]) | | | | | | | | | | | | |
| **Inhaled corticosteroids** | | | | | | | | | | | | |
| [36]/7 | Corticosteroids | FEV1(l) | >12 | 19 | 3271 | | | | | | 0.56 (0.45-0.66)*** | 0.33 (0.26-0.40)*** |
| | | Exacerbation | >12 | 11 | 8999 | ni | ni | ni | ni | 54% (38-66)* | ne | |

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | [1]RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [37]/10 | Beclomethasone | FEV1(l) | 14 | 6 | 612 | | | | | | 0.42 (0.22-0.49)*** | 0.36 (0.26-0.58)*** |
| | | DO exacerbation | 14 | 10 | 1185 | 15.4 | 3.1 | 11% (3-18)** | 9 (6-33) | 71% (54-81)*** | *0.96 (0.67-1.24)* | |
| [38] | Fluticasone | FEV1 (l) | 14 | 21 | 4790 | | | | | | 0.67 (0.24-0.38)*** | 0.31 (0.53-0.81)*** |
| | | DO exacerbation | 14 | 4 | 702 | 11.4 | 2.0 | 11% (1-21)* | 9 (5-100) | 80% (58-90)*** | *1.01 (0.56-1.46)* | |
| **Long-acting beta-2-agonists** | | | | | | | | | | | | |
| [39]/11 | LAB2(add on) | FEV1 (l or %) | 19 | 17 | 3926 | | | | | | 0.35 (0.28-0.42)*** | 0.19 (0.11-0.27)*** |
| | | Exacerbation | 19 | 17 | 4027 | 27.4 | 22.4 | 5% (3-7)*** | 20 (14-33) | 17% (7-25)*** | *0.15 (0.07-0.23)* | |
| [40]/9 | LAB2(partly add on) | Hospitalization | 26 | 12 | 5091 | 0.6 | 1.7 | -0.7% (-1.3--0.1)* | -143 (-100--1000) | -114% (-15--297)* | *0.58 (0.26-0.90)* | |
| [36]/7 | LAB2 | FEV 1 (%) | > 12 | 13 | 3888 | | | | | | 0.33 (0.24-0.42)*** | ni |
| | LAB2(add on) | Exacerbation | > 12 | 9 | 2854 | ni | ni | ni | ni | 25% (12-36)*** | ne | |
| [41]/6 | LAB2(add on) | Exacerbation | 12 | 24 | 7549 | 8.3 | 4.9 | 2.5% (1.4-3.6)*** | 40 (28-71)*** | 35% (20-45)*** | *0.31 (0.21-0.41)* | |
| **Third line treatments** (we did not find a systematic review on theophylline) | | | | | | | | | | | | |
| [36]/7[10)] | Leukot. Antg. | FEV 1 (%) | > 12 | 7 | 4375 | | | | | | 0.25 (0.12-0.38)*** | ni |
| | | Exacerbation | > 12 | 7 | 4375 | ni | ni | ni | ni | 41% (29-51)* | ne | |
| **Chronic obstructive pulmonary disease (COPD)** | | | | | | | | | | | | |
| [42]/10[13)] | Tiotropium | FEV 1 (l) | > 4 | 4 | 1735 | | | | | | 0.99 (0.89-1.09)*** | 0.20 (0.18-0.22)*** |
| | | Exacerbations | > 4 | 8 | 5644 | 30.8 | 23.2 | 5% (3-7)*** | 20 (14-33) | 17% (10-24)*** | *0.21 (0.15-0.28)* | |
| | | Mortality | > 4 | 2 | 1723 | 10.6 | 9.8 | 1% (0-2)ns | 100 (50-∞) | 47% (-39-20)ns | *0.05 (-0.12-0.22)* | |
| [43]/10 | Anticholinergics | Hospitalization | 1.7y | 3 | 3552 | 8.4 | 5.7 | 2.7% (ni)ni | 37 (ni)ni | 33% (14-47)*** | *0.23 (0.09-0.37)* | |
| | | Mortality | 1.7y | 5 | 7881 | 0.3 | 0.05 | 0.25% (ni)ni | 400 (ni)ni | 73% (19-91)* | *0.99 (0.16-1.82)* | |
| [44]/10 | Inh. corticosteroids | FEV 1 (l) | 8-24 | 3 | 952 | | | | | | 0.36 (0.23-0.49)*** | 0.10 (0.06-0.13)*** |
| | | Exacerb/p/y | > 26 | 4 | 2063 | | | | | | 0.20 (0.11-0.29)*** | 0.26 (0.14- 0.38)*** |
| [12)] | | Mortality | > 26 | 9 | 8390 | 7.6 | 7.7 | 0.0% (-0.01-0)ns | ne | -1% (-15-14)ns | *-0.01 (-0.10-0.08)* | |
| [45]/10 | Short-act ß-2-ag. | FEV 1(l) | 3 | 6 | 196 | | | | | | 0.37 (0.08-0.65)** | 0.14 (0.04-0.25)** |
| | | Exacerbation | 3 | 5 | 198 | 46.5 | 22.2 | 26% (12-40)*** | 4 (3-8) | 47% (14- 67)** | *0.61 (0.27-0.95)* | |
| [43]/10 | Long-act ß-2-ag. | Exacerbation | 1.7y | 11 | 5333 | 10.6 | 7.8 | 2.8% (ni)ni | 35.7 (ni) | 19% (5-32)*** | *0.19 (0.08-0.29)* | |
| | | Resp. Mortality | 1.7y | 4 | 2404 | 0.7 | 1.6 | -0.9% (ni)ni | -111 (ni)ni | -147% (-12--445)* | *0.46 (0.01-0.91)* | |
| [46]/6 | Long-act ß-2-ag. | Exacerbation | 18 | 9 | 4198 | ni | ni | ni | ni | 21% (10-31)* | ne | |
| | | Mortality | 18 | 9 | 4198 | ni | ni | ni | ni | 24% (-48-61)ns | ne | |

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | [1]RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [47]/10 | Theophylline | FEV1 (l) | >1 | 13 | 244 | | | | | | 0.28 (0.10 - 0.46)** | 0.10 (0.04 - 0.16)** |
| | | Exacerbations | n.i. | 2 | 45 | ni | ni | 13% (1-26)* | 8 (4-100) | 67% (-14 – 90)ns | ne | |
| **Diabetes** | | | | | | | | | | | | |
| [48]/11 | Metformin | HbA1c (%) | 21.5 | 12 | 1587 | | | | | | 0.97 (0.69-1.25)*** | 1.06 (0.73-1.38)*** |
| | | Fasting glucose (mmol/l) | 21.5 | 12 | 1587 | | | | | | 0.87 (0.61-1.13)*** | 1.84 (1.30-2.38)*** |
| | | Mort.(vs conv. treat) | 10.7y | 1 | 753 | 21.7 | 14.6 | 7% (2-13)** | 14 (8-50) | 32% (7-51)** | *0.27 (0.06-0.47)* | |
| [49]/11 | α -gluc.-inhib. | HbA1c (%) | 30 | 28 | 2831 | | | | | | 0.64 (0.49-0.80)*** | 0.77 (0.60- 0.90)*** |
| | | Fasting glucose (mmol/l) | 30 | 28 | 2831 | | | | | | 0.54 (0.39-0.69)*** | 1.09 (0.83-1.36)*** |
| | | Mortality | 1.7y | 2 | 385 | 2.2 | 2.5 | 0% (-2-3)ns | ne | -10% (-301-70)ns | *-0.07 (-0.80-0.66)* | |
| [50]/8 | GLP-1 anal. | HbA1c (%) | > 12 | 6 | 1285 | | | | | | 0.70 (ni) | 0.97 (0.81-1.13)*** |
| | DPP4 inhib. | HbA1c (%) | > 12 | 16 | 4109 | | | | | | 0.40 (ni) | 0.74 (0.62-0.85)*** |
| [51]/10 | Meglitinide add-on | HbA1c (%) | 12 | 1 | 54 | | | | | | 0.87 (0.31-1.43)** | 1.08 (0.43-1.73)*** |
| **Chronic hepatitis C** | | | | | | | | | | | | |
| [52]/10 | Interferon | Virol. resp. | > 26 | 8 | 409 | 1.0 | 38.3 | 35% (23-47)*** | 3 (2-4) | 1070% (370-2850)*** | *2.27 (1.49-3.04)* | |
| [53]/10 | Ribavirin | Virol. resp. | 45 | 10 | 511 | 1.3 | 1.4 | 0% (-2-2)ns | ne | 0% (-20-340)ns | *0.04 (-0.79-0.87)* | |
| | | Morb. and Mort. | 45 | 11 | 521 | 0.4 | 0.7 | -0% (-2-3)ns | ne | -34% (-90-10)ns | *-0.31 (-1.64-1.02)* | |
| [54]/10 | Interf. + Ribav. | Virol. resp. | 30 | 52 | 8354 | 13 | 37 | 20% (16-24) *** | 5 (4-6) | 160% (120-210)*** | *0.75 (0.69-0.82)* | |
| | | Morb. and Mort. | 29 | 79 | 9991 | 0.44 | 0.20 | 0% (0-0)ns | ne | 51% (4-75)* | *0.44 (0.02-0.85)* | |
| **Reflux oesophagitis** | | | | | | | | | | | | |
| [55]/9 | PPI | Clin. Remission | 8 | 5 | 645 | 28.3 | 83.2 | 58% (47-68)*** | 2 (2-2) | 256% (111-500)*** | *1.39 (1.18-1.60)* | |
| [56]/9 | PPI (maint. dose) | Relapse | 26-51 | 5 | 1465 | 75.4 | 36.1 | 39% (35-44)*** | 3 (2-3) | 54% (43-62)*** | *0.93 (0.81-1.06)* | |
| [56]/9 | PPI (healing dose) | Relapse | 26-51 | 10 | 1385 | 78.8 | 21.7 | 57% (53-62)*** | 2 (2-3) | 74% (64-81)*** | *1.43 (1.29-1.57)* | |
| **Ulcerative colitis** | | | | | | | | | | | | |
| [57]/9 | 5-ASA | Clin. Remission | 8 | 4 | 892 | 10.0 | 19.9 | 8% (4-13)*** | 13 (8-25) | 70% (10-160)** | *0.44 (0.23-0.66)* | |
| [58]/9 | 5-ASA | Maint. Remission | 26 | 5 | 881 | 36.7 | 52.9 | 18% (12-24)*** | 6 (4-8) | 50% (30-70)*** | *0.36 (0.22-0.51)* | |
| **Multiple Sclerosis** | | | | | | | | | | | | |
| [59]/10[14)] | Corticosteroids | Improvement | < 5 | 3 | 93 | 27.9 | 68.0 | 41% (23-59)*** | 2 (2-4) | 140% (40-290)*** | *0.93 (0.45-1.42)* | |
| [60]/10[15)] | Interferon | Exacerbation | 2.0y | 3 | 919 | 69.5 | 55.2 | 14% (8-20)*** | 7 (5-13) | 19% (11-26)*** | *0.34 (0.19-0.49)* | |
| **Parkinson's disease** | | | | | | | | | | | | |

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | [1]RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [61] | Levodopa | UPDRS | 42 | 1 | 311 | | | | | | 0.93 (0.65-1.20)*** | 7.01 (5.00-9.01)*** |
| | | Striatal CIT uptake change (%) | 40 | 1 | 116 | | | | | | -0.44 (-0.01-(-) 0.88)* | -4.22 (-0.10-(-)8.34)* |
| **Breast cancer** | | | | | | | | | | | | |
| [62]/4[16)] | PCT (pg. 1692 fig. 2) | Mort. (age <50) | 15.0y | 60 | 28764 | 42.4 | 32.4 | 10% (ni)*** | 10 (ni) | 24% (ni)*** | *0.24 (0.21-0.26)* | |
| | | Mort. (age 50-69) | 15.0y | | | 50.4 | 47.4 | 3% (ni)*** | 33 (ni) | 6% (ni)*** | *0.07 (0.04-0.09)* | |
| | Tamox. (pg 1704 fig.8) | Mort. | 15.0y | 12 | 10386 | 34.8 | 25.6 | 9% (ni)*** | 11 (ni) | 26% (ni)*** | *0.24 (0.20-0.29)* | |
| **Non-small cell lung cancer** | | | | | | | | | | | | |
| [63]/8 | adjuvant CT | Mortality | 4.5y | 21 | 7408 | ni | ni | 3% (3-4)ni | 30 (28-32) | 9% (3-15)* | *ne* | |
| **Antibiotics for various diseases** | | | | | | | | | | | | |
| [64]/6 | Rhinosinusitis | Cure | 11.8d | 10 | 2785 | 56.6 | 63.9 | 7% (ni)ni | 15 (T7-H 190)ns | 13% (6-20)*** | *0.17 (0.08-0.25)* | |
| [65]/8[17)] | Otitis media | With pain | 2–7d | 10 | 2791 | 22.2 | 16 | 6.2% (ni)ni | 17 (ni) | 28% (26-30)*** | *0.22 (0.12-0.33)* | |
| [66]/8 | Cystitis | Cure | 3-17d | 4 | 1062 | 25.7 | 61.8 | 36.1% (ni)ni | 3 (ni) | 139%(74-195)*** | *0.85 (0.71-0.99)* | |
| [67]/10 | Colorectal surgery | Wound infection | ni | 10 | 813 | 38.6 | 10.2 | 28.4% (23-34)*** | 4 (3-4) | 70% (59-78)*** | *0.94 (0.73-1.15)* | |

Ref = reference, AMSTAR = AMSTAR quality score (range of possible values 0-11), N = number of studies, n = number of participants, % PBO = percentage of patients with the outcome in the placebo group, % Drug = percentage of patients with the outcome in the drug group, ARD = absolute response or risk difference, CI = 95% confidence interval, NNT/H = number needed to treat or number needed to harm, RRR/RR: 'Negative outcomes' (mortality, relapse, exacerbation, hospitalization, dropout etc) are presented as percentage relative risk reductions (RRR), while positive outcomes (response to treatment, improvement, remission) are presented as percentage response ratios (RR). Positive values mean superiority of drug, SDM = standardized difference of means, WMD = weighted mean difference, *** = p<0.001, ** = p<0.01, * = p<0.05 or statistically significant but p-value not indicated, ns= not significant, ni = not indicated, ne = not estimable, Antihyp. = antihypertensive drug, ACE = angiotensin-converting enzyme, ARBs = Angiotensin receptor blockers, CV events = cardiovascular events, vasc. ev. = vascular events, mort. = mortality, maj. = major, ASA = acetylsalicylic acid, prim.prev. = primary prevention, sec.prev. = secondary prevention, mod.-term = moderate term, no. tend. joints = number of tender joints, DO = dropout, ACR20 response = 20% improvement in American College of Rheumatology criteria, Ifx=infliximab, (+ Mtx) = added to methotrexat, Mig. freq. = migraine frequency, FEV1 (l) = forced expiratory volume in one second and in liters, Leukot. Antg. = leukotriene-antagonists, Anti-IgE = Anti-IgE antibodies, Short-act ß-2-ag. = short acting ß-2 agonists, long-act ß-2-ag. = long-acting ß-2 agonists, Mort.(vs conv. treat) = mortality versus conventional treatment, Exacerb/p/y = Exacerbation per patient and year, HbA1c = glycated haemoglobin, α -gluc.-inhib. = alpha glucosidase inhibitors, GLP-1 analogues = glucagon- like peptide analogues, DPP4 inhibitors = dipeptidyl peptidase 4 inhibitors, Virol. resp. = virological response, Morb. and Mort. = morbidity and mortality, PPI = proton pump inhibitors, maint. = maintenance, 5-ASA = 5 aminosalicylic acid, clin. = clinical, maint. remission = maintenance of remission, UPDRS = Unified Parkinson's Disease Rating Scale, PCT = adjuvant polychemotherapy, Tamox. = tamoxifen

The following footmarks correspond to systematic reviews which were of similar quality and were similarly up-to-date as the included ones and yielded comparable results: 1) Wald et al. 2009[68]; 2) BLTTC 2008[69]. This update was based on even more participants, but presented results only based on the subgroups of younger and older participants separately; 3) Lindholm et al. 2005[70], 4) Berger et al. 2006 (presented results on men and women separately)[71]; 5) O'Regan et al. 2008[72], Ward et al. 2007[73], Cheung et al. 2004[74]; 6) Saha et al. 2007[75]; 7) Lechat et al. 1998[76],

Shibata et al. 2001[77], Bouzamondo et al. 2001[78], Heidenreich et al. 1997[79], Krum et al. 2005 (in ACE-inhibitor naïve patients[80]); 8) Weinblatt et al. 1999[81]; 9) Ferrari et al. 2001 and 2002[82,83]; 10) Ducharme et al. 2004[84]; 11) Holgate et al. 2001[85], Bousquet et al. 2004[86]; 12) Drummond et al. 2008[87] and Gartlehner et al. 2006[88]; 13) Rodrigo et al. 2007[89]; 14) Miller et al. 2000[90]; 15) Filippini et al. 2003[91]; 16) a more recent article the same group[92] focussed on oestrogen-receptor-poor breast cancer and found polychemotherapy to be effective, as well, while tamoxifen was not; 17) Vouloumanolou et al. 2009[93] and Rovers et al. 2006[94]

**Table DS4 Systematic reviews on the efficacy of psychiatric drugs versus placebo (full version of Table 2 in the print version with more drugs and meta-analyses, confidence intervals and NNTs)**

| Study (Ref) AM-STAR score | Therapy | Outcome | Mean weeks | N | n | % PBO | % Drug | ARD (CI) | NNT/H (CI) | RRR/ RR (CI) | SDM (CI) | WMD (CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Schizophrenia – acute treatment** | | | | | | | | | | | | |
| [95]/10 | SGAs | Response | 9 | 28 | 4498 | 23.7 | 40.6 | 18% (14-22)*** | 6 (5-7) | 70% (50-90)*** | *0.43 (0.36-0.51)* | |
| | | PANSS/BPRS | 10 | 35 | 5568 | | | | | | 0.51 (0.43-0.58)*** | ni |
| [95]/10 | Haloperidol[1)] | Response | 6 | 10 | 1440 | 19.5 | 29.3 | 12% (7-17)*** | 9 (6-15) | 60% (30-90)*** | *0.30 (0.16-0.43)* | |
| | | PANSS/BPRS | 6 | 11 | 1540 | | | | | | 0.53 (0.43-0.64)*** | ni |
| **Schizophrenia – maintenance treatment** | | | | | | | | | | | | |
| [96]/10 | Antipsychotics | Relapse | 42 | 62 | 6392 | 57.0 | 22.0 | 38% (33-43)*** | 3 (2-3) | 65% (59-69)*** | *0.92 (0.86-0.97)* | |
| **Bipolar – acute manic episode** | | | | | | | | | | | | |
| [97]/6 | Lithium | Response | 3 | 6 | 811 | 34.0 | 52.0 | 17% (8-27)*** | 6 (4-13) | 50% (20-100)** | *0.41 (0.25-0.57)* | |
| | | YMRS/MRS | 3 | 7 | 1165 | | | | | | 0.40 (0.28-0.53) *** | ni |
| [98]/9[3)] | Valproate | Response | 3 | 2 | 182 | 21.1 | 47.1 | 27% (14-40)*** | 4 (3-7) | 150% (10-490)* | *0.66 (0.30-1.02)* | |
| | | YMRS/MRS | 3 | 4 | 782 | | | | | | 0.40 (0.21-0.66)*** | ni |
| [98]/9[3)] | Carbamazepine | Response | 3 | 2 | 443 | 25.5 | 51.1 | 25% (12-38)*** | 4 (3-8) | 100% (60-160)*** | *0.61 (0.39-0.83)* | |
| | | YMRS | 3 | 2 | 331 | | | | | | 0.53 (0.31-0.75) *** | 6.6 (3.9-9.3)*** |
| [99]/10 | SGAs and haloperidol | Response | 3 | 12 | 2939 | 30.8 | 49.9 | 20% (15-24)*** | 5 (4-7) | 60% (5o-80)*** | *0.44 (0.36-0.53)* | |
| | | YMRS/MRS/MS | 3 | 12 | 2939 | | | | | | 0.45 (0.32-0.57)*** | 4.7[2)] (4.1-7.2)*** |
| **Bipolar disorder – depressive episode** | | | | | | | | | | | | |
| [100]/9 | ADs | Response | 7 | 4 | 662 | 34.1 | 57.7 | 34% (15-53)*** | 4 (2-7) | 130% (30-280)** | *0.53 (0.36-0.71)* | |
| **Bipolar disorder – maintenance therapy** | | | | | | | | | | | | |
| [101]/ | Lithium | AR | n.i. | 9 | 421 | 81.4 | 36.2 | 53% (n.i.)*** | 2 (n.i.) | 51% (n.i.)*** | *1.12 (0.88-1.37)* | |
| [102]/8[4)] | Lithium | AR | 73 | 5 | 770 | 61.0 | 40.0 | 24% (8-39)** | 5 (3-13) | 35% (16-50)** | *0.47 (0.31-0.63)* | |
| | | MR | 73 | 4 | 565 | 23.6 | 13.8 | 10% (1-18)* | 10 (5-100) | 38% (5-60)* | *0.36 (0.12-0.60)* | |
| | | DR | 73 | 4 | 565 | 32.3 | 25.0 | 8% (-1-17)ns | 14 (H100-T6) | 28% (-7-51)ns | *0.20 (0.00-0.40)* | |
| [103]/10[5)] | Valproate | AR | 52 | 1 | 281 | 38.3 | 24.1 | 14% (3-26)* | 7 (4-33) | 37% (10-56)* | *0.37 (0.09-0.65)* | |
| | | MR | 52 | 1 | 281 | 22.3 | 17.6 | 5% (-5-15)ns | 20(H20-T7) | 21% (-29-51)ns | *0.16 (-0.16-0.49)* | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | DR | 52 | 1 | 281 | 16.0 | 6.4 | 10% (1-18)* | 10 (6-100) | 60% (18-80)* | *0.56 (0.12-1.01)* | |
| **Major depressive disorder – acute episode** | | | | | | | | | | | | |
| [104]/8[6)] | Paroxetine | Response | 7.5 | 22 | 5112 | 42.4 | 53.2 | 10% (7-13)*** | 10 (8-14) | 20% (20-30)*** | *0.24 (0.18-0.30)* | |
| | | HAM-D | 7.5 | 34 | 5764 | | | | | | 0.31 (0.22-0.40)*** | 2.62 (2.00-3.25)*** |
| [105]/4 | TCAs (new AD studies) | Response | 6 | 32 | 4314 | 31.0 | 46.0 | 15% (11-17)*** | 7 (5-8) | 50% (n.i.)*** | *0.35 (0.28-0.42)* | |
| | | HAM-D | 6 | | | | | | | | 0.33 (0.27-0.39)*** | 2.65 (2.17-3.13)*** |
| [106]/7 | Fluoxetine | Response | 6 | 16 | 2761 | 24.2 | 37.8 | 13.6% (n.i.)*** | 7 (n.i.) | 65% (44-85)*** | *0.35 (0.26-0.45)* | |
| | | HAM-D | 6 | 7 | n.i. | | | | | | 0.30 (0.21-0.39)n.i.. | n.i. |
| [107]/7[7)] | New ADs | HAM-D | 6 | 35 | 5133 | | | | | | 0.32 (0.25-0.40)*** | 1.80 (n.i.)*** |
| [108]/11 | TCAs (low-dose) | Response[12)] | 4 | 22 | 1119 | 29.6 | 46.5 | 27% (17-37)*** | 4 (3-6) | 64% (35-98)*** | *0.40 (0.26-0.54)* | |
| | | Severity[12)] | 4 | 16 | 861 | | | | | | 0.40 (0.21-0.59)*** | n.e. |
| **Major depressive disorder – maintenance treatment** | | | | | | | | | | | | |
| [109]/9 | ADs | Relapse | 63 | 35 | 5032 | 41.0 | 18.0 | 23% (n.i.)ni | 4 (n.i.) | 58% (49-68)*** | *0.64 (0.56-0.71)* | |
| [110]/10 | New ADs | Recurrence | 68 | 11 | 3326 | 48.0 | 26.0 | 22% (n.i.)ni | 5 (4-6) | 44% (34-52)*** | *0.53 (0.45-0.61)* | |
| [101]/ | Lithium | Relapse (UpD) | n.i. | 9 | 227 | 75.0 | 36.0 | 39% (n.i.)ni | 3 (n.i.) | 53% (63-79)*** | *0.92 (0.61-1.23)* | |
| **Obsessive compulsive disorder** | | | | | | | | | | | | |
| [111]/11 | SSRIs | YBOCS | 10 | 17 | 3097 | | | | | | 0.44 (0.36-0.52)*** | 3.21 (2.57-3.84)*** |
| | | Response | 10 | 13 | 2709 | 22.6 | 43.3 | 20% (17-24)*** | 5 (4-6) | 84% (56-117)*** | *0.53 (0.44-0.62)* | |
| [112]/3[8)] | Clomipramine | YBOCS | (8-13) | 7 | 808 | | | | | | 0.48 (0.34-0.62)*** | 8.19 (5.85-10.53)*** |
| | Various SSRIs | YBOCS | (8-13) | 18 | 1794 | | | | | | 0.31 (0.21-0.41)*** | 1.85 (1.27-2.43)*** |
| **Panic disorder** | | | | | | | | | | | | |
| [113]/4[9)] | TCAs | Anxiety | 8 | 23 | n.i. | | | | | | 0.41 (n.i.)* | n.i. |
| [113]/4[10)] | SSRIs | Anxiety | 8 | 17 | n.i. | | | | | | 0.41 (n.i.)* | n.i. |
| [113]/4 | Benzodiazepines | Anxiety | 8 | 25 | n.i. | | | | | | 0.40 (n.i.)* | n.i. |
| **Dementia** | | | | | | | | | | | | |
| [114]/8[11)] | ChE inhibitors | ADAS-cog | 26 | 10 | 4236 | | | | | | 0.41 (0.30-0.51)*** | 2.38 (1.79-2.97)*** |
| | | MMSE | 28 | 9 | 3118 | | | | | | 0.39 (0.21-0.57)*** | 1.33 (0.73-1.92)*** |
| | | UoI | 26 | 8 | 3402 | 16.8 | 24.4 | 7% (3-11)*** | 14 (9-33) | 43% (18-73)*** | *0.26 (0.17-0.35)* | |
| **Attention-deficit/hyperactivity disorder** | | | | | | | | | | | | |
| [115]/9 | Methylphenidate | Hyperactivity | 3.3 (0.5-28) | 22 | 963 | | | | | | 0.78 (0.64-0.91)*** [13,14)] | n.i. |
| [116]/5 | Amphetamine | ADHD symptoms | 6 | 6 | 384 | | | | | | 1.00 (0.91-1.10) *** [14)] | n.i. |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [117]/8 | Atomoxetine | Global symptoms | n.i | 7 | 1615 | | | | | | 0.64 (0.52-0.76)*** | n.i. |
| | | Response | n.i. | 6 | 814 | 34.3 | 63.4 | 29% (22-35)*** | 3 (3-4) | 79% (52-110)*** | *0.66 (0.50-0.82)* | |

Ref = reference, AMSTAR = AMSTAR quality score (range of possible values 0-11), N = number of studies, n = number of participants, % PBO = percentage of patients with the outcome in the placebo group, % Drug = percentage of patients with the outcome in the drug group, ARD = absolute response or risk difference, CI = 95% confidence interval, NNT/H = number needed to treat or number needed to harm, RRR/RR: 'Negative outcomes' (mortality, relapse, exacerbation, hospitalization, dropout etc) are presented as relative risk reductions (RRR), while positive outcomes (response to treatment, improvement, remission) are presented as percentage response ratios (RR). Positive values mean superiority of drug, SDM = standardized difference of means, WMD = weighted mean difference, *** = p<0.001, ** = p<0.01, * = p<0.05 or statistically significant but p-value not indicated, ns= not significant, ni = not indicated, SGA = second generation antipsychotics, PANSS/BPRS = total score of either the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale, YMRS/MRS/MS = Young Mania Rating Scale or Mania Rating Scale or Mania Scale, ADs = Antidepressants, AR = Any relapse, DR = Depressive relapse, MR = Manic relapse, H = harm, T = treat, HAM-D = Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale, MMSE = Mini Mental State Examination, SSRIs = selective serotonin reuptake inhibitors, TCAs = Tricyclic Antidepressants, new AD studies = here TCAs were active comparators in studies comparing new antidepressants with placebo, SleepOL = sleep onset latency, d = days, min = minutes, UoI = Unchanged or improved, UpD = Unipolar depression, ChE = Cholinesterase, Benzod. = Benzodiazepines, ADAS-cog = change from baseline of the Alzheimer's Disease Assessment Scale - cognitive subscale; 1) in studies on SGAs, 2) Only studies based on the YMRS 3) updated and supplemented by our own searches, 4) consistent with Burgess et al. 2001[118] and Beynon et al. 2008[119], 5) consistent with Beynon et al. 2008[119], 6) consistent with Katzman et al. 2007[120], 7) consistent with Turner et al. 2008[121], 8) all studies published after 1989, 9) consistent with Gould et al. 1995[122] and Australian and New Zealand College 2003[123], 10) consistent with Otto et al. 2001[124], 11) consistent with Raina et al. 2008[125] and Hansen 2008[126], 12) after correspondence with the primary author a clear outlier with extremly positive results was excluded, 13) teacher rated, parent rated result was 0.54 (0.40-0.67), 14) consistent with the most recent meta-analysis which was poorly reported [127]

**Fig. DS1: PRISMA diagram - hypertension**

(MEDLINE search term: „Hypertension"[Mesh] AND "Meta-Analysis "[Publication Type])

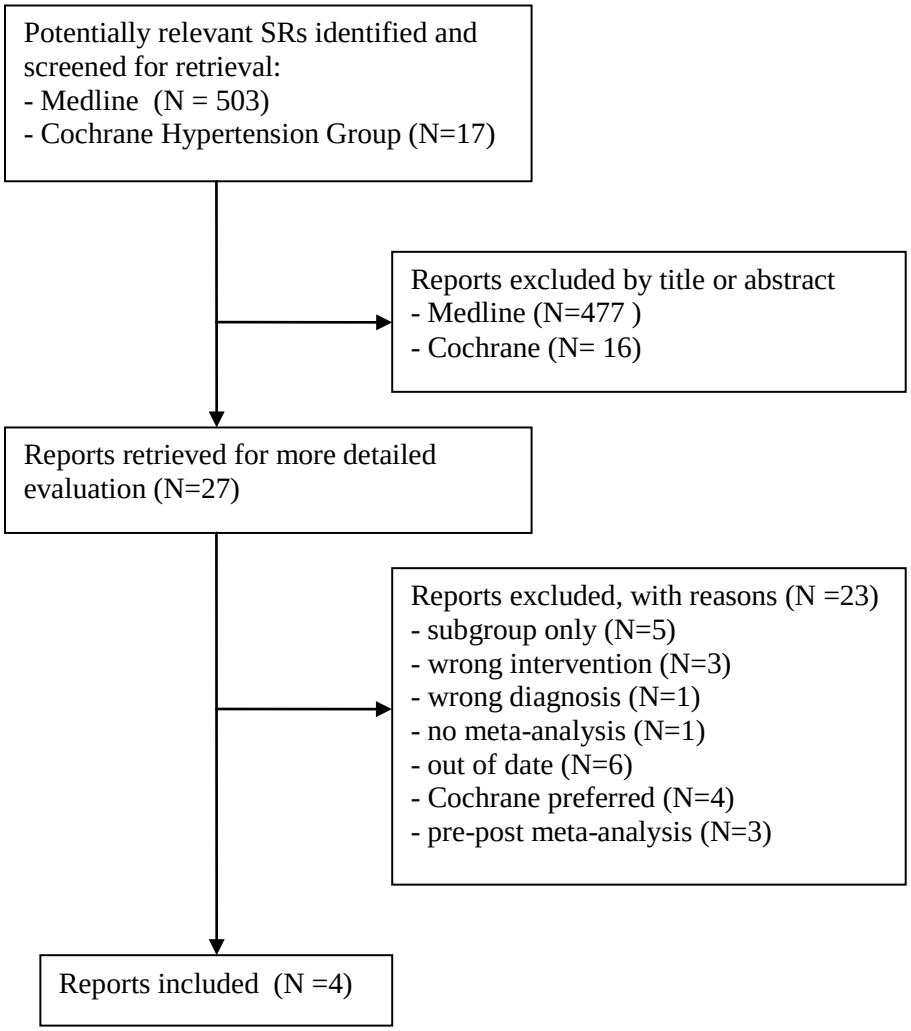


**Fig. DS2: PRISMA diagram - stroke**

(MEDLINE search term: „Stroke"[Mesh] AND "Meta-Analysis "[Publication Type])

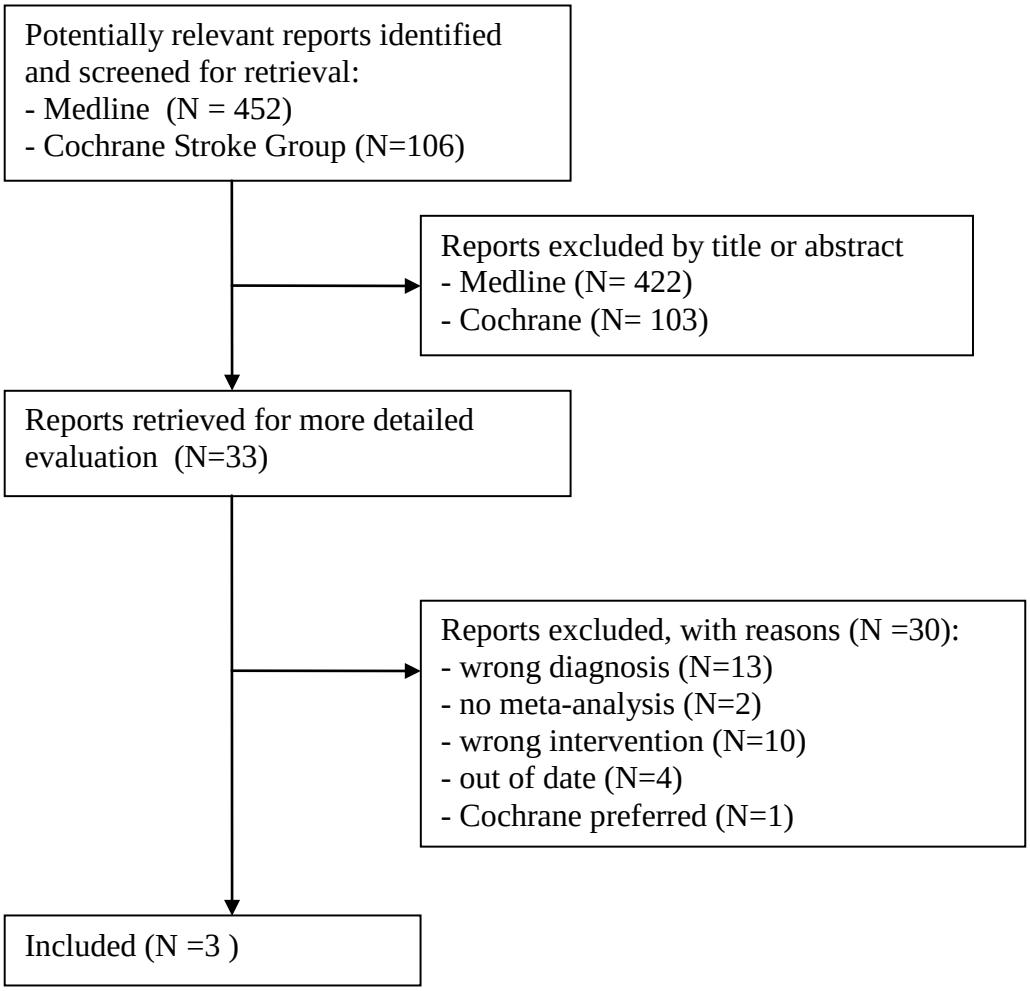


**Fig. DS3: PRISMA diagram - prevention of cardiovascular diseases**

(MEDLINE search term: „Cardiovascular disease"[Mesh] AND „prevention“ [Mesh] AND "Meta-Analysis "[Publication Type])

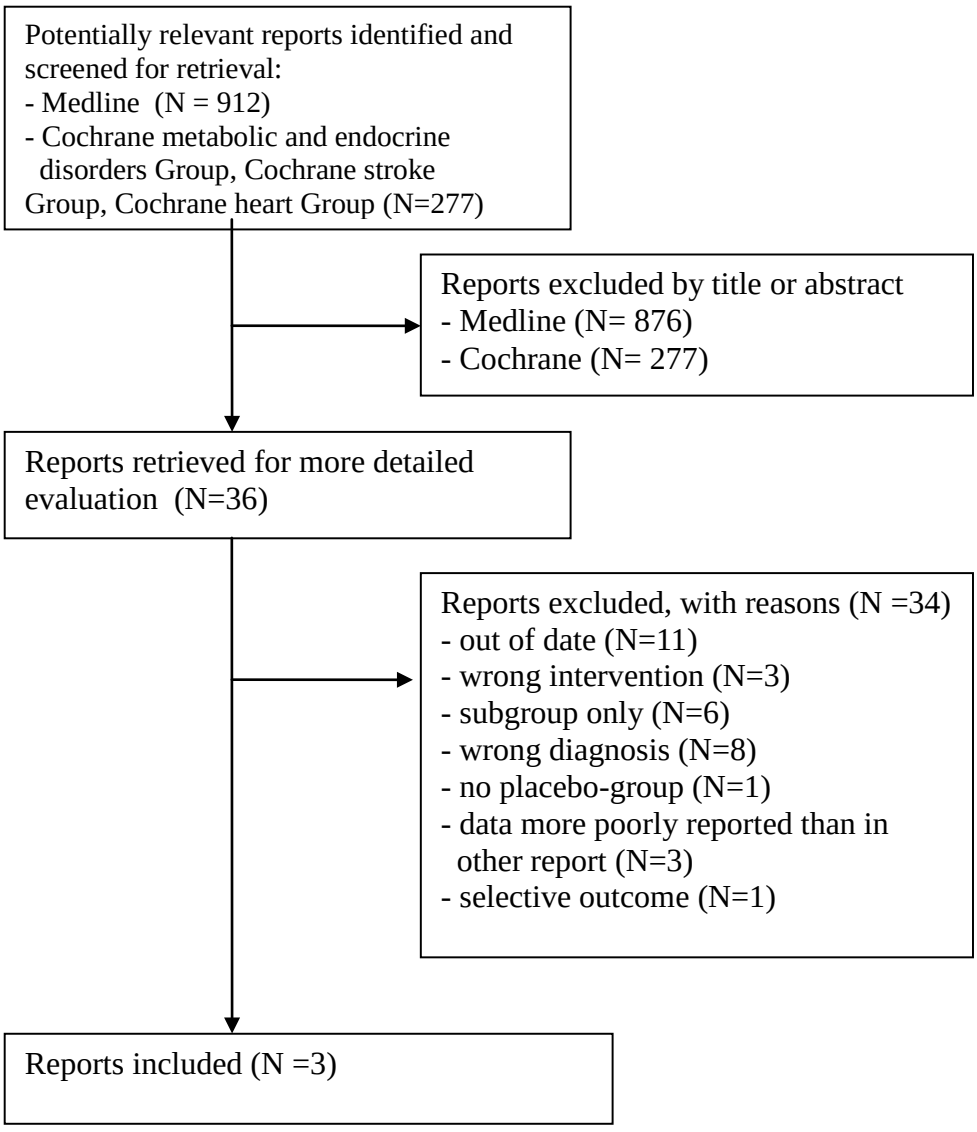


**Fig. DS4: PRISMA diagram - heart failure**

(MEDLINE search term: „Heart failure"[Mesh] AND "Meta-Analysis "[Publication Type])

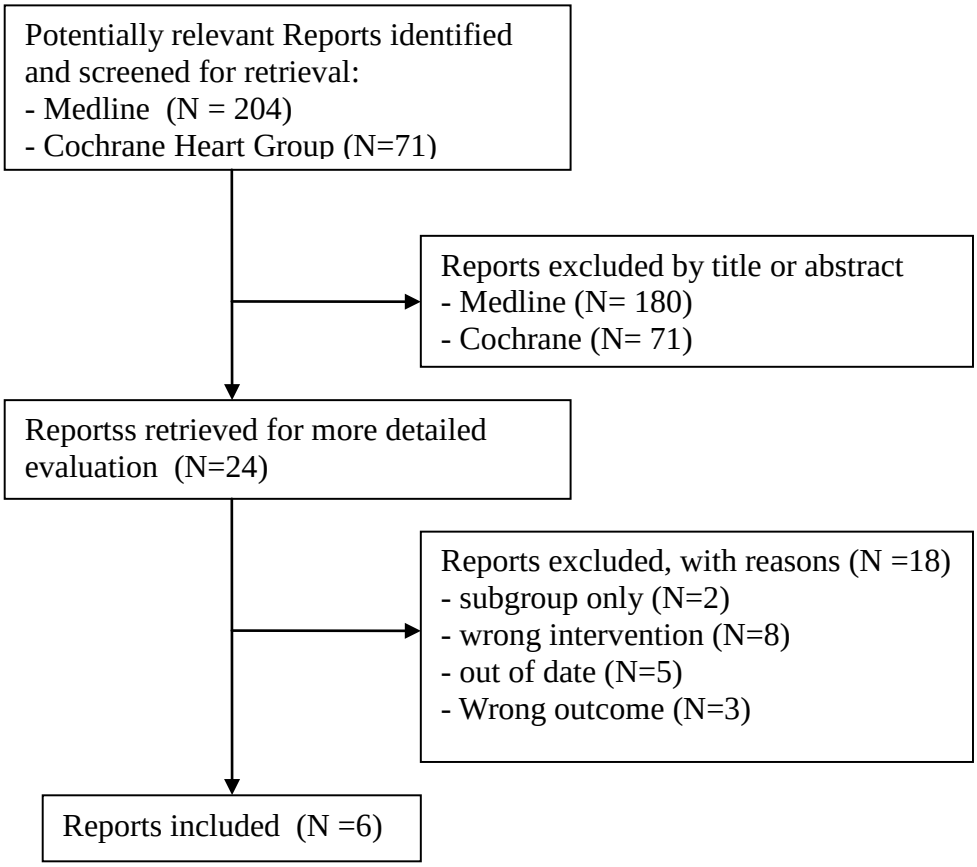


**Fig. DS5: PRISMA diagram - rheumatoid arthritis**

(MEDLINE search term: „Arthriris, rheumatoid"[Mesh] AND "Meta-Analysis "[Publication Type])

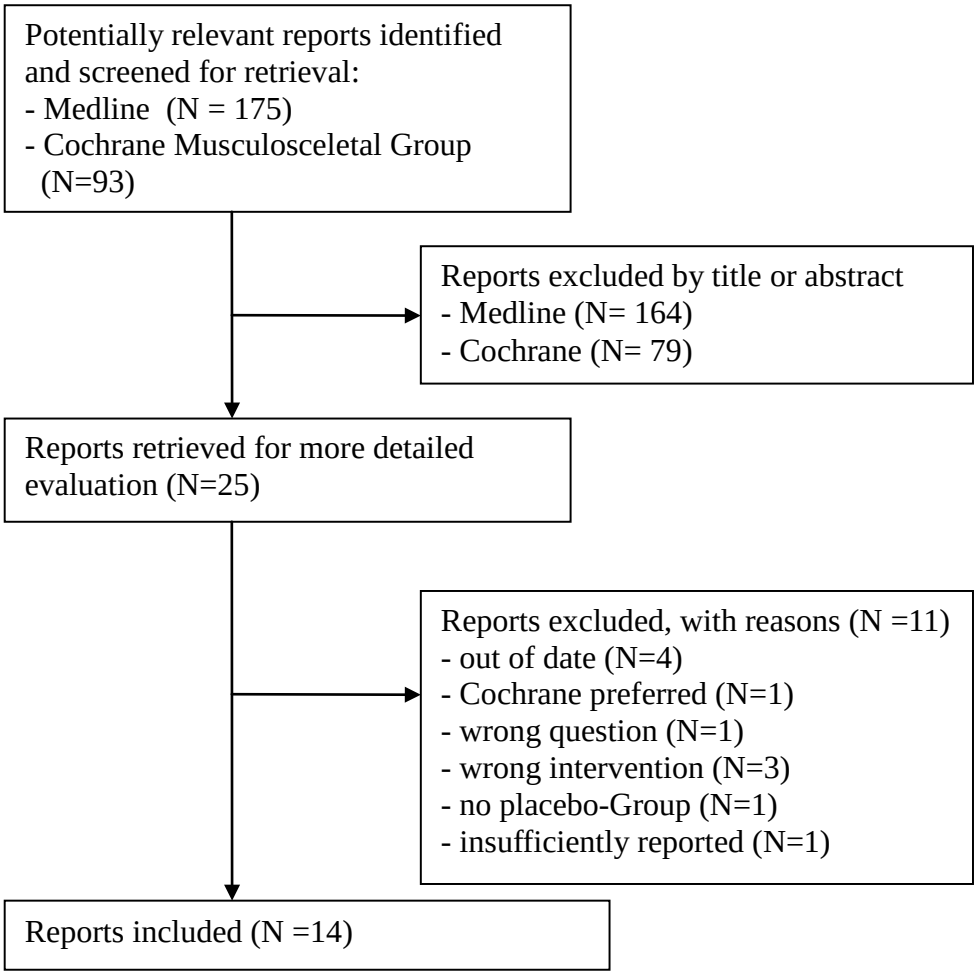


**Fig. DS6: PRISMA diagram - migraine**

(MEDLINE search term: „Migraine Disorders"[Mesh] AND "Meta-Analysis "[Publication Type])

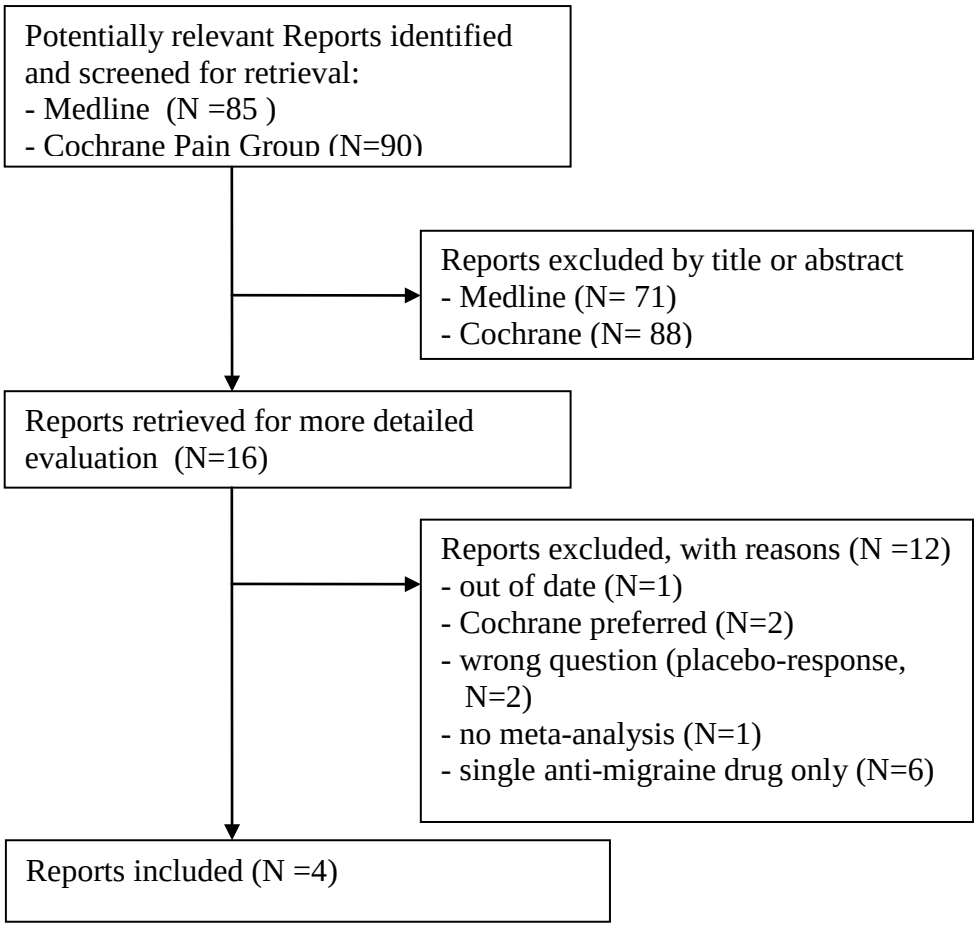


**Fig. DS7: PRISMA diagram - asthma**

(MEDLINE search term: „Asthma"[Mesh] AND "Meta-Analysis "[Publication Type])

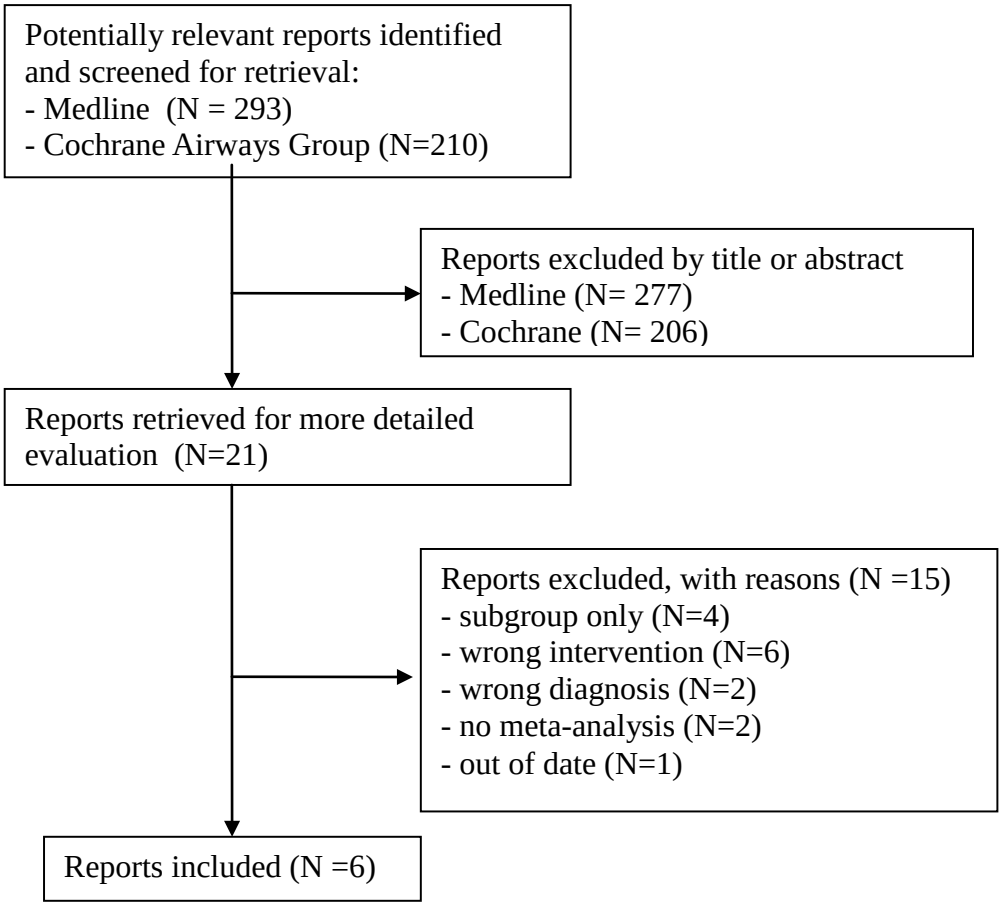


**Fig. DS8: PRISMA diagram - chronic obstructive pulmonary disease**

(MEDLINE search term: „Chronic obstructive pulmonary disease"[Mesh] AND "Meta-Analysis "[Publication Type])

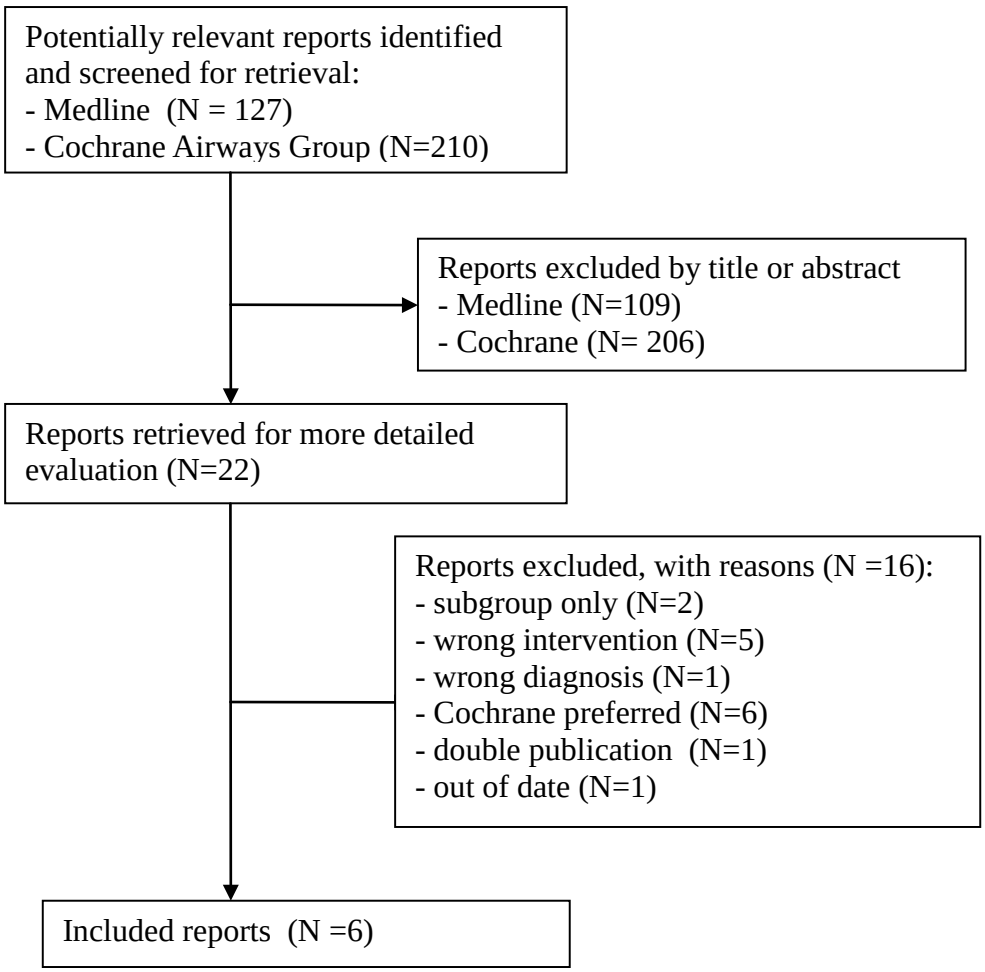


**Fig. DS9: PRISMA diagram - diabetes mellitus**

(MEDLINE search term: „Diabetes mellitus"[Mesh] AND "Meta-Analysis "[Publication Type])

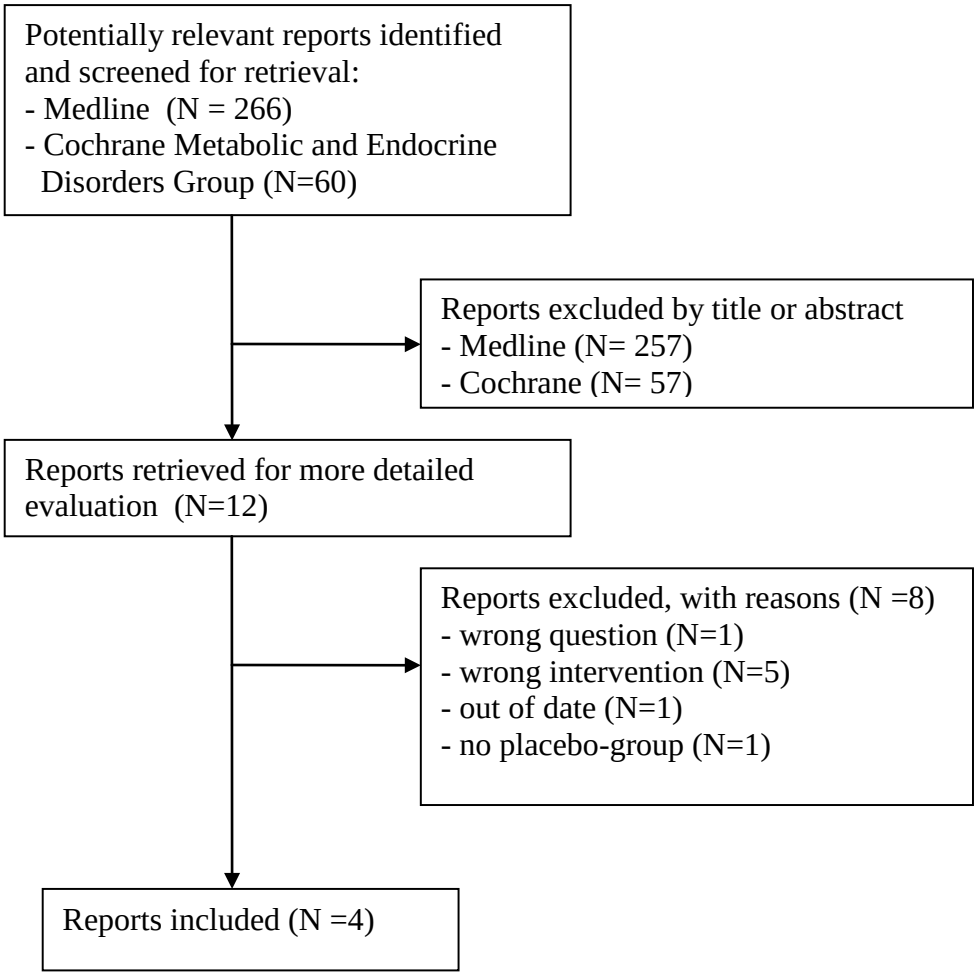


**Fig. DS10: PRISMA diagram - hepatitis C**

(MEDLINE search term: „Hepatitis C"[Mesh] AND "Meta-Analysis "[Publication Type])

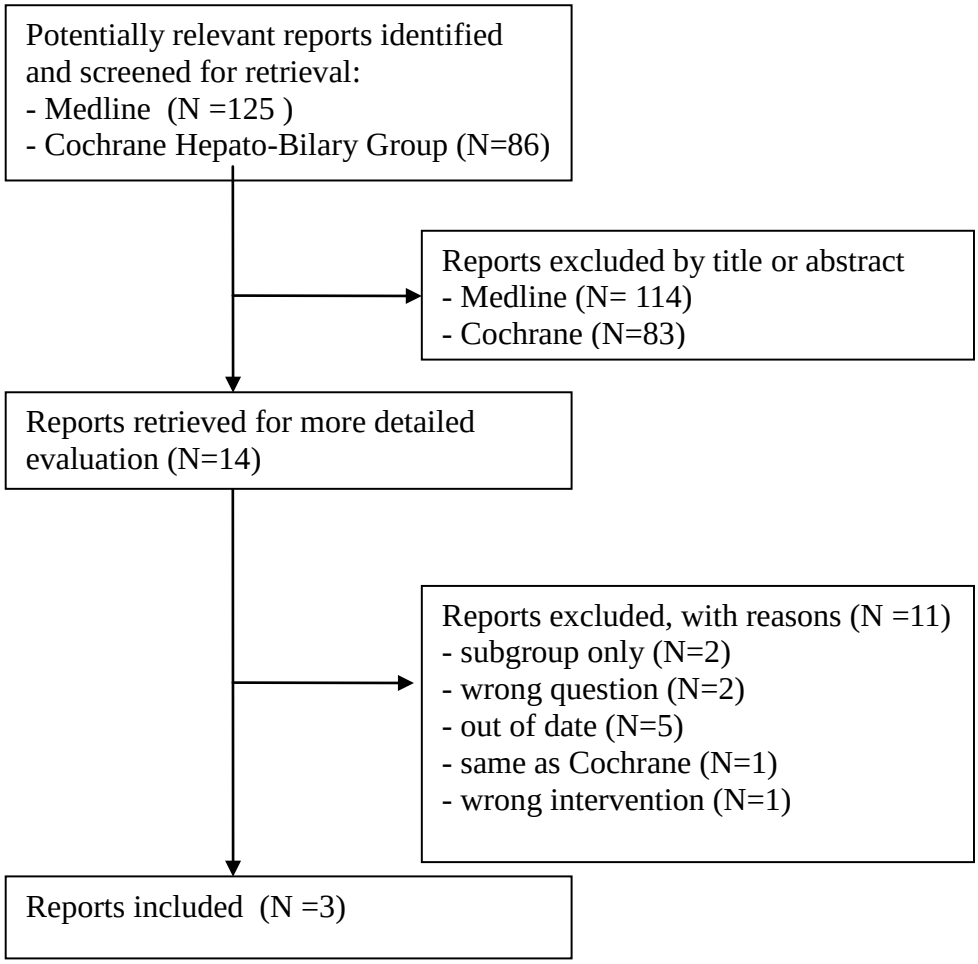


**Fig. DS11: PRISMA diagram - proton pump inhibitors for esophagitis**

(MEDLINE search term: "Esophagitis, Peptic"[Mesh] "Meta-Analysis "[Publication Type])

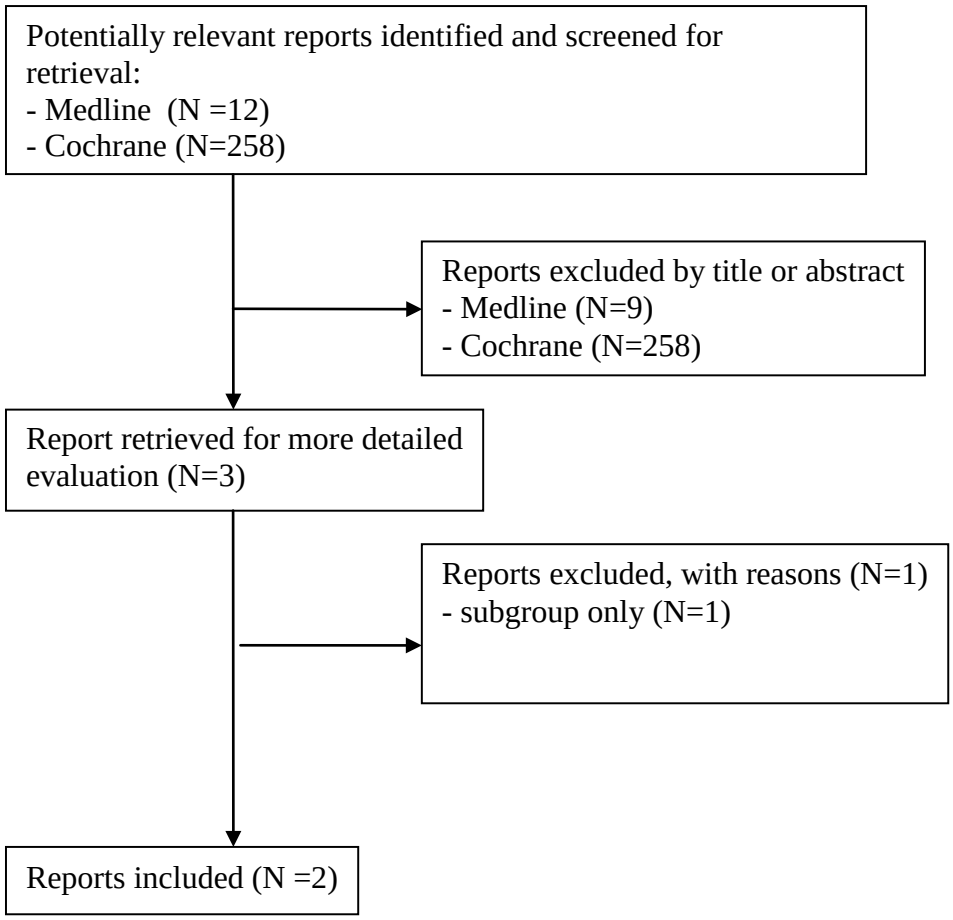


**Fig. DS12: PRISMA diagram - ulcerative colitis**

(MEDLINE search term: „Colitis, ulcerative"[Mesh] AND "Meta-Analysis "[Publication Type])

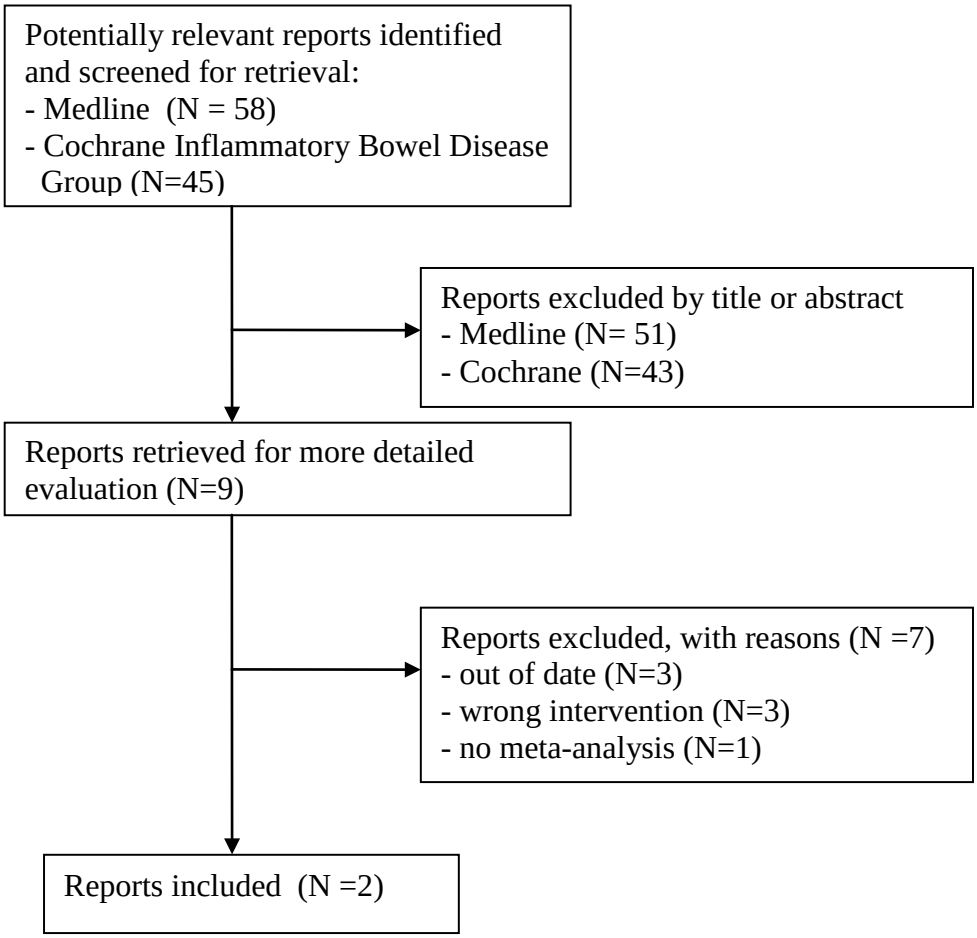


**Fig. DS13: PRISMA diagram - multiple sclerosis**

(MEDLINE search term: „Multiple Sclerosis"[Mesh] AND "Meta-Analysis "[Publication Type])

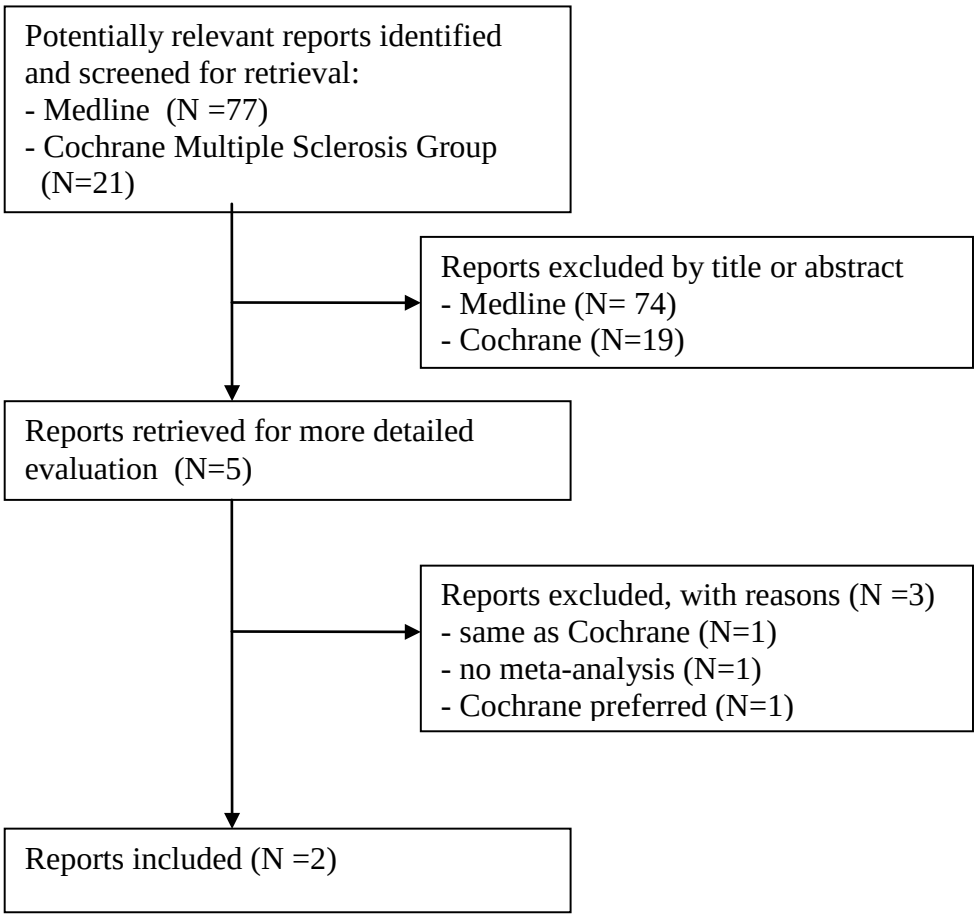


**Fig. DS14: PRISMA diagram - Parkinson disease**

(MEDLINE search term: „Parkinson Disease"[Mesh] AND "Meta-Analysis "[Publication Type])

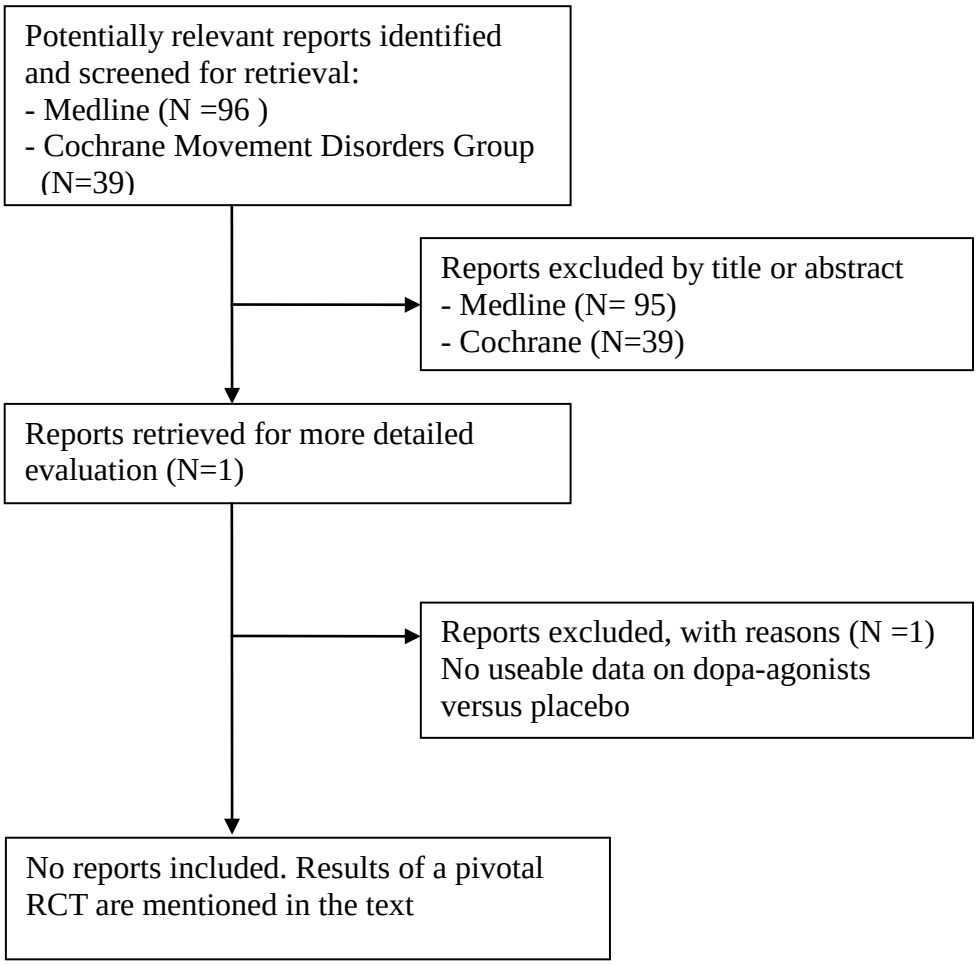


**Fig. DS15: PRISMA diagram - breast cancer**

(MEDLINE search term: „Breast Neoplasms"[Mesh] AND "Meta-Analysis "[Publication Type])

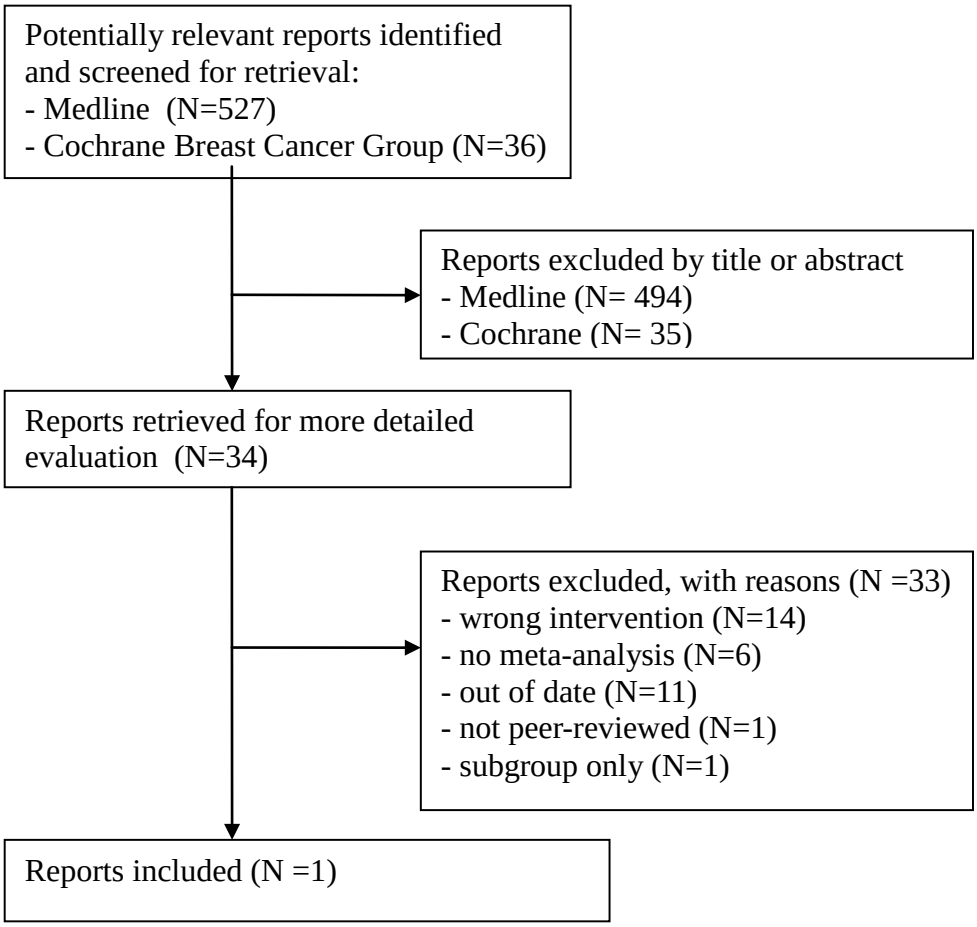


**Fig. DS16: PRISMA diagram - lung cancer**

(MEDLINE search term: „Lung Neoplasms"[Mesh] AND "Meta-Analysis " [Publication Type])

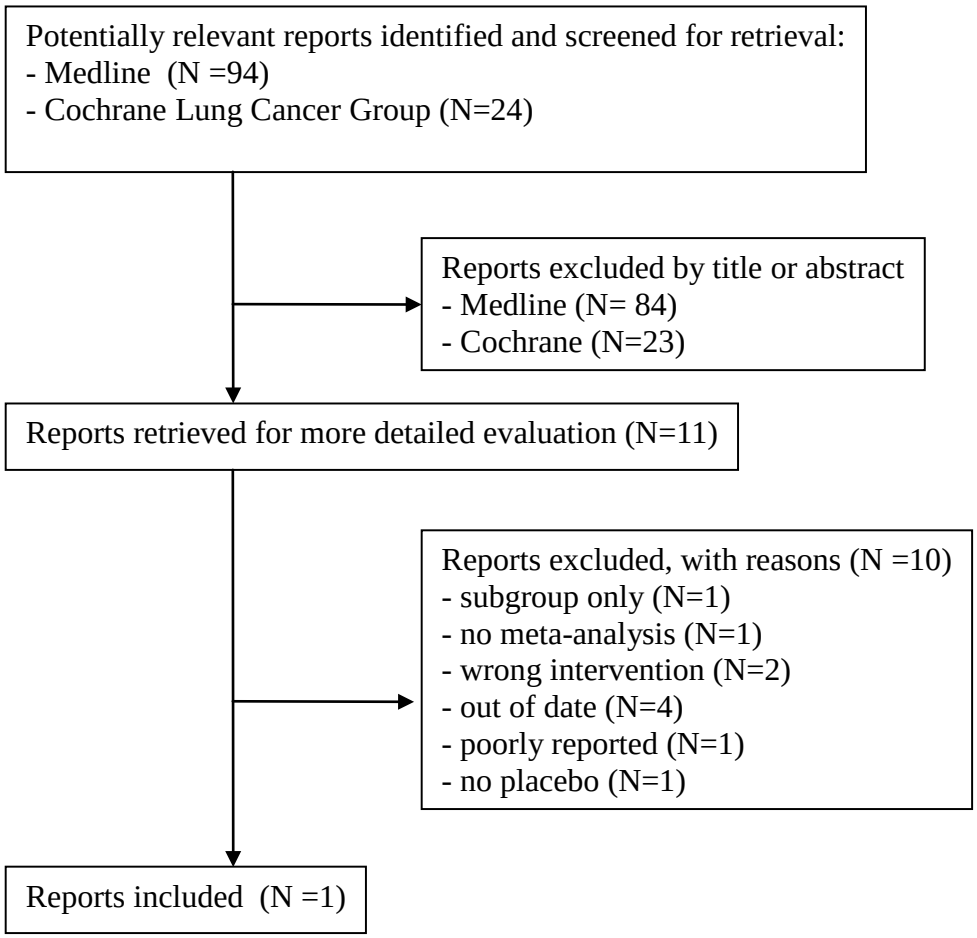


**Fig. DS17: PRISMA diagram - antibiotics**

(MEDLINE search term: „Antibacterial agents"[Mesh] AND "Meta-Analysis "[Publication Type])

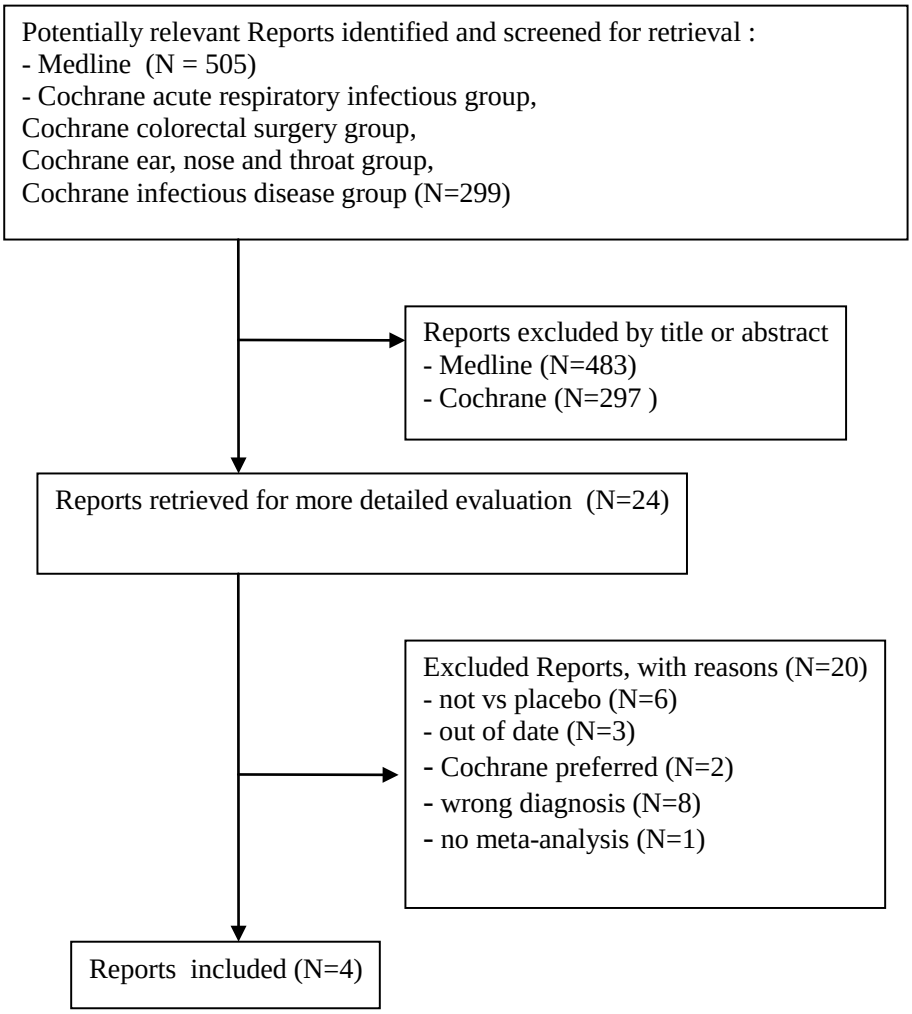


**Fig. DS18: PRISMA diagram - schizophrenia**

(MEDLINE search term: „Schizophrenia"[Mesh] AND "Meta-Analysis "[Publication Type])

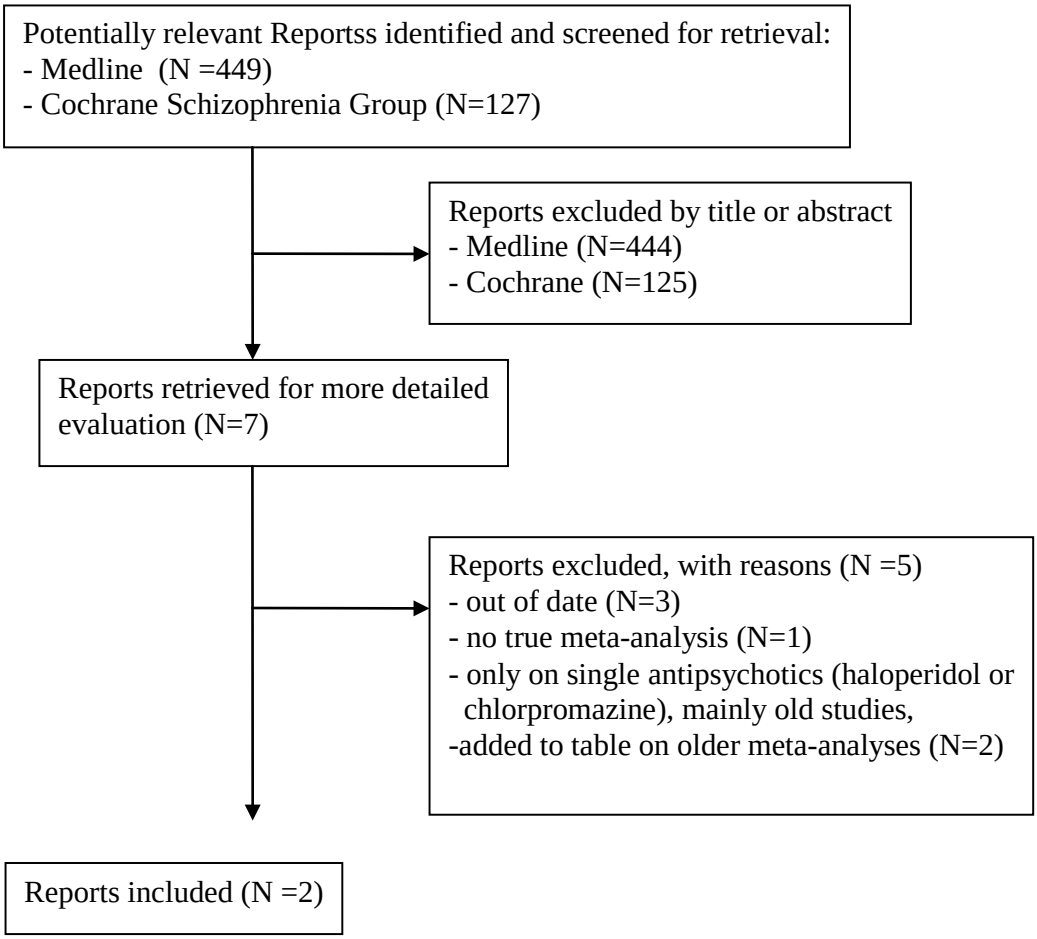


**Fig. DS19: PRISMA diagram - bipolar disorder**

(MEDLINE search term: „Bipolar Disorder"[Mesh] AND "Meta-Analysis "[Publication Type])

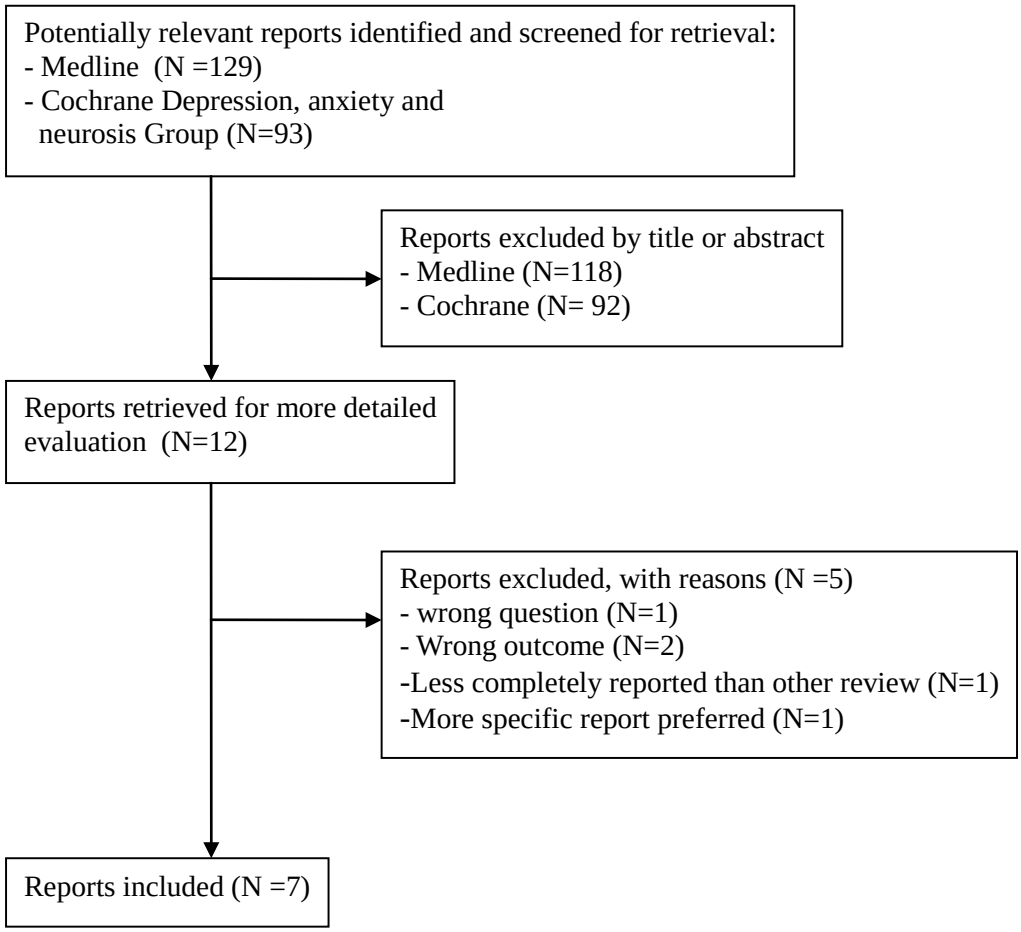


**Fig. DS20: PRISMA diagram – obsessive–compulsive disorder**

(MEDLINE search term: „Obsessive-compulsive disorder"[Mesh] AND "Meta-Analysis "
[Publication Type])

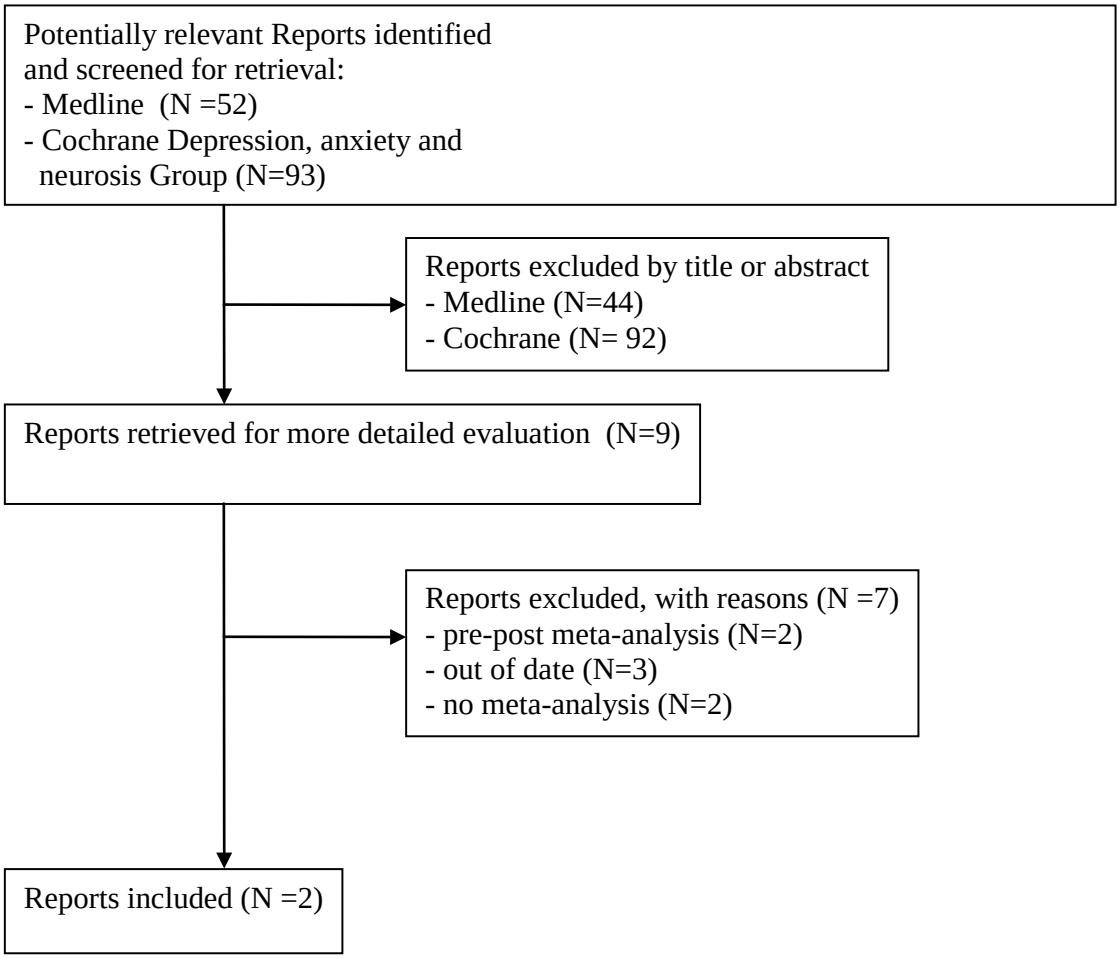


**Fig. DS21: PRISMA diagram - major depressive disorder**

(MEDLINE search term: „Depressve Disorder"[Mesh] AND "Meta-Analysis [Publication Type])

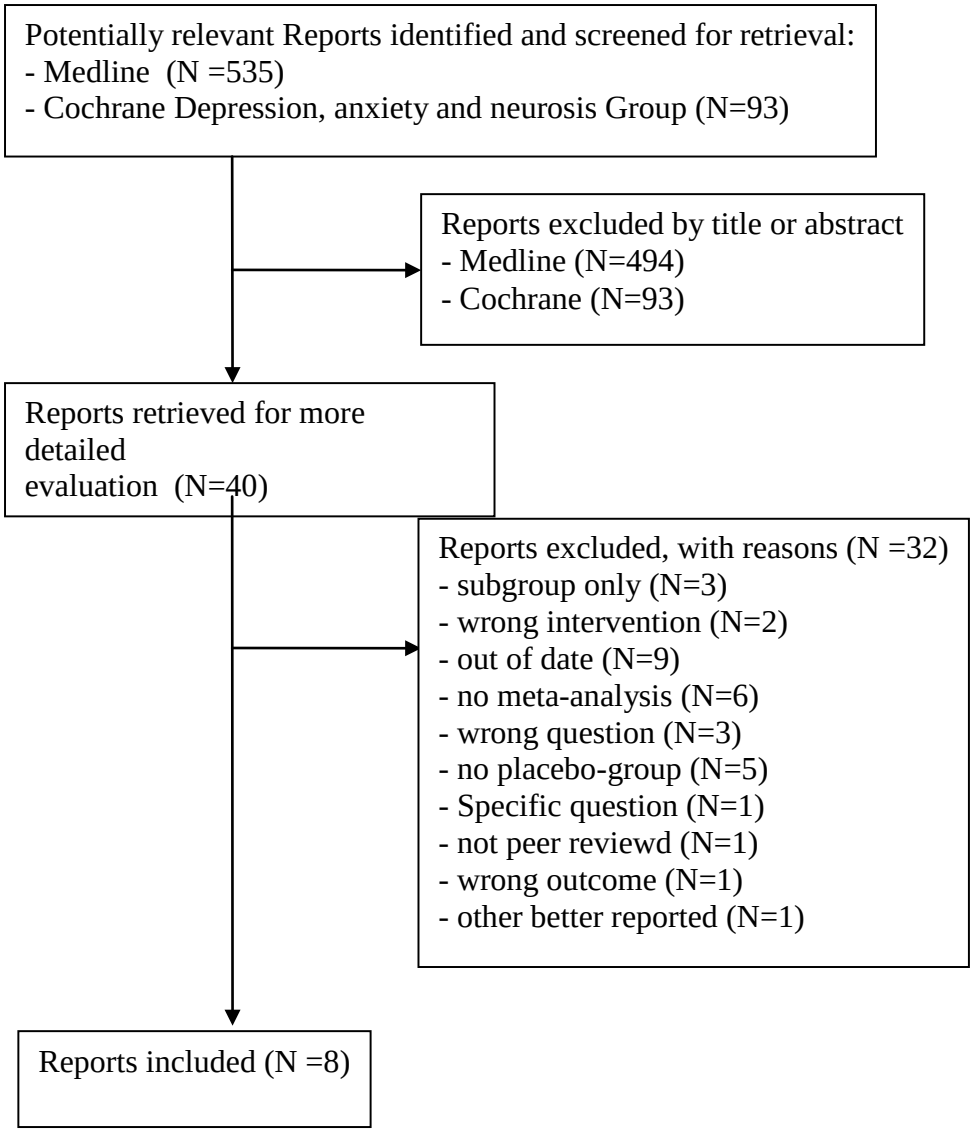


**Fig. DS22: PRISMA diagram - panic disorder**

(MEDLINE search term: „Panic disorder"[Mesh] AND "Meta-Analysis "[Publication Type])

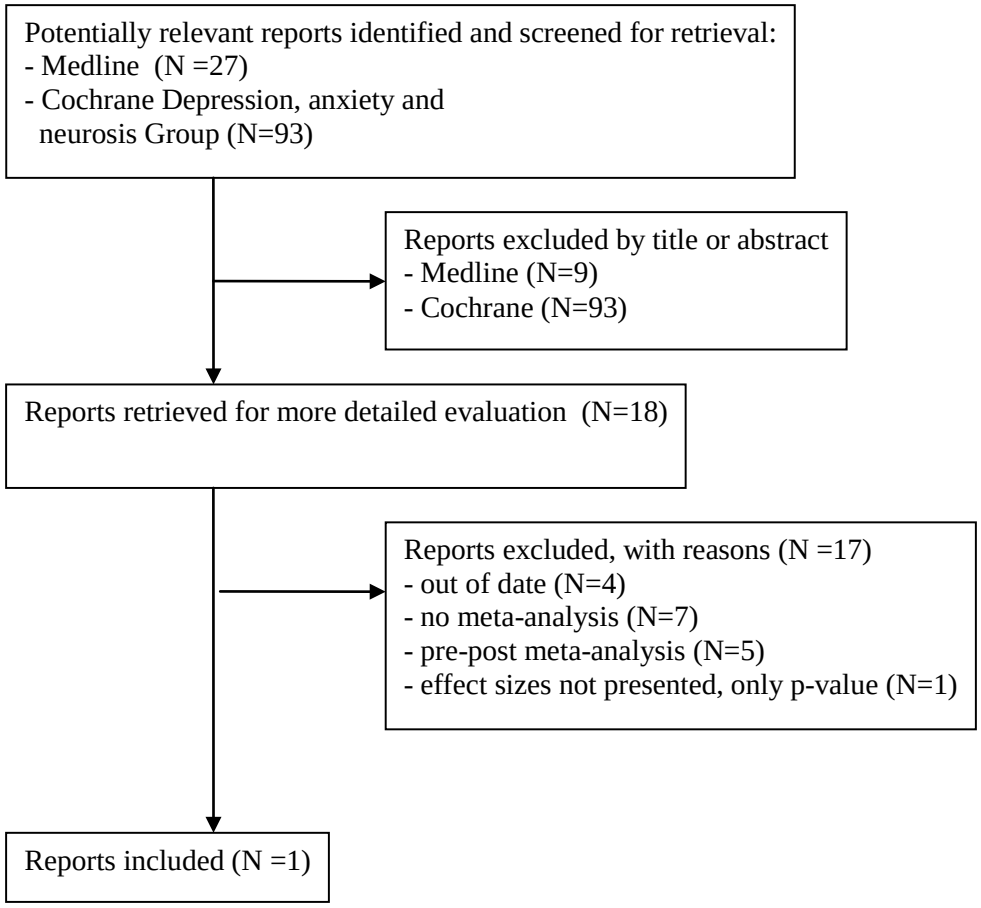


**Fig. DS23: PRISMA diagram - dementia**

(MEDLINE search term: „Dementia"[Mesh] AND "Meta-Analysis "[Publication Type])

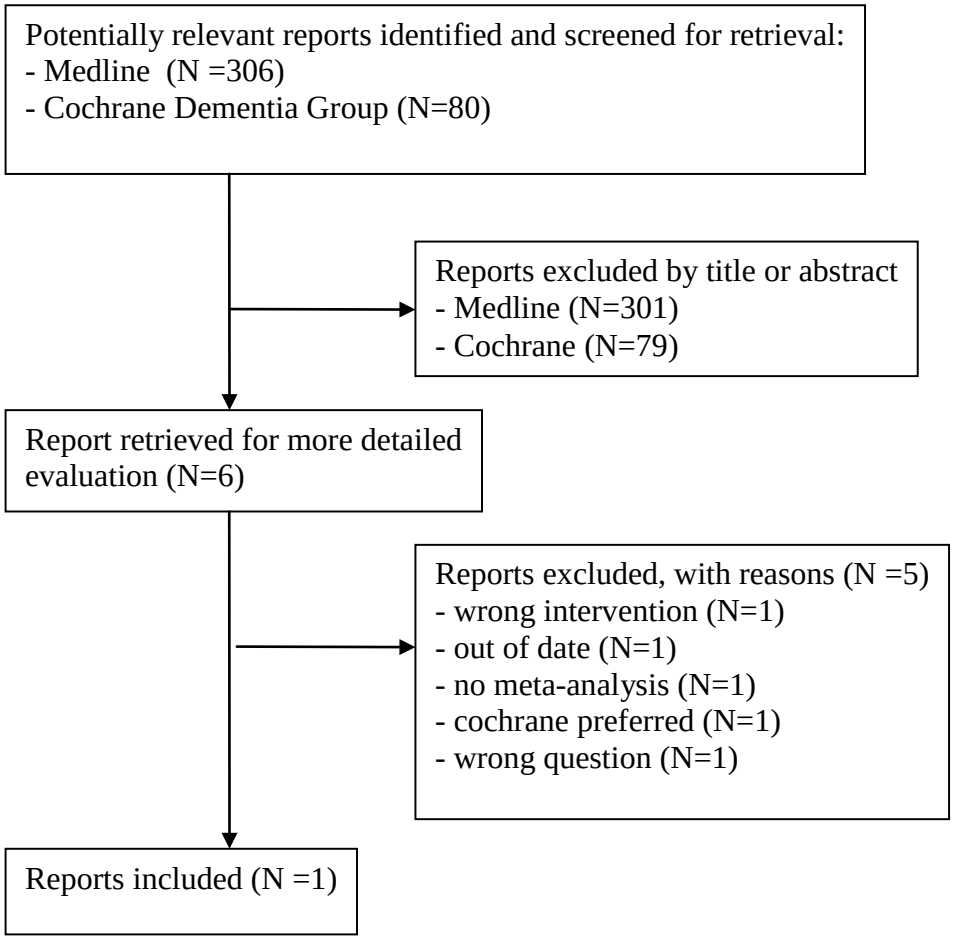


**Fig. DS24: PRISMA diagram - attention-deficit hyperactivity disorder**

(MEDLINE search term: Attention Deficit and Disruptive Behavior Disorders"[Mesh] "Meta-Analysis "[Publication Type])

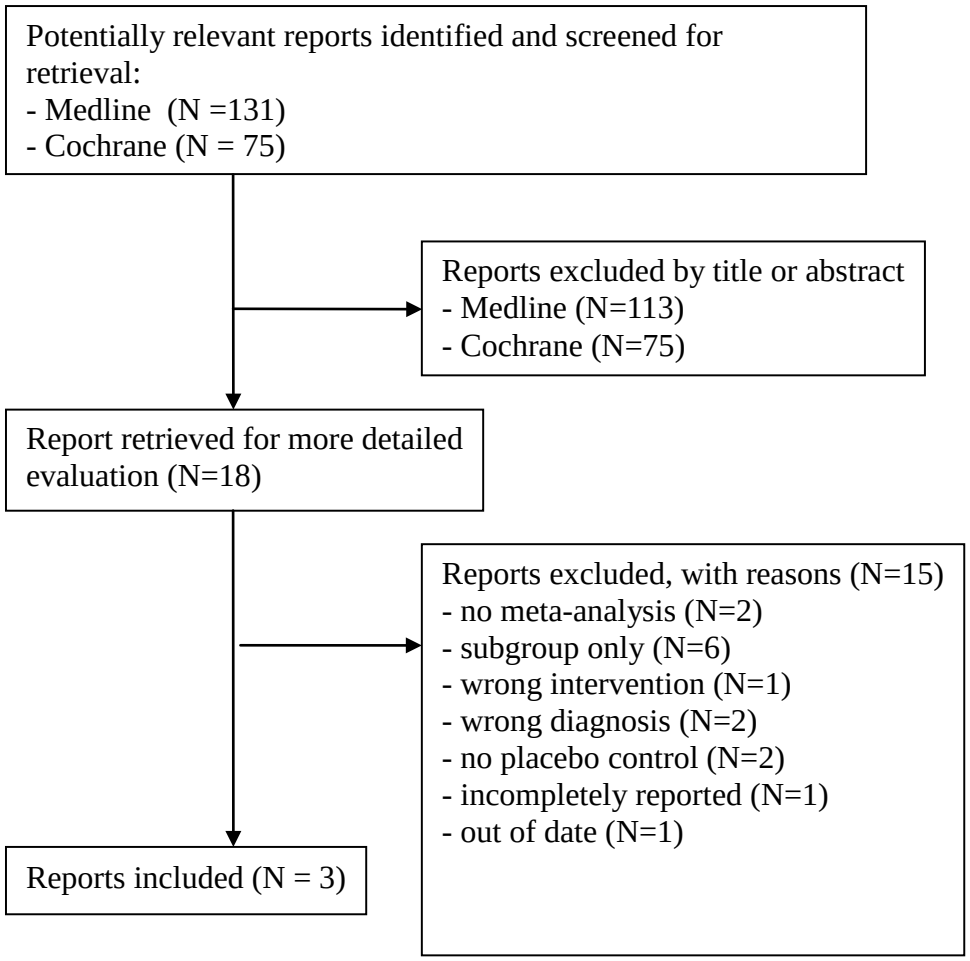


**Fig. DS25 Systematic presentation of the effect sizes in Figure 1 labelled by 'Disease − Drug – Outcome.** This figure presents the same results as Fig. 1 in the print version, but indicates exactly which result corresponds to which result in the text and Tables 1 and 2. To enable verification Tables 1 and 2 the bars are consistently labelled by 'Disease – Drug – Outcome'.

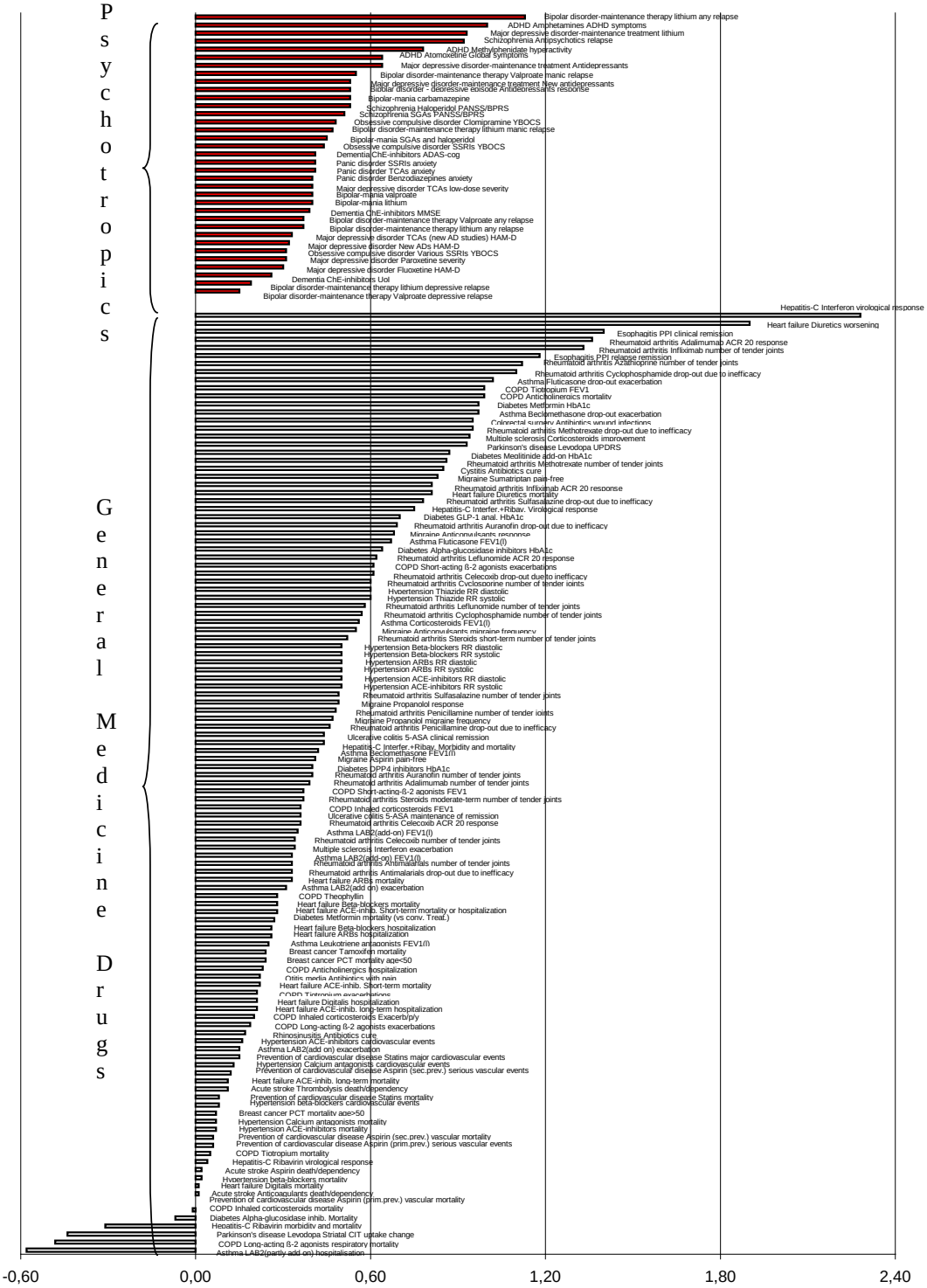


**Fig. DS26 Summary of the percentage relative risk reductions/response ratios presented in Tables DS3 and DS4: dot plot.** All relative risk reductions in Tables DS3 and DS4 are presented. Data on older meta-analyses from Table DS1 are not included. Effect sizes of general medicine medication are presented on the left-hand side as black dots (median 29, mean 56, 95% CI 29–84), psychiatric drugs on the right-hand side as red dots (median 61, mean 58, 95% CI 48–73).

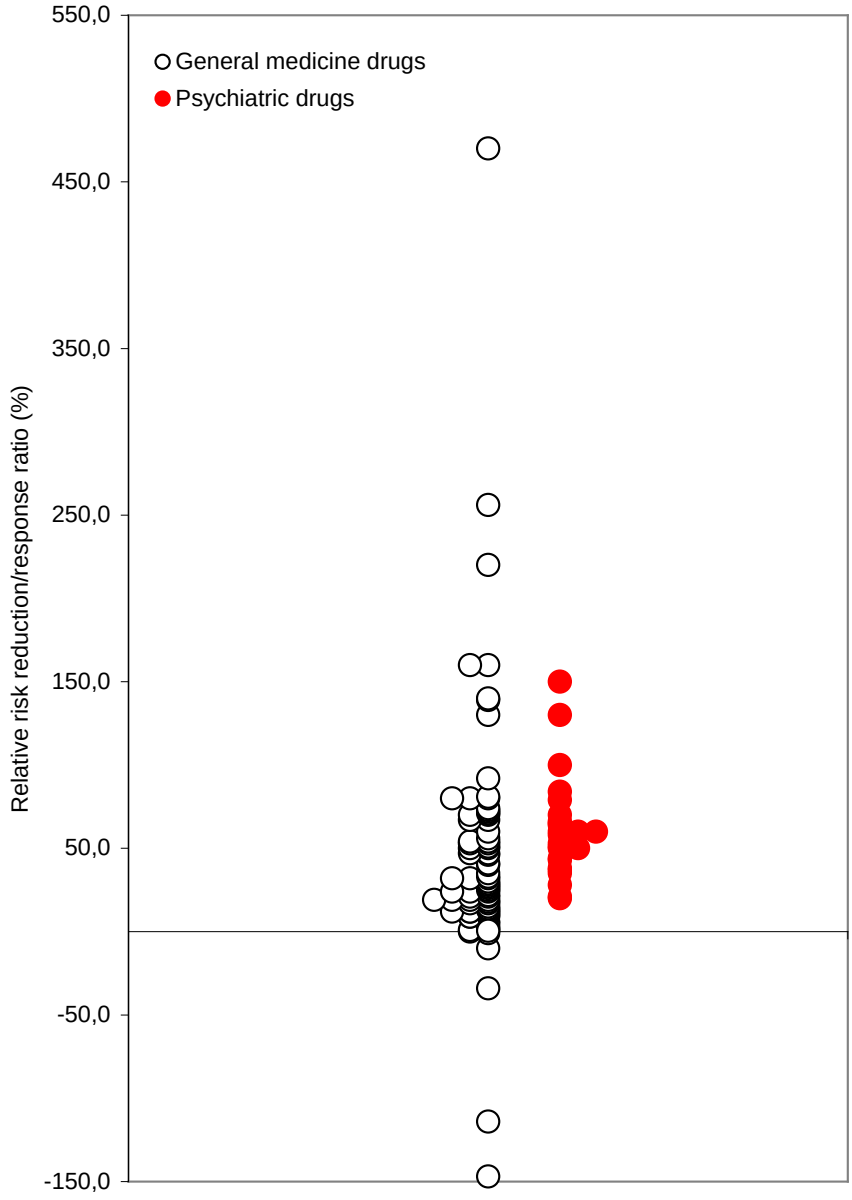


**Fig. DS27 Summary of the percentage relative risk reductions/response ratios presented in Tables DS3 and DS4: bar chart.** This figure presents the same results as Fig. DS26, but indicates exactly which corresponds to which result in Tables DS3 and DS4.

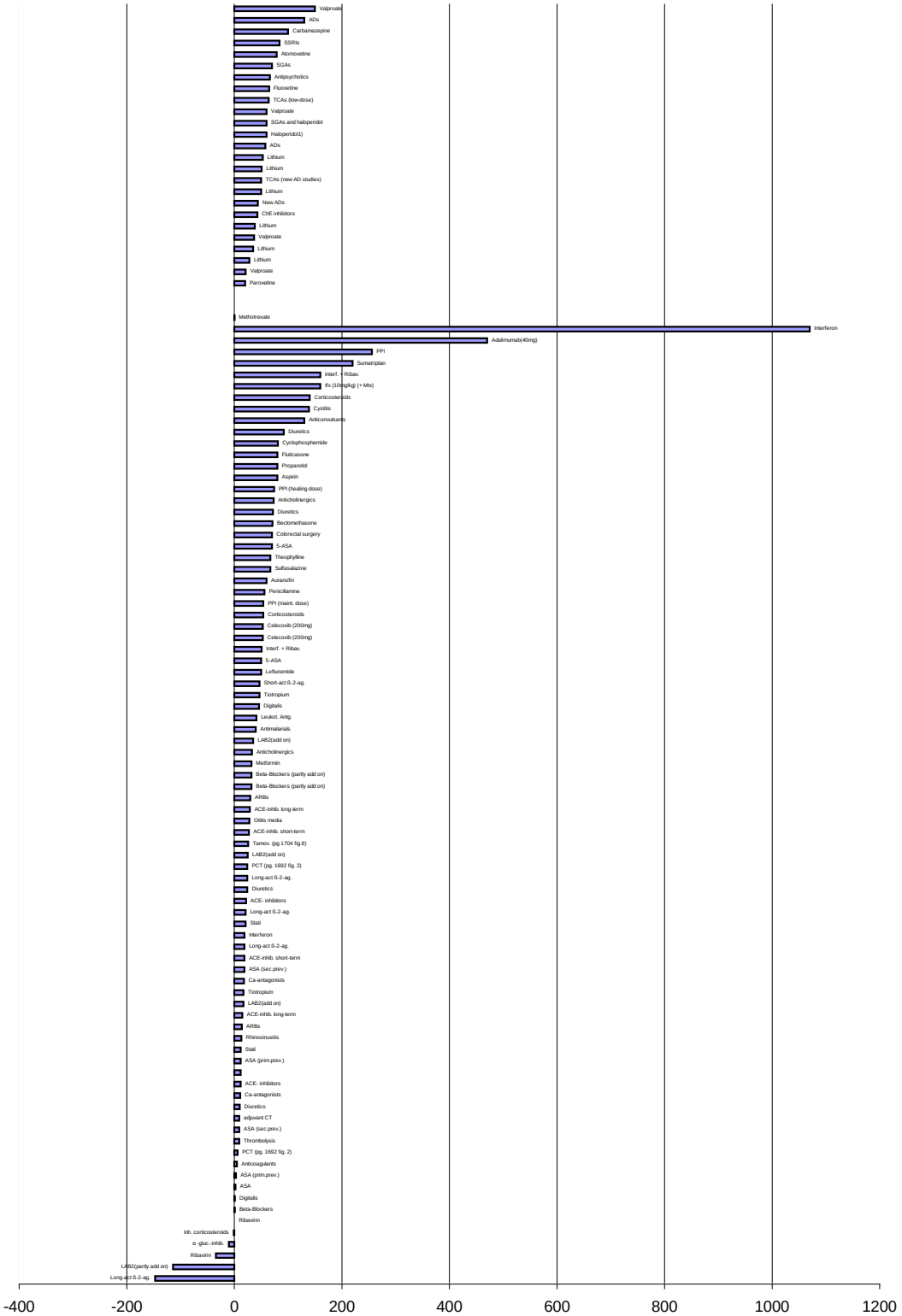


**Fig. DS28 Summary of the percentage absolute risk/response differences presented in Tables DS3 and DS4: dot plot.** All absolute risk/response differences in Tables DS3 and DS4 are presented. Data on older meta-analyses from Table DS1 are not included. Effect sizes of general medicine medication are presented on the left-hand side as black dots (median 5, mean 10.1, 95% CI 7.2–12.9), psychiatric drugs on the right-hand side as red dots (median 20.0, mean 20.8, 95% CI 16.0–25.5). One outlier – interferon for hepatitis B (relative risk reduction 1070%) – could not be presented for graphical reasons.

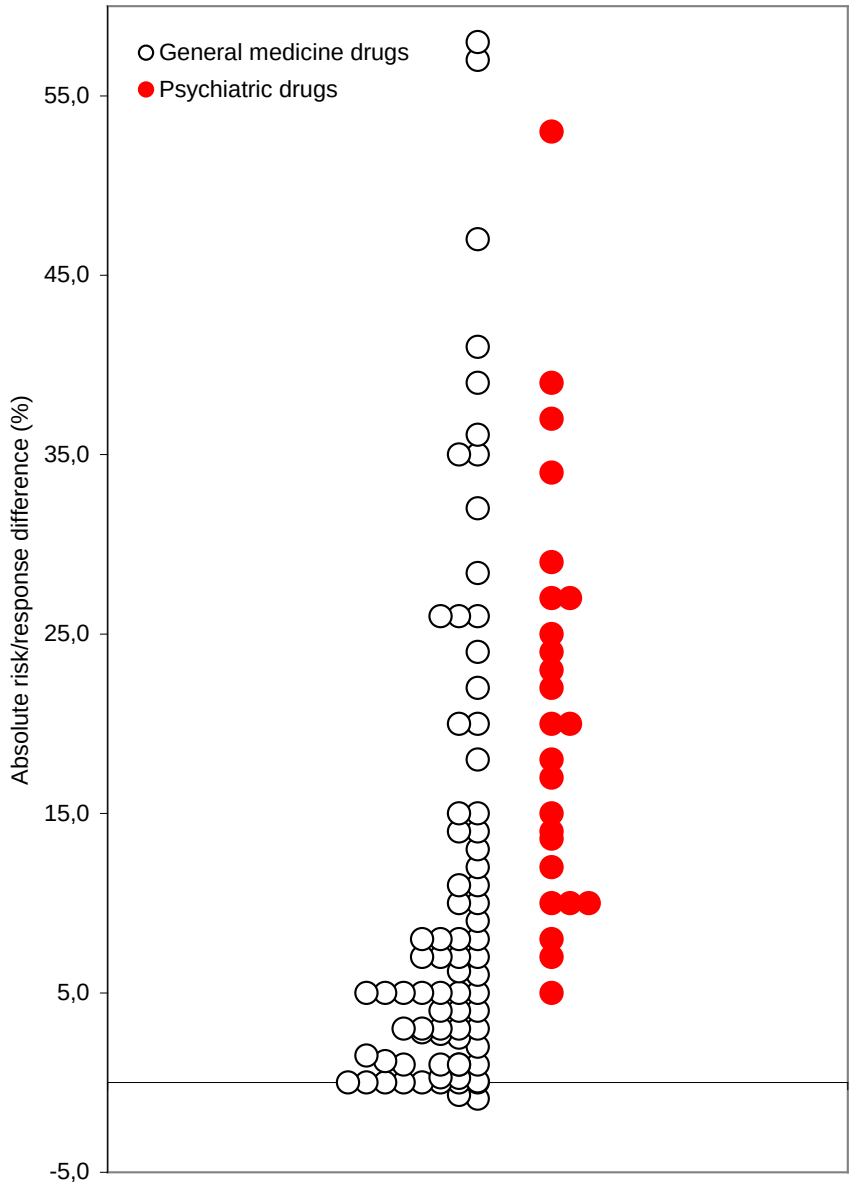
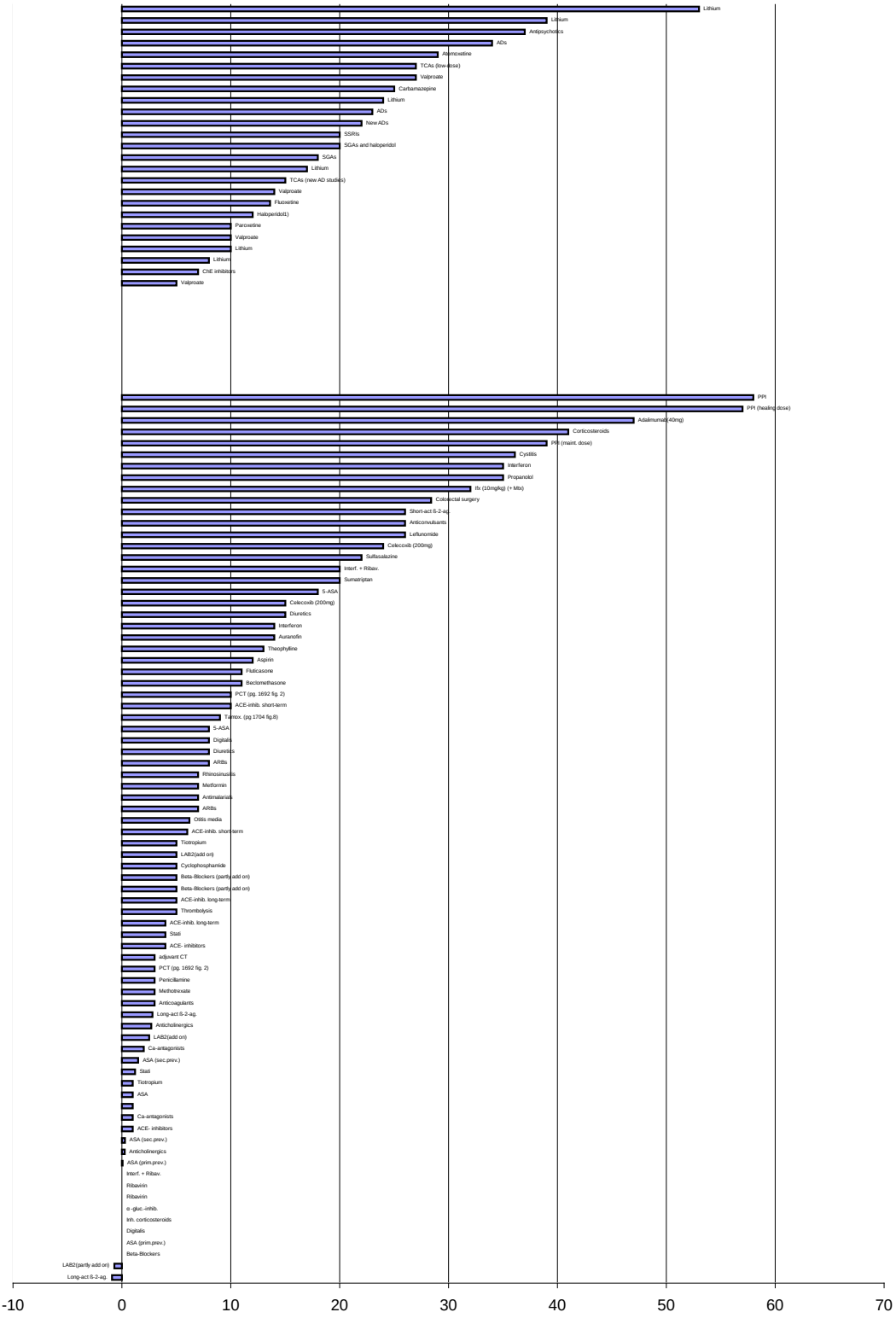


**Fig. DS29 Summary of the percentage absolute risk/response differences presented in Tables DS3 and DS4: bar chart.** This figure presents the same results as Fig. DS28, but it indicates exactly which corresponds to which result in Tables DS3 and DS4.



## Explanation of statistical indices

The following text explains the parameters and indices that are presented in Tables DS1 and DS4 summarising the results. To understand their meaning is important for the interpretation of meta-analytic results. Table DS3 presents the formula.

**Statistical significance**
Statistical significance means that a result is unlikely to have occurred by chance. For example, p=0.03 means that there is only a 3% probability that the null-hypothesis (no difference between groups) has been wrongly rejected. If a result is not statistically significant it may be due to chance alone, but it does not tell about the magnitude of the difference or clinical importance. This magnitude of the difference is addressed by effect size.

**Effect size**
**1) continuous data**
The simplest effect size is the **Difference of the means (DM)** which used the raw units. For example, 75kg mean bodyweight at study end in drug and 70kg mean bodyweight in placebo, DM = 5kg.
The **Standardised difference of means (SDM)** is DM divided by the pooled standard deviation of both groups. This measure thus expresses the Difference in means in standard deviation units. The general formula is (mean group A – mean group B)/pooled standard deviation. This formula is sometimes slightly modified to account for specific situations (Cohen's D, Hedges's g etc). SDM is useful in two situations: when in the single studies of a meta-analysis different instruments are used to measure the same concept (e.g. two schizophrenia scales). For example, a 10 point difference in the Positive and Negative Syndrome Scale (PANSS) is not equivalent to a 10 point difference in the Brief Psychiatric Rating Scale (BPRS), because the PANSS has 30 items and its total score goes from 30 to 210, while the BPRS has 18 items and goes from 18 to 126. The other situation is when an outcome unit is not intuitive for the reader. For example, general practicioners will not know whether a 5 points difference in PANSS total score is a large or small difference. In this situation SDM's might be easier to interpret. According to Cohen (8) a SDM of 0.2 is a small, 0.5 a medium and 0.8 a large effect size, but Cohen described this as a rule of thumb only and the interpretation depends on the context.

**2) dichotomous data**
Dichtomous (binary) outcomes can be classified as "yes or no", such as death, relapse or remission. We presented the **percentage patients with an outcome in the drug and the placebo groups**. The knowledge of these percentages is crucial for the interpretation of the effect sizes presented below, and the examples will illustrate this point.

The **absolute risk or response difference (ARD)** *subtracts* the percentage in the drug group from that of the placebo group, e.g. 3% mortality in placebo and 1% mortality in drug, thus 3% - 1% = 2% ARD. This is the most straightforward effect size for dichotomous outcomes, but its use in meta-analyses can be problematic when the baseline risk in the different studies varies. The relative risk (reduction) partly accounts for such differences in baseline risk.
The **relative risk reduction (RRR)** *divides* the absolute risk reduction by the

percentage in the placebo group, thus 2%/3% = 67% (in decimals: 0.02/0.03 = 0.67). Positive outcomes such as response were presented as a **percent response ratio (RR)** in a similar fashion. For example, in mania, 50% responded to antipsychotics and 31% to placebo, thus 50%/31% = 1.61 times or 61% (RR) more responders.

The **number-needed-to-treat** (NNT) indicates how many patients must be treated with an intervention to avoid one bad outcome (e.g.death). It was calculated as the inverse of the absolute risk difference, in the example above 1/2% = 1/0.02 = 50. Thus one out of 50 treated patients will not die. There are ways to incorporate assumptions about the baseline risk in the calculation of NNT, but we always used the baseline risk in the trials for the calculation of NNT.

Importantly, ARD, RRR/RR, NNT are based on the same numbers, but a 67% relative risk reduction looks much more impressive than a 2% absolute risk difference or a NNT of 50. As the relative risk reduction is often larger than the absolute risk reduction, authors often prefer to present the former. On the other hand, the maximal absolute risk reduction can not exceed 3% (3% placebo – 0% drug = 3% ARD). Therefore, all these indices must be interpreted in the context of the percentage patients with an outcome in the drug and the placebo group.

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