Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

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Review article

Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

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Background
The efficacy of psychopharmacological treatments has been called into question. Psychiatrists are unfamiliar with the effectiveness of common medical drugs.

Aims
To put the efficacy of psychiatric drugs into the perspective of that of major medical drugs.

Method
We searched Medline and the Cochrane Library for systematic reviews on the efficacy of drugs compared with placebo for common medical and psychiatric disorders, and systematically presented the effect sizes for primary efficacy outcomes.

Results
We included 94 meta-analyses (48 drugs in 20 medical diseases, 16 drugs in 8 psychiatric disorders). There were some general medical drugs with clearly higher effect sizes than the psychotropic agents, but the psychiatric drugs were not generally less efficacious than other drugs.

Conclusions
Any comparison of different outcomes in different diseases can only serve the purpose of a qualitative perspective. The increment of improvement by drug over placebo must be viewed in the context of the disease's seriousness, suffering induced, natural course, duration, outcomes, adverse events and societal values.

Declaration of interest
In the past 3 years S.L. has received fees for consulting and/or lectures from the following companies: Bristol-Myers Squibb, Actelion, Sanofi-Aventis, Eli Lilly, Essex Pharma, AstraZeneca, MedAvante, Alkermes, Janssen/Johnson & Johnson, Lundbeck Institute and Pfizer, and grant support from Eli Lilly. W.K. has received fees for consulting and/or lectures from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis and Eli Lilly. All authors work in psychiatry.

There is a deep mistrust of psychiatry fostered by reports suggesting that psychotropic drug efficacy is very small. Kirsch *et al* concluded that antidepressants should only be used in severely ill patients;[1] the efficacy of cholinesterase inhibitors in Alzheimer's disease and of lithium prophylaxis in bipolar disorder has been questioned;[2,3] and we found a smaller antipsychotic drug–placebo difference in schizophrenia than we intuitively expected.[4] These reviews inspired an article in *The New Yorker* summarising them,[5] and fuelled a vocal antipsychiatry movement.[6,7] Psychiatrists, patients, caregivers and the press are unsettled by these findings and some may think that psychiatric medication is not worth the bother. But is this small efficacy really true, and what about other medical interventions? As medicine is becoming highly specialised, few psychiatrists are familiar with the evidence of general medicine and psychiatric drugs. In this context we reviewed the efficacy of psychiatric pharmacotherapy in the perspective of standard medical drugs, making this paper the first attempt to provide a panoramic overview of major drugs. It is not possible to compare qualitatively different outcomes in qualitatively different diseases, but one can compare the percentages of patients helped with a drug or placebo, keeping in mind the differences in outcome for the mere purpose of perspective. We hasten to add a warning not to be overly concrete and to interpret this review as a qualitative perspective and not as a comparison. Therefore we discuss major factors that need to be taken into account in the interpretation of clinical trials and systematic reviews.

Method

Identification of diseases of interest and search strategy

We reviewed textbooks,[8,9] identified common diseases by consensus (S.L., S.H. and J.M.D.) based on frequency, importance and available treatment, and consulted national and international guidelines to identify primary treatments. We hand-searched the Cochrane Library, and searched Medline combining MeSH terms for the medical and psychiatric disorders with the MeSH term for meta-analysis (no time or language limit, last search May 2009) and references of included reports for systematic reviews of randomised controlled trials that applied meta-analysis and compared monotherapy of these treatments with placebo.

We first excluded meta-analyses of studies of subgroups (e.g. elderly people) and chose reviews of classes of drugs rather than single drugs (e.g. any antipsychotic, rather than only haloperidol) if available, based on the assumption that the original reviewers had made an appropriate decision to pool the drugs. We then chose the most recent reviews, because even if methodologically better an older review would have certainly been out of date. This was a conservative decision, because old meta-analyses in psychiatry usually had higher effect sizes (see Discussion and online Table DS1). The rare exceptions were slightly older meta-analyses that reported the indices necessary for our analysis more completely. These usually were Cochrane reviews which were

preferred in case of doubt, because they use similar methodology and always fully report the data. To corroborate these decisions we always compared different reviews for consistency of results and contacted authors in the rare case that the results were discrepant. (These additional reviews are quoted in the footnotes of the tables in the online data supplement.) The quality of the included systematic reviews was evaluated with the AMSTAR score (range of possible values 0–11).[10] Only primary efficacy outcomes in the areas of interest according to the treatment guidelines were extracted.

Statistical analysis

For continuous outcomes we extracted effect sizes and their 95% confidence intervals, presented both as differences in original units (mean difference) and as standardised mean differences (SMD). Mean differences were calculated according to the general formula (mean group A) − (mean group B), e.g. 75 kg in the drug group minus 70 kg in the placebo group gives a mean difference in body weight of 5 kg. Standardised mean differences (SMDs) provide a difference in standard deviation units (mean group A − mean group B) / standard deviation, e.g. (75 − 70) / 10 = 0.50, using the values from the previous example.

For dichotomous outcomes we presented the percentage of participants improved in the drug and placebo groups, the absolute risk/response difference (ARD; % responder drug – % responder placebo); the relative risk reduction (RRR; 1 – (% risk drug / % risk placebo) or relative response (RR) ratio (% responder drug / % responder placebo); and the number needed to treat (NNT), with their 95% confidence intervals. We also presented the *P* value, the number of studies and participants included and the average study duration (see online Table DS2 for a detailed description of these parameters).

Where our five standard parameters (mean difference, SMD, ARD, RRR, RR, NNT) were not reported in the studies, we transformed the existing data, or re-calculated meta-analyses by entering single study results using Review Manager version 5.0 or Comprehensive Meta-analysis version 2 for Windows.[11,12] S.H. ran the searches, S.H. and S.L. selected the reports. S.H. extracted the data, S.L. independently verified them, disagreements were resolved by J.M.D. and W.K., and M.D. rated the AMSTAR score.

Results

The Medline searches yielded 6175 abstracts and we hand-searched 1830 titles of Cochrane reviews – see online Figs DS1–24 for Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagrams of the selection process.[13] We included 94 meta-analyses of 48 drugs in 20 medical diseases (median AMSTAR score 9.0, 95% CI 8.2–9.2) and 33 meta-analyses of 16 drugs in 8 psychiatric disorders (median AMSTAR score 8.0, 95% CI 6.9–8.9). In the text we systematically present the raw numbers (for dichotomous outcomes the percentage responders in the placebo and drug groups; for continuous outcomes the average mean difference) and the average effect size (ARD and RRR/RR for dichotomous outcomes, SMD for continuous outcomes). Tables 1 and 2 present only some examples. Online Tables DS3 and DS4 present a comprehensive list including number of studies/participants, numbers needed to treat, *P* values and confidence intervals for each outcome and each intervention. A positive sign means that a drug either increased a positive outcome (e.g. response) or reduced a negative outcome (e.g. relapse). All the effect sizes in online Tables DS3 and DS4 are presented in Fig. 1 to give the overall gestalt. For this purpose, effect sizes for dichotomous outcomes (ARD, RR/RRR) were converted to SMDs in Comprehensive Meta-analysis 2.[12,14] This figure corresponds to online Fig. DS25 which indicates which dot relates to which study or outcome. Figures DS26 and DS28 present the same gestalt for relative and absolute risk/responder differences.

Medical disorders

In Tables 1 and DS3 the data are presented in an abbreviated 'participants – intervention – comparator – outcome' (PICO) format (the comparator is always placebo or no treatment).

Hypertension: antihypertensives for reduction of blood pressure, prevention of cardiovascular events and mortality

Several drug classes yielded similar results (Table DS3). Combining all agents, blood pressure was reduced by 9.4 mmHg systolic and 5.5 mmHg diastolic in the short term (SMDs 0.54 and 0.56 respectively).[15] In the long term all drug classes significantly reduced cardiovascular events, e.g. angiotensin-converting enzyme (ACE) inhibitors reduced such events from 18% to 14% (ARD 4%, RRR 22%).[16] A significant reduction of mortality has not been shown for all of them (Table DS3).

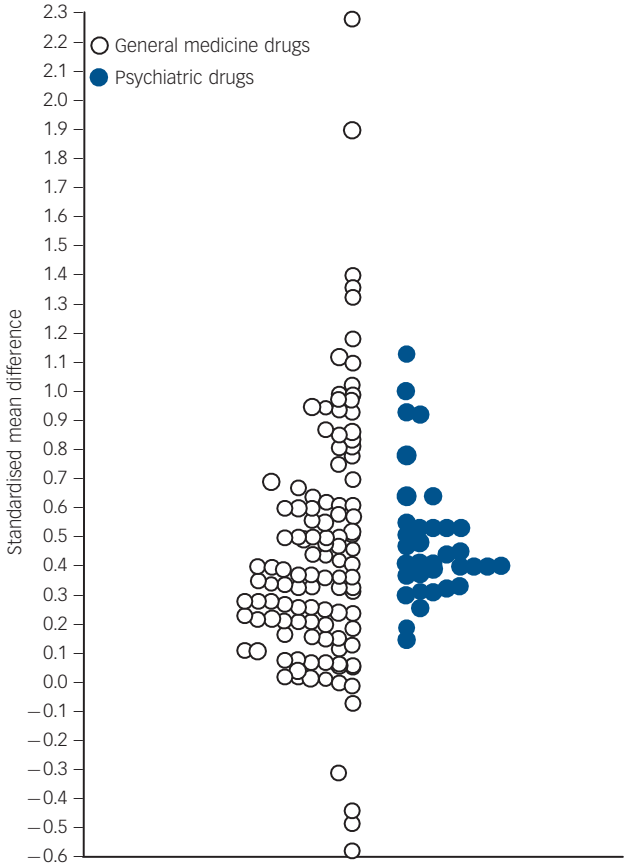

Fig. 1 Summary of effect sizes.

All effect sizes in online Tables DS3 and DS4 are presented except for duplicates (e.g. effect size on dichotomous response and continuous reduction of severity in schizophrenia). Online Fig. DS25 identifies which dot corresponds to which result, and Figs DS26–29 present the results of dichotomous outcomes as relative and absolute risk/responder differences. Data on older meta-analyses from Table DS1 are not included. Effect sizes of dichotomous outcomes were converted to standardised mean differences expressed as Hedges' *g*. Effect sizes of general medicine medication are presented on the left-hand side (median 0.37, mean 0.45, 95% CI 0.37–0.53) and psychiatric drugs on the right-hand side (median 0.41, mean 0.49, 95% CI 0.41–0.57).

Table 1 Examples of the efficacy of general medicine drugs *v.* placebo (full version is given in online Table DS3)

Study/AMSTAR[a]	Therapy	No. of studies	*n*	Duration, mean	Outcome (units)	Participants with outcome %		ARD[b] %	RRR/RR %	MD	SMD[c]
						Placebo	Drug				
Hypertension											
Effects on blood pressure											
Law *et al*[15]/5	Any antihypertensive	94	17 641	8 wk	RR systolic (mmHg)					9.4***	0.56***
		94	17 641	8 wk	RR diastolic (mmHg)					5.5***	0.54***
Long-term effects on cardiovascular events and mortality											
BPLTTC[16]/5	ACE inhibitors	5	18 229	3.9 yr	Cardiovascular events	18.1	14.1	4 NI	22***		*0.16*
Acute stroke											
Wardlaw[17]/9	Thrombolysis	22	6283	12–26 wk	Death/dependency	55.8	50.9	5**	9**		*0.11*
Prevention of cardiovascular disease and stroke											
Baigent *et al*[21]/5	Aspirin (primary prev.)	6	95 000	5.8 yr	Cardiovascular events	0.57/yr	0.51/yr	0.07/yr	12/yr***		*0.06*
Baigent *et al*[21]/5	Aspirin (secondary prev.)	16	17 000	NI	Cardiovascular events	8.2/yr	6.7/yr	1.5/yr	19/yr***		*0.12*
Law *et al*[22]/5	Statins	164	~38 000	2–6 wk	LDL cholesterol (mmol/l)					1.54***	NI
Baigent *et al*[23]/6	Statins	14	90 056	5.0 yr	Cardiovascular events	17.8	14.1	4***	21***		*0.15*
Chronic heart failure											
Flather *et al*[98]/6	ACE inhibitors long term	5	12 763	2.9 yr	Mortality	26.8	23.0	4***	15***		*0.11*
Rheumatoid arthritis											
Suarez-Almazor *et al*[99]/10	Methotrexate	5	218	> 12 wk	Tender joints					NE	0.86***
Migraine											
McCrory & Gray[31]/8	Sumatriptan	8	2221	2 h	Pain-free	8.5	29.5	20***	220***		*0.41*
Linde & Rossnagel[33]/9	Propanolol	4	205	13 wk	Response	30.9	52.3	35*	80*		*0.49*
Asthma											
Sin *et al*[36]/7	Corticosteroids	19	3271	> 12 wk	FEV_1 (l)					0.33***	0.56***
		11	8999	> 12 wk	Exacerbations	NI	NI	NI	54*		NE
Chronic obstructive pulmonary disease											
Yang *et al*[42]/10	Inhaled corticosteroids	3	952	8–24 wk	FEV_1 (l)					0.10***	0.36***
		4	2063	> 26 wk	Exacerbations					0.26***	0.20***
Diabetes											
Saenz *et al*[44]/11	Metformin	12	1587	21.5 wk	Fasting glucose (mmol/l)					1.84***	0.87***
		1	753	10.7 yr	Mortality	21.7	14.6	7**	32**		*0.27*
Chronic hepatitis C											
Myers *et al*[46]/10	Interferon	8	409	> 26 wk	Virological response	1.0	38.3	35***	1070***		*2.27*
Reflux oesophagitis											
Moayyedi *et al*[48]/9	Proton pump inhibitors	5	645	8 wk	Remission	28.3	83.2	58***	256***		*1.39*
Ulcerative colitis											
Sutherland & Macdonald[50]/9	5-ASA	4	892	8 wk	Remission	10.0	19.9	8***	70**		*0.44*
Multiple sclerosis											
Rice *et al*[53]/10	Interferon	3	919	2.0 yr	Exacerbation	69.5	55.2	14***	19***		*0.34*
Breast cancer											
EBCTCG[56]/4	Polychemotherapy	60	28 764	15.0 yr	Mortality age < 50	42.4	32.4	10***	24***		*0.24*
Non-small cell lung cancer											
Bria *et al*[57]/8	Adjuvant chemotherapy	21	7408	4.5 yr	Mortality	NI	NI	3 NI	9*		NE
Antibiotics for various diseases											
Glasziou *et al*[60]/10	Otitis media	10	2791	2–7 d	With pain	22.2	16	6.2 NI	28***		*0.22*
Falagas *et al*[61]/8	Cystitis	4	1062	3–17 d	Cure	25.7	61.8	36.1 NI	139***		*0.85*

ACE, angiotensin-converting enzyme; ARD, absolute response or risk difference; ASA, acetylsalicylic acid; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; d, day; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; FEV_1, forced expiratory volume in 1 s; h, hours; LDL, low-density lipoprotein; MD, mean difference; NE, not estimable; NI, not indicated; NNT, number needed to treat; NS, not significant; prev., prevention; RRR/RR, response ratio/relative risk reductions; SMD, standardised mean difference; wk, week; yr, year.

a. AMSTAR quality score (range of possible values 0–11).

b. Positive values always mean superiority of drug.

c. Italics indicate mean estimated values.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Results on absolute and relative risk/responder differences do not always exactly match with the formulae presented in the manuscript due to weighting processes in meta-analyses.

Acute ischaemic stroke: thrombolysis, aspirin and heparin for prevention of death or dependency

Thrombolysis reduced death or dependency from 56% to 51% (ARD 5%, RRR 9%),[17] but when administered after 4.5 h mortality is increased by haemorrhages.[18] Aspirin reduced death or dependency from 46% to 45%,[19] whereas heparin was ineffective.[20]

Cardiovascular disease: aspirin for primary and secondary prevention of cardiovascular events and mortality

In secondary prevention, low-dose aspirin reduced serious cardiovascular events per year from 8.2% to 6.7% (ARD 1.5%, RRR 19%) and vascular mortality per year from 4.1% to 3.7% (ARD 0.29%, RRR 9%, $P = 0.05$).[21] In primary prevention, aspirin reduced the number of cardiovascular events per year from 0.57% to 0.51%, but there was no effect on mortality because the reduction of occlusive events was balanced by an increase in major bleeds (mortality per year: placebo 0.19%, drug 0.19%).[21]

Hypercholesterolaemia: statins for reduction of cholesterol levels and prevention of cardiovascular disease and mortality

In the short term, statins reduced low-density lipoprotein (LDL) cholesterol by 1.54 mmol/l or 31%.[22] In the long term, cardiovascular events were reduced from 18% to 14% (primary and secondary prevention combined, ARD 4%, RRR 21%) and 5-year mortality from 9.7% to 8.5%.[23]

Chronic heart failure: various drugs for reduction of mortality

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and diuretics respectively reduced mortality rates from 27% to 23% (ARD 4%, RRR 15%), from 18% to 11%, from 13% to 8% and from 12% to 3%.[24–27] Digitalis significantly reduced hospital admission (from 33% to 25%) but not mortality.[28]

Rheumatoid arthritis: antirheumatic drugs for the reduction of tender joints

Various immunosuppressants, corticosteroids and other agents reduced the number of tender joints with reasonably good SMDs between 0.33 and 1.33 (raw values for mean differences were not presented; Table DS3).[29,30]

Acute migraine: effects of sumatriptan and aspirin on the number of patients pain-free after 2 h

Sumatriptan increased the percentage of patients pain-free after 2 h from 9% to 30% (ARD 20%, RR 220%)[31] and intravenous aspirin increased it from 15% to 27%.[32]

Prophylaxis of migraine: effects of propanolol and anticonvulsants on responder rates and on the number of migraine attacks

Fifty-two per cent responded to propanolol prophylaxis and 31% to placebo (ARD 35%, RR 80%).[33] Patients had approximately one migraine attack less (SMD 0.47).[33] The results of anticonvulsants were similar.[34]

Chronic asthma: effects of inhaled corticosteroids and beta-2-agonists on forced expiratory volume and on asthma exacerbations

The first-line drugs for chronic, severe asthma are inhaled corticosteroids and beta-2-agonists (short-acting as needed, long-acting in patients with refractory disease).[35] Inhaled corticosteroids increased forced expiratory volume in 1 s (FEV_1) by 330 ml (SMD 0.56).[36] The addition of long-acting beta-2-agonists improved FEV_1 by 190 ml (SMD 0.35),[37] but the reduction of asthma exacerbations found by some meta-analyses is controversial,[36,38] because another meta-analysis found more severe exacerbations.[39]

Chronic obstructive pulmonary disease: effects of various agents on FEV_1 and on disease exacerbations

Guidelines recommend anticholinergics, beta-2-agonists and inhaled corticosteroids.[40] The anticholinergic tiotropium improved FEV_1 by 200 ml (SMD 0.99).[41] It reduced exacerbations from 31% to 23% (ARD 5%, RRR 17%).[41] Inhaled corticosteroids improved FEV_1 by 100 ml (SMD 0.36) and the number of exacerbations per patient and year by 0.26 (SMD 0.20).[42] The data on long-acting beta-2-agonists are equivocal. They reduced exacerbations (e.g. Salpeter *et al*),[43] but one systematic review found them to increase respiratory deaths.[43]

Type 2 diabetes: various antidiabetics for reduction of HbA_{1c} and mortality

Metformin reduced HbA_{1c} by 1% (SMD 0.97) and α-glucosidase inhibitors reduced it by 0.8% (SMD 0.64).[44,45] In the long term, metformin reduced the death rate from 22% to 15% (ARD 7%, RRR 32%),[44] but α-glucosidase inhibitors have not been shown to change the death rate.[45]

Hepatitis C: effects of interferon and ribavirin on virological response/morbidity and mortality

Interferon increased the number of participants with no detectable virus at treatment end (virological response) from 1% to 38% (ARD 35%, RR 1070%).[46] Ribavirin was only efficacious in combination with interferon.[47]

Reflux oesophagitis: proton pump inhibitors for clinical remission and relapse prevention

Proton pump inhibitors are highly effective in acute treatment (response: placebo 28%, drug 83%, ARD 58%, RR 256%),[48] and also in maintenance treatment (relapse: placebo 75%, drug 36%).[49]

Ulcerative colitis: 5-aminosalicylic acid for clinical remission and maintenance of remission

Five-aminosalicylic acid (5-ASA) increased remission from 10% with placebo to 20% (ARD 8%, RR 70%),[50] and maintenance of remission from 37% to 53% (ARD 18%, RR 50%).[51]

Multiple sclerosis: corticosteroids for treatment of acute episodes and interferon for prevention of exacerbations

Acute treatment with corticosteroids increased the proportion of responders from 28% with placebo to 68% (ARD 41%, RR 140%).[52] In the first 2 years, prevention with interferon beta reduced exacerbations from 70% to 55% (ARD 14%, RRR 19%).[53]

Parkinson's disease: effects of levodopa on disease symptoms

There was no systematic review of the standard treatments levodopa or dopamine agonists with data compared with placebo. We parenthetically note that the National Institute for Health and Clinical Excellence (NICE) guideline based its recommendation on a pivotal 42-week trial in which levodopa produced 7 points more improvement in the Unified Parkinson's Disease Rating

Scale total score than placebo (SMD 0.93),[54] but also a 7% stronger decline of striatal dopamine transporter density (SMD −0.44), suggesting a possible acceleration of nigrostriatal dopamine nerve terminal loss.[55]

Breast and lung cancer: polychemotherapy for reduction of mortality

Breast cancer is the most frequent neoplasm in women and lung cancer is the leading cause of cancer death. Polychemotherapy reduced the 15-year breast cancer mortality in younger women (<50 years) from 42% to 32% (ARD 10%, RRR 24%) but in older women only from 50% to 47%.[56] Tamoxifen added to polychemotherapy reduced the 15-year mortality in oestrogen receptor-positive patients from 35% to 26%.[56] In the study by Bria *et al*, adjuvant chemotherapy led to a small reduction of 5-year lung-cancer mortality (ARD 3%, RRR 9%),[57] confirming a landmark previous meta-analysis.[58]

Infectious diseases: antibiotics for rhinosinusitis, otitis media, uncomplicated cystitis and prophylaxis of wound infection after surgery

The effects of antibiotics depend on the infection. We did not find meta-analyses on severe infections such as pneumonia or on antivirals (monotherapy *v.* placebo) for HIV. A meta-analysis concluded against their general use in rhinosinusitis owing to small effect size (response: placebo 57%, drug 64%, ARD 7%, RRR 13%).[59] The use of antibiotics in otitis media is debated, as within 2–7 days 78% of patients recovered spontaneously compared with 84% taking antibiotics (ARD 6%, RR 28%).[60] In contrast, the efficacy in uncomplicated cystitis (response: placebo 26%, drug 62%) and for the prophylaxis of wound infections after major operations (infections: placebo 39%, antibiotics 10%) was clear.[61,62]

Psychiatric disorders

Full data are given in Table DS4; examples are summarised in Table 2.

Schizophrenia: antipsychotics for reduction of overall symptoms and relapse prevention

In acute treatment, second-generation antipsychotics increased the percentage responding from 24% with placebo to 41% (ARD 18%, RR 70%), and reduced the Brief Psychiatric Rating Scale/Positive and Negative Syndrome Scale total score by 9/10 points (SMD 0.51).[4] Antipsychotic maintenance treatment reduced relapse rates from 57% to 22% within approximately 10 months (ARD 38%, RRR 65%).[63]

Bipolar disorder: mood stabilisers for acute mania, antidepressants for depression and mood stabilisers for relapse prevention

Various antimania agents increased the percentage responding from approximately 30% with placebo to approximately 50% within 3 weeks (response to lithium 52% *v.* placebo 34%, ARD 17%, RR 50%;[64] response to valproate 47% *v.* placebo 21%, ARD 27%, RR 150%;[65] response to carbamazepine 51% *v.* placebo 26%, ARD 25%, RRR 100%;[65] response to antipsychotics 50% *v.* placebo 31%, ARD 20%, RR 60%).[66] In bipolar depression, antidepressants increased the response rate from 34% to 58% (ARD 34%, RR 130%).[67] In maintenance treatment, lithium reduced relapse rates from 81% to 36% (ARD 53%, RRR 51%),[68] or from 61% to 40% after excluding studies in which lithium was suddenly discontinued (ARD 24%, RRR 35%).[69]

Major depressive disorder: antidepressants for acute depression and relapse prevention

The absolute responder differences in recent meta-analyses of various selective serotonin reuptake inhibitors (SSRIs) (or tricyclic antidepressants used as an active comparator in SSRI *v.* placebo studies)[70] *v.* placebo in major depressive disorder were 10–15% (Table DS4). For example, paroxetine increased the percentage responding from 42% to 53% (ARD 10%, RR 20%) and reduced the Hamilton Rating Scale for Depression score by 3 points (SMD 0.32).[71] These studies were currently primarily conducted in out-patients with less severe disorder (e.g. 90% of the sample were out-patients in the meta-analysis by Barbui *et al*).[71]

Maintenance treatment with any antidepressant reduced the relapse rate from 41% with placebo to 18% (ARD 23%, RRR 58%),[72] consistent with another meta-analysis restricted to new antidepressants (placebo 48% *v.* drug 26%, ARD 22%, RRR 44%).[73]

Obsessive–compulsive disorder: effects of SSRIs on responder rates and overall symptoms

Selective serotonin reuptake inhibitors increased the proportion of patients responding in the acute phase from 23% to 43% (ARD 20%, RRR 84%).[74] These drugs reduced the mean Yale–Brown Obsessive Compulsive Scale score by 3.2 points (SMD 0.44).[74]

Panic disorder: tricyclic antidepressants, SSRIs and benzodiazepines for anxiety symptoms

The mean SMDs (raw differences in rating scale scores or responder rates were not indicated) of tricyclic antidepressants, SSRIs and benzodiazepines in acute treatment were 0.40–0.41.[75]

Alzheimer's disease: cholinesterase inhibitors for prevention of cognitive decline

Within 6 months, cholinesterase inhibitors increased the percentage of participants unchanged or improved from 17% to 24% (ARD 7%, RRR 43%).[76] The cognitive subscore of the Alzheimer's Disease Assessment Scale was better by 2 points (SMD 0.41).[76]

Attention-deficit hyperactivity disorder: effects of various drugs on symptoms

Methylphenidate (SMD 0.78), amphetamines (SMD 1.00) and atomoxetine (SMD 0.64) showed robust effect sizes in overall reduction of attention-deficit hyperactivity disorder symptoms (raw differences in rating scale scores or responder rates were not indicated).[77–79]

Discussion

Any comparison of treatments for different diseases can only be qualitative in nature and therefore Fig. 1 is no more than a way to place psychiatric drugs in the perspective of general medicine medication. Some general medical drugs have very high effect sizes, but those obtained by psychiatric drugs are in the same range as most general medical pharmacotherapeutics. This said, the increment of improvement by a drug must be viewed in the context of the seriousness of the disease, the suffering induced, the outcome in question, societal values and the natural course including the duration of the disease. In the following paragraphs we discuss a number of these issues which readers should take into account in interpreting the results.

Table 2 Examples of efficacy of psychiatric drugs *v.* placebo (full version is given in online Table DS4

Study/AMSTAR[a]	Therapy	No. of studies	*n*	Weeks, mean	Outcome (units)	Participants with outcome %		ARD[b] %	RRR/RR %	MD	SMD[b]
						Placebo	Drug				
Schizophrenia											
Acute treatment											
Leucht *et al*[4]/10	SGAs	28	4498	9	Responders	23.7	40.6	18***	70***		*0.43*
		35	5568	10	PANSS/BPRS					NI	0.51***
Leucht *et al*[4]/10	Haloperidol[d]	10	1440	6	Responders	19.5	29.3	12%***	60%***		*0.30*
		11	1540	6	PANSS/BPRS					NI	0.53***
Maintenance treatment											
Leucht *et al*[63]/10	Antipsychotics	62	6392	42	Relapse	57.0	22.0	38%***	65***		*0.92*
Bipolar affective disorder											
Acute manic episode											
Storosum *et al*[64]/6	Lithium	6	811	3	Responders	34.0	52.0	17***	50**		*0.41*
		7	1165	3	YMRS/MRS					NI	0.40***
Smith *et al*[65]/19[e]	Valproate	2	182	3	Responders	21.1	47.1	27%***	150%*		*0.66*
		4	782	3	YMRS/MRS					NI	0.40***
Smith *et al*[65]/9[e]	Carbamazepine	2	443	3	Responders	25.5	51.1	25%***	100%***		*0.61*
		2	331	3	YMRS					6.6***	0.53***
Scherk *et al*[66]/10	SGAs and haloperidol	12	2939	3	Responders	30.8	49.9	20***	60***		*0.44*
		12	2939	3	YMRS/MRS/MS					4.7[c]***	0.45***
Depressive episode											
Gijsman *et al*[67]/9	Antidepressants	4	662	7	Responders	34.1	57.7	34***	130**		*0.53*
Maintenance therapy											
Davis *et al*[68]	Lithium	9	421	NI	Any relapse	81.4	36.2	53***	51***		*1.12*
Geddes *et al*[69]/8	Lithium	5	770	73	Any relapse	61.0	40.0	24**	35**		*0.47*
Macritchie *et al*[100]/10	Valproate	1	281	52	Any relapse	38.3	24.1	14%*	37%*		*0.37*
Major depressive disorder											
Acute episode											
Barbui *et al*[71]/8	Paroxetine	22	5112	7.5	Responders	42.4	53.2	10***	20***		*0.24*
		34	5764	7.5	HRSD					2.62***	0.31***
Storosum *et al*[70]/4	TCAs (new AD studies)	32	4314	6	Responders	31.0	46.0	15***	50***		*0.35*
				6	HRSD					2.65***	0.33***
Bech *et al*[101]/5	Fluoxetine	16	2761	6	Responders	24.2	37.8	13.6%***	65%***		*0.35*
		7	NI	6	HRSD					NI	0.30
Kirsch *et al*[1]/7	New ADs	35	5133	6	HRSD					1.80***	0.32***
Maintenance treatment											
Geddes *et al*[72]/9	Antidepressants	35	5032	63	Relapse	41.0	18.0	23 NI	58***		*0.64*
Hansen *et al*[100]/10	New ADs	11	3326	68	Recurrence	48.0	26.0	22 NI	44***		*0.53*
Davis *et al*[68]	Lithium	9	227	NI	Relapse	75.0	36.0	39 NI	53***		*0.92*
Obsessive–compulsive disorder											
Soomro *et al*[74]/11	SSRIs	17	3097	10	Y–BOCS					3.21***	0.44***
		13	2709	10	Responders	22.6	43.3	20***	84***		*0.53*
Panic disorder											
Mitte[75]/4	TCAs, SSRIs, BZDs	17–25	NI	8	Anxiety					NI	0.41*
Dementia											
Birks[76]/8	Cholinesterase inhibitors	10	4236	26	ADAS-Cog					2.38***	0.41***
		9	3118	28	MMSE					1.33***	0.39***
		8	3402	26	Not worse	16.8	24.4	7***	43***		*0.26*
Attention-deficit hyperactivity disorder											
Schachter *et al*[77]/9	Methylphenidate	22	963	3.3	Hyperactivity[f]					NI	0.78***

AD, antidepressant; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; ARD, absolute response or risk difference; BPRS, Brief Psychiatric Rating Scale; BZD, benzodiazepine; HRSD, Hamilton Rating Scale for Depression; MD, mean difference; MMSE, Mini-Mental State Examination; MRS, Mania Rating Scale; MS, Mania Scale; NI, not indicated; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; RRR/RR, response ratio/relative risk reduction; SMD, standardised mean difference; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Y–BOCS, Yale–Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale.

a. AMSTAR quality score (range of possible values 0–11).

b. Italics indicate mean estimated values.

c. YMRS only.

d. In studies on SGAs.

e. Updated and supplemented by our own searches.

f. Teacher rated.

*$P<0.05$, **$P<0.01$, ***$P<0.001$. Results on absolute and relative risk/responder differences do not always exactly match with the formulae presented in the manuscript due to weighting processes in meta-analyses.

Outcomes

Psychiatry is often criticised for using rating scales which are subjective and considered 'soft' outcomes, whereas many medical treatments prevent 'hard' outcomes such as death or major events (stroke, heart attack, etc.). High blood pressure or cholesterol levels *per se* do not lead to suffering, therefore they should not be the primary outcome, rather their long-term consequences. Sometimes an intermediate outcome is improved but mortality increases; for example, in a large multicentre effectiveness trial for asthma ($n = 26\,000$), long-acting beta-2-agonists increased respiratory-related deaths.[80] In diabetes, aggressive glycaemic control reduced glucose levels compared with standard care, but increased mortality rates ($n = 10\,251$).[81]

Other drugs reduce the symptoms and suffering originating directly from the disease such as oesophagitis or migraine, but their pathophysiological disease processes do not progress to death. Psychiatric drugs fall in this category. Therefore, reduction of disease severity (e.g. degree of delusions and hallucinations in schizophrenia) and prevention of future episodes are primary outcomes, and it is not entirely appropriate to criticise psychiatry for using 'soft' outcomes. This said, there is considerable room for improvement in psychiatric outcome measures,[82] and death or suicide should be always reported. The example of lithium shows that some psychiatric drugs may reduce suicide rates.[83,84]

Placebo effects

Readers may be surprised that many effect sizes in both areas were not larger. The median of all effect sizes was 0.40, similar to that found in another analysis of Cochrane reviews (0.32).[85] In this context there is a general misconception that with placebo all patients will have a poor outcome, but many patients will recover spontaneously owing to the natural course of the disorder (for example, a manic episode will remit by itself) and placebo effects.

Effect sizes for dichotomous and continuous outcomes

For dichotomous outcomes both relative and absolute risk reductions should be considered. There is substantial evidence showing that clinicians tend to overestimate treatment effects presented as relative risk reductions.[86] For example, statins reduced cardiovascular events from approximately 18% to approximately 14%.[23] The relative risk reduction of 22% ($(1-(0.14/0.18)) \times 100$) is more impressive than the absolute risk difference of 4% ($14\% - 18\% = |-4\%|$). On the other hand, if the risk in the placebo group is low, the maximally possible absolute risk reduction must be lower than the base rate (here 18%), making the relative risk reduction more important.

In continuous outcomes the standardised mean difference (Cohen's *d*, Hedges' *g* etc.) is necessary when different instruments are used to measure the same concept (e.g. two depression scales) or if the original unit is difficult to interpret intuitively (e.g. the score of an unknown rating scale). As the SMD is relative to the pooled standard deviation, large variability will reduce it. In psychiatry this often occurs with rating scales in somewhat ill-defined, 'variable' diseases such as depression, whereas in general medicine the measure may be a highly accurate laboratory test (e.g. serum cholesterol concentration) in a well-defined disease entity. Cohen's rule that an SMD of 0.2 is a small effect size, 0.5 medium and 0.8 a large effect size is often used, but Cohen hastened to say that the interpretation depends on the context;[87] a small SMD for a fatal disease is more important than a large SMD for a transitory rash. In the future, quality-adjusted life years (QALYs) could be a uniform measure for comparisons across treatments, but these are not yet available for all drugs and we did not find this outcome in the meta-analyses. In addition, there is much debate about the validity of QALYs (see, for example, studies by Schlander[88] and Griebsch *et al*[89]).

Sample size

Meta-analyses in somatic medicine sometimes include impressively large patient numbers, e.g. 95 000 participants in studies of the primary prevention of cardiovascular events with aspirin.[21] Aspirin reduced the risk of a cardiovascular event from 0.57% per year to 0.51% per year. Angiotensin-converting enzyme inhibitors for hypertension reduced 5-year mortality from 10.4% to 9.2% in 18 229 participants.[16] In such situations, large sample sizes are needed for two reasons: first, the aspirin *v.* placebo difference was 0.07% event and the ACE inhibitors *v.* placebo difference was 1.2% events, requiring large sample sizes for statistical significance; second, the base rate (equivalent to the risk in the placebo group) was very low (e.g. 0.57% per year without aspirin), limiting the drug effect to a maximum 0.57% per year. Nevertheless, for mortality even a small difference can be clinically meaningful. In psychiatry the difference in percentages of those responding to drug or placebo is usually higher and it has been shown that here meta-analyses with at least 1000 participants are robust.[90]

Drug effects could accumulate over time

The mean duration of the studies included in a meta-analysis should always be considered. For example, treated or not, few patients with hypertension will die in the course of a year. Thus, to obtain a large difference in mortality, studies of many years' duration would be necessary, but such studies are almost impossible to conduct for many reasons. Therefore, shorter studies are performed which show only small differences. Although only very long-term studies could prove this, it is likely that the reduction of mortality accumulates over time. In this context, many psychiatric drugs not only improve the acute episode but also prevent further episodes. Patients with severe recurrent depression might have 20 episodes in their lifetime, which could be reduced by medication to 10.[72]

Has drug efficacy decreased over the decades?

To be systematic we generally chose the most up-to-date systematic reviews, but there is an impression that earlier meta-analyses in psychiatry yielded higher effect sizes (see online Table DS1 for some examples). In the first 103 double-blind studies in depression, summarised in 1993, approximately two-thirds responded to tricyclic antidepressants or monoamine esterase inhibitors compared with a third responding to placebo.[91] The large National Institute of Mental Health schizophrenia trial, published in 1964, reported that 69% responded to antipsychotics and 24% to placebo (NNT 2, effect size 1.31).[92] In the first large obsessive–compulsive disorder trial, published in 1991, half the sample responded to clomipramine and only 5% to placebo.[93] Recent meta-analyses found much smaller effect sizes for both the new SSRIs and clomipramine.[94] The reasons for decreasing effect sizes are not entirely understood. The early trials were often small and single-centre, and methodology less well developed (blinding, scales, external auditing, statistical methods). There may also have been more publication bias, as efforts to control it have expanded only in the past two decades. Modern trials are often large, multicentre studies but have other problems such as the impossibility of recruiting severely ill patients with truly acute disorders because of ethical concerns, the availability of effective medication leaving few drug-naive patients, and the phenomenon of symptomatic volunteers answering an

advertisement for free medication and thereby increasing placebo response.[95] It is possible that there are similar temporal trends in general medicine and the phenomenon needs thorough examination.

Limitations

We made a considerable effort to be systematic, but for the reasons stated below we could not meet all criteria of a systematic review. We did not examine a single drug but put different medications in perspective, for which an established methodology does not exist.

First, we could not present a complete collection, but we chose common diseases by consensus based on frequency, importance and available treatment. It would be difficult to operationalise the selection. For example, there are diseases that are frequent but not severe (an extreme example is the common cold). Others are extremely severe but rare (e.g. certain cancers). The selection was made *a priori*, and once chosen all diseases and drugs were presented. We feel that the selection is representative and that the major diseases of the industrialised world are included; nevertheless, the selection process may have introduced bias.

Second, in the selection among reviews, we emphasised up-to-dateness and full presentation, but we compared the results of different meta-analyses on the same topic which were usually consistent. Third, a review of reviews is observational by nature: our unit of analysis was published meta-analyses, which does not exist for all drugs/indications, and the included reports differed in the exact methods, publication dates, inclusion criteria, etc. Fourth, many meta-analyses did not present the data in a consistent manner, resulting in a major challenge for us. We made substantial efforts to present the results in a consistent way by back-calculating indices, but stringent following of the PRISMA statement would facilitate future attempts.[13]

Fifth, we did not address side-effects. These are a serious problem of many psychotropic drugs, although improvements have been made. For example, SSRIs have much less serious toxicity than tricyclic antidepressants. General medicine drugs also have important side-effects, for example death induced by bleeding from thrombolysis or aspirin or cancer chemotherapies. It would have been simply impossible to describe side-effects as well and to balance them with efficacy, because there are many subjective judgement calls. Finally, publication bias is a major problem for meta-analyses. For example, Turner *et al* (see Table DS4) showed that the inclusion of unpublished antidepressant trials reduced the effect size.[96] Publication bias exists in general medicine as well (see, for example, Rising *et al*),[97] and we are not aware of evidence comparing its degree in different fields.

There are many reasons why doctors, patients and caregivers are and should be critical about psychotropic drug treatment, such as unclear disease aetiology, lack of diagnostic tests, commercial conflict of interest, unclear mechanism of drug action and side-effects. Moreover, some people think that psychiatric disorders are purely psychological conditions that should be treated exclusively with psychotherapy. However, the efficacy of psychotropic drugs is supported by randomised controlled trials. In this context we have put psychiatric drugs in the perspective of general medicine medication.

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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

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

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 numbers needed to treat (NNTs))

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

Figs DS28, DS29: Summary of the percentage absolute risk/response differences presented in Tables DS3 and DS4

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%| 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])

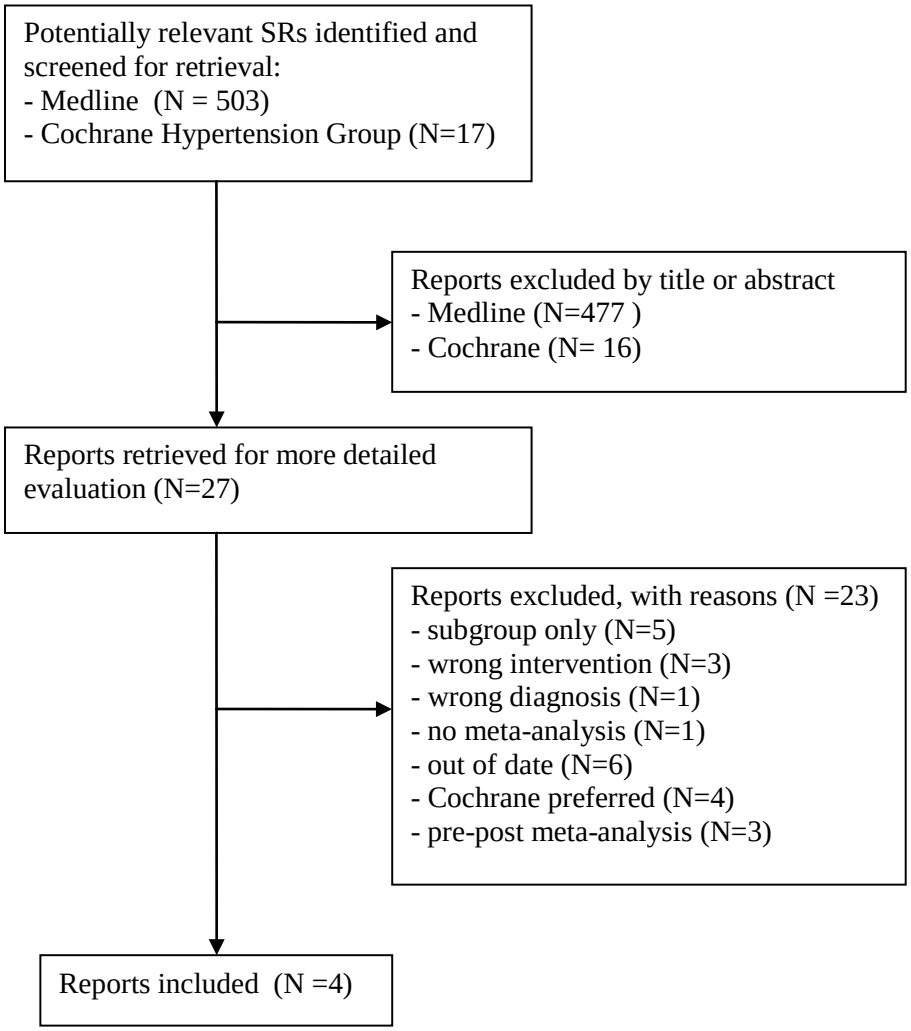


Fig. DS2: PRISMA diagram - stroke

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

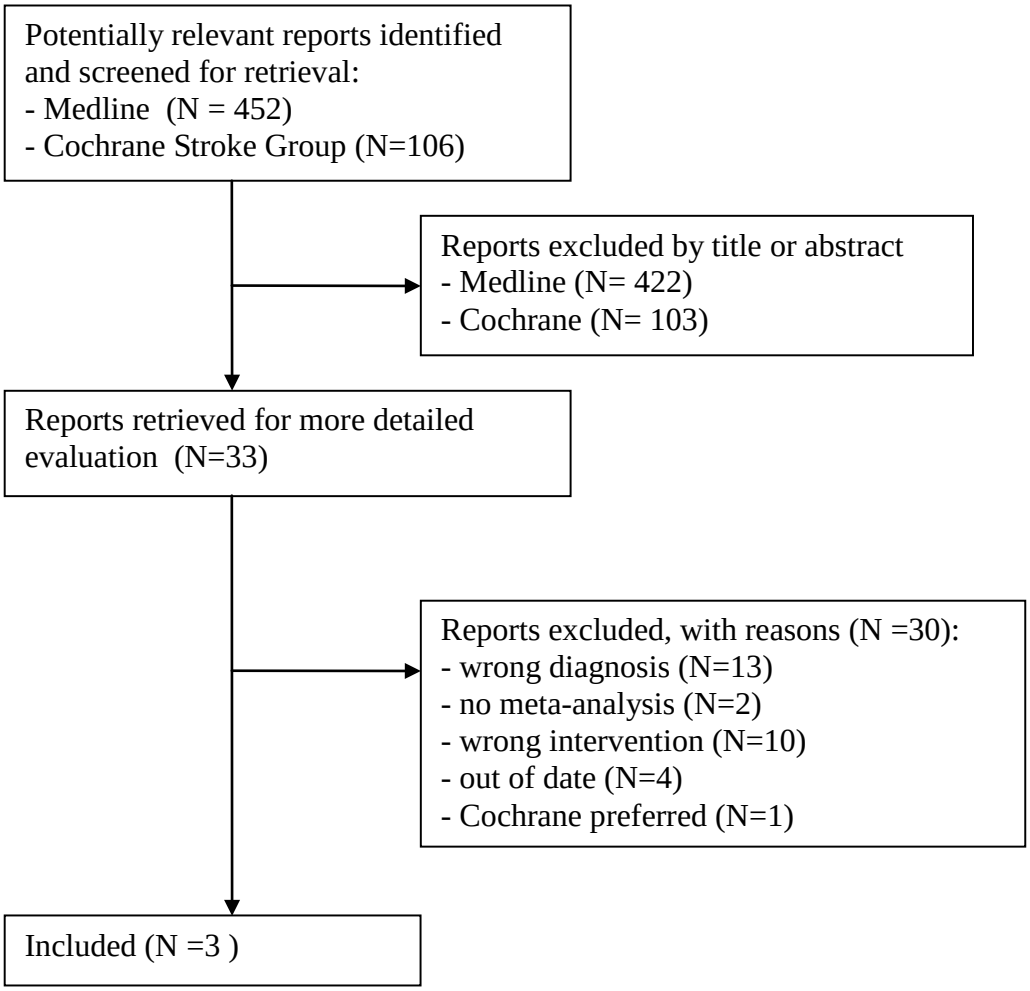


Fig. DS3: PRISMA diagram - prevention of cardiovascular diseases

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

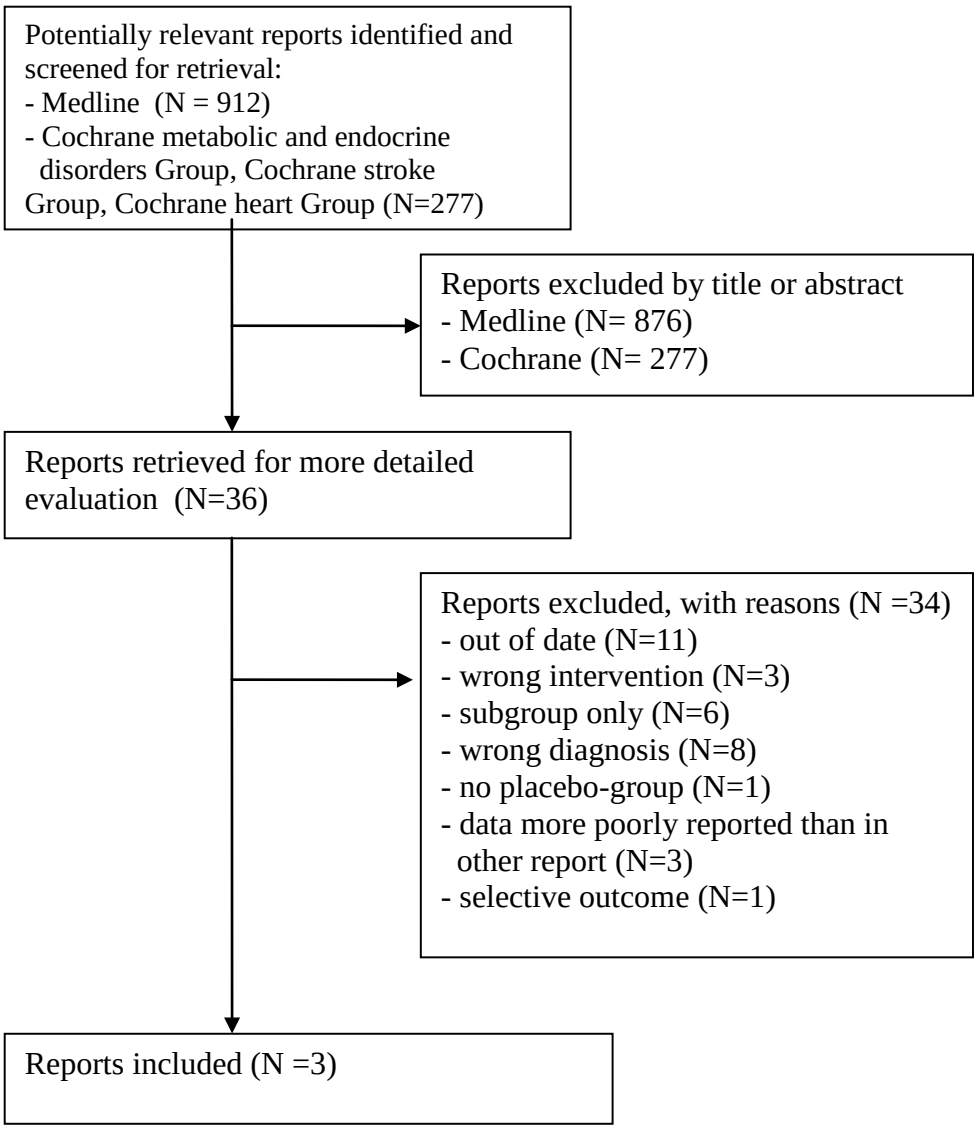


Fig. DS4: PRISMA diagram - heart failure

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

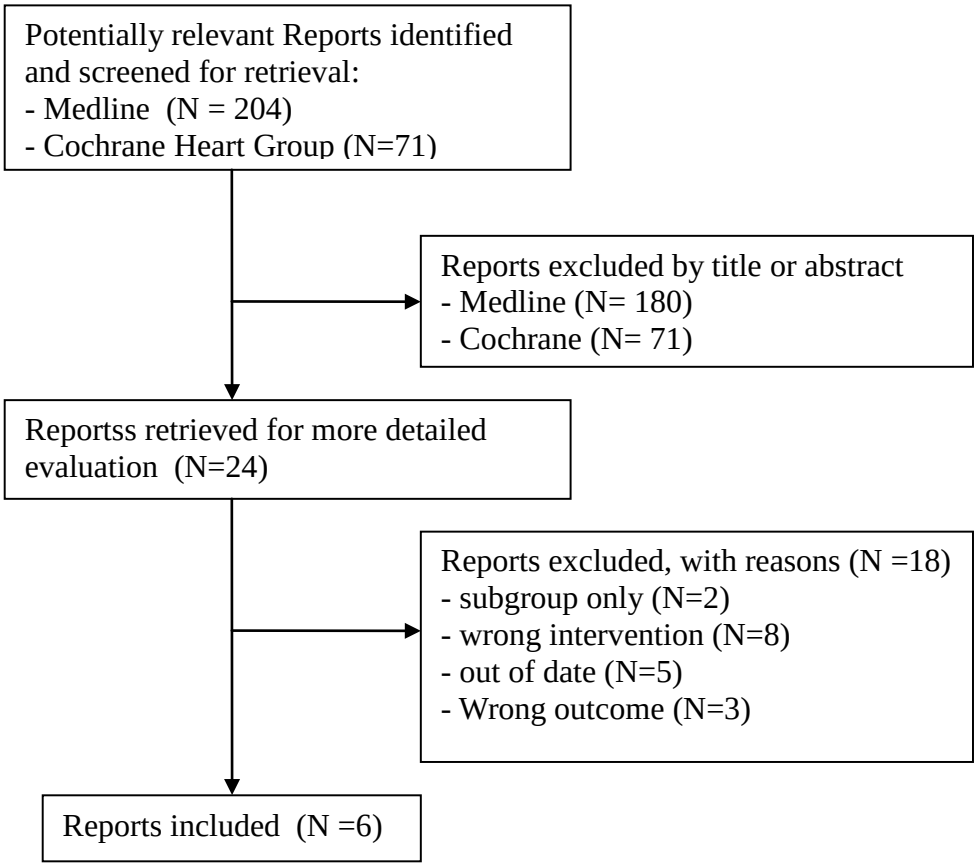


Fig. DS5: PRISMA diagram - rheumatoid arthritis

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

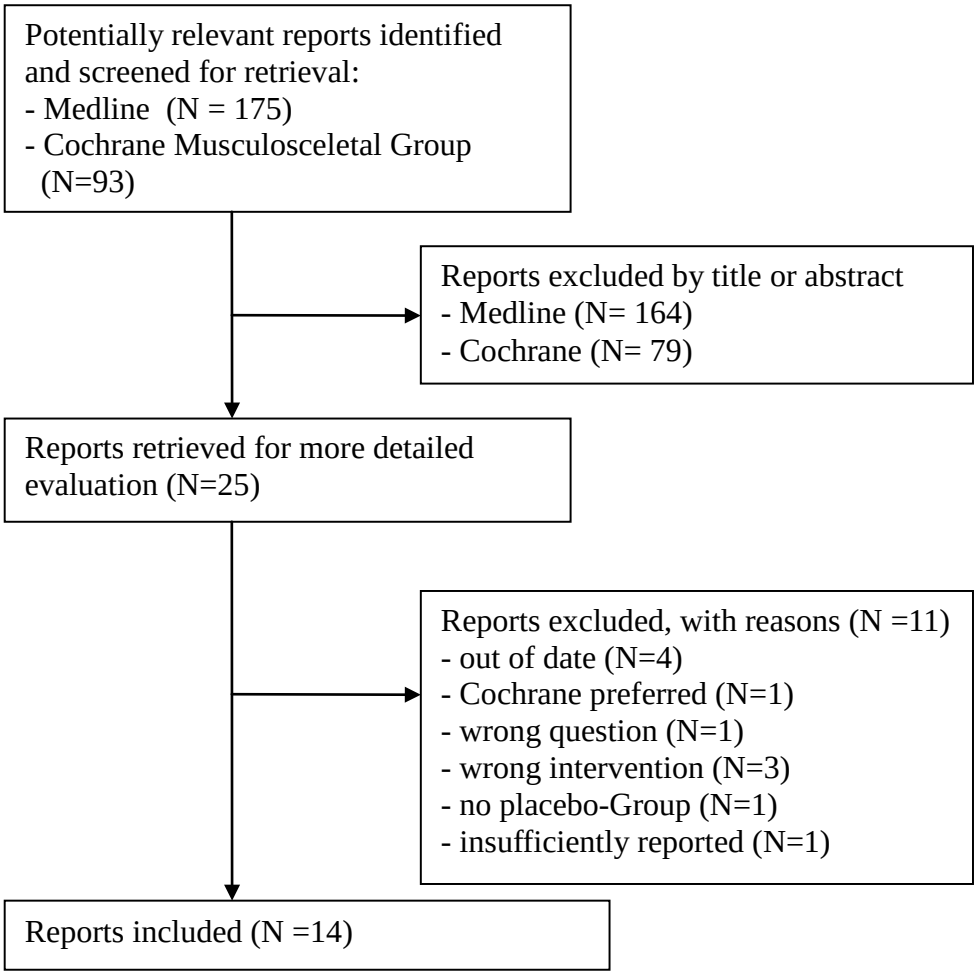


Fig. DS6: PRISMA diagram - migraine

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

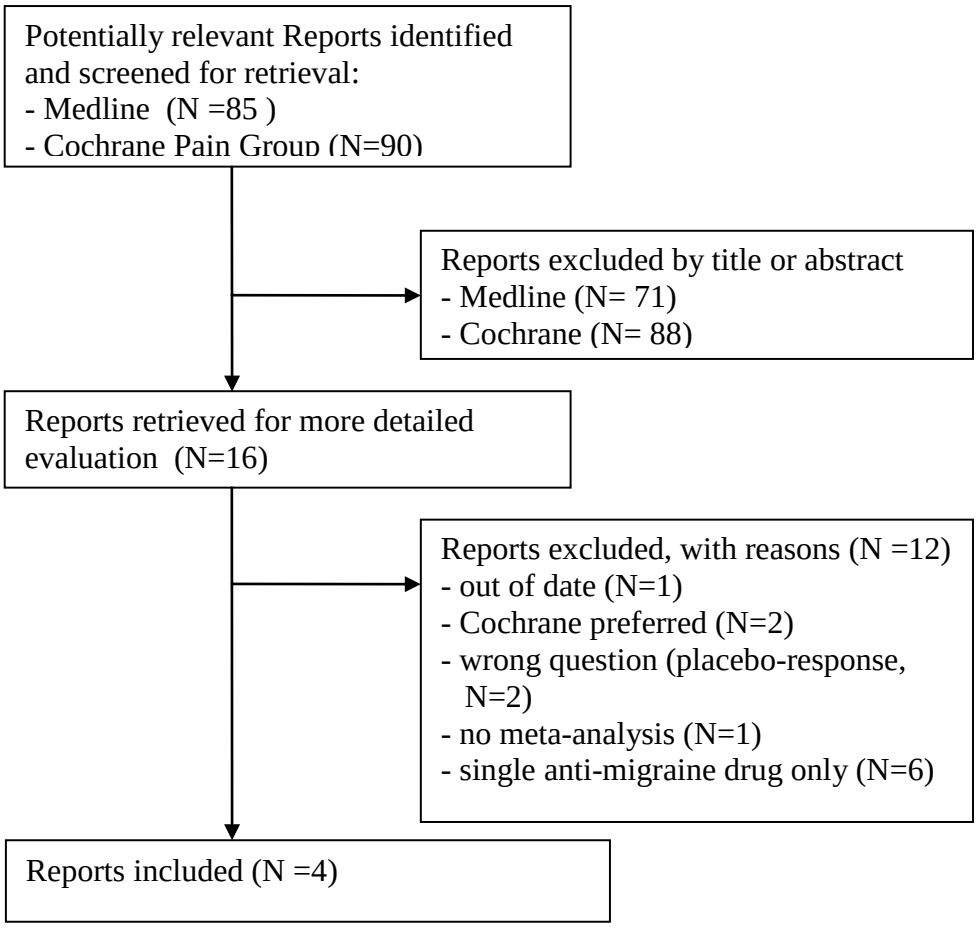


Fig. DS7: PRISMA diagram - asthma

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

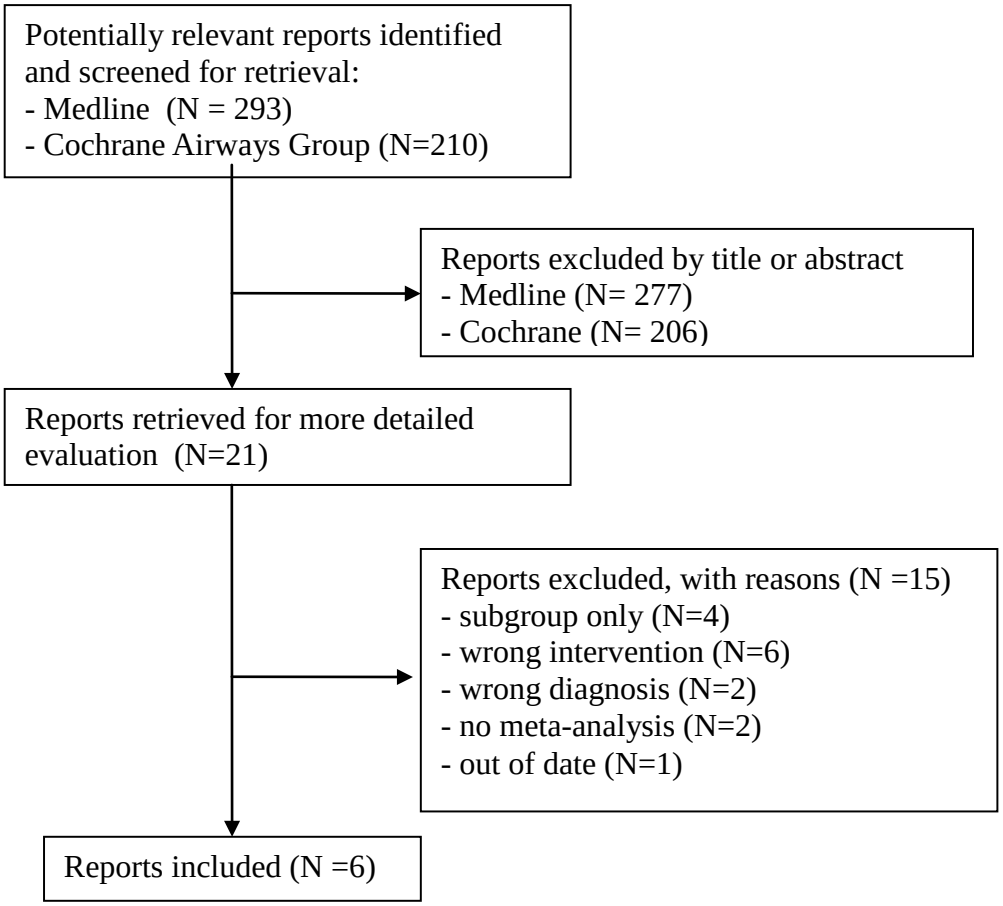


Fig. DS8: PRISMA diagram - chronic obstructive pulmonary disease

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

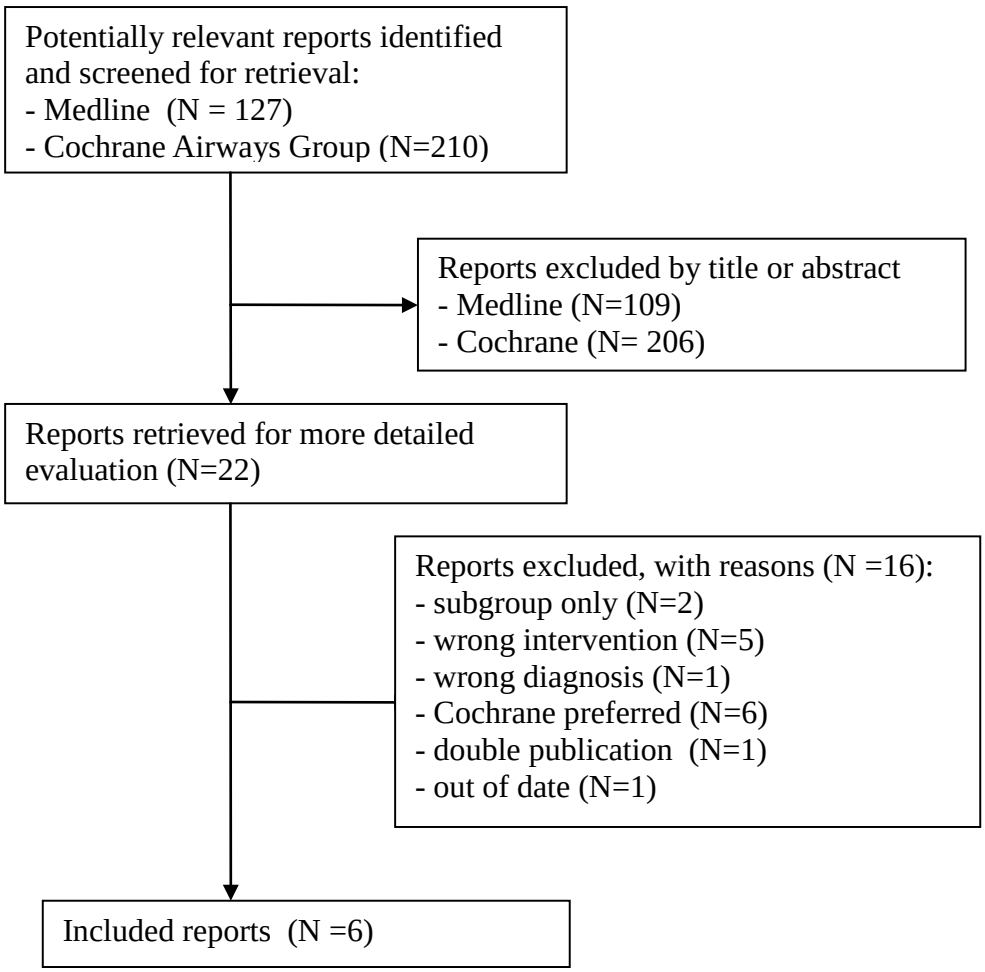


Fig. DS9: PRISMA diagram - diabetes mellitus

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

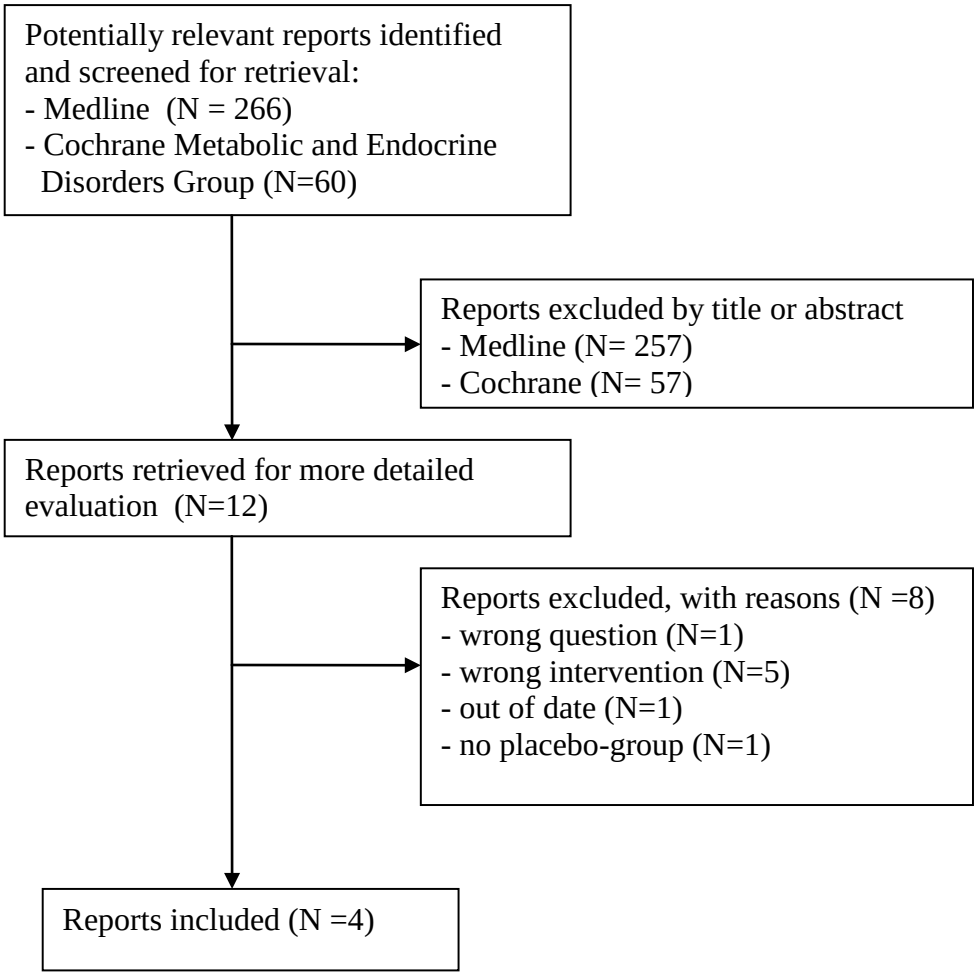


Fig. DS10: PRISMA diagram - hepatitis C

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

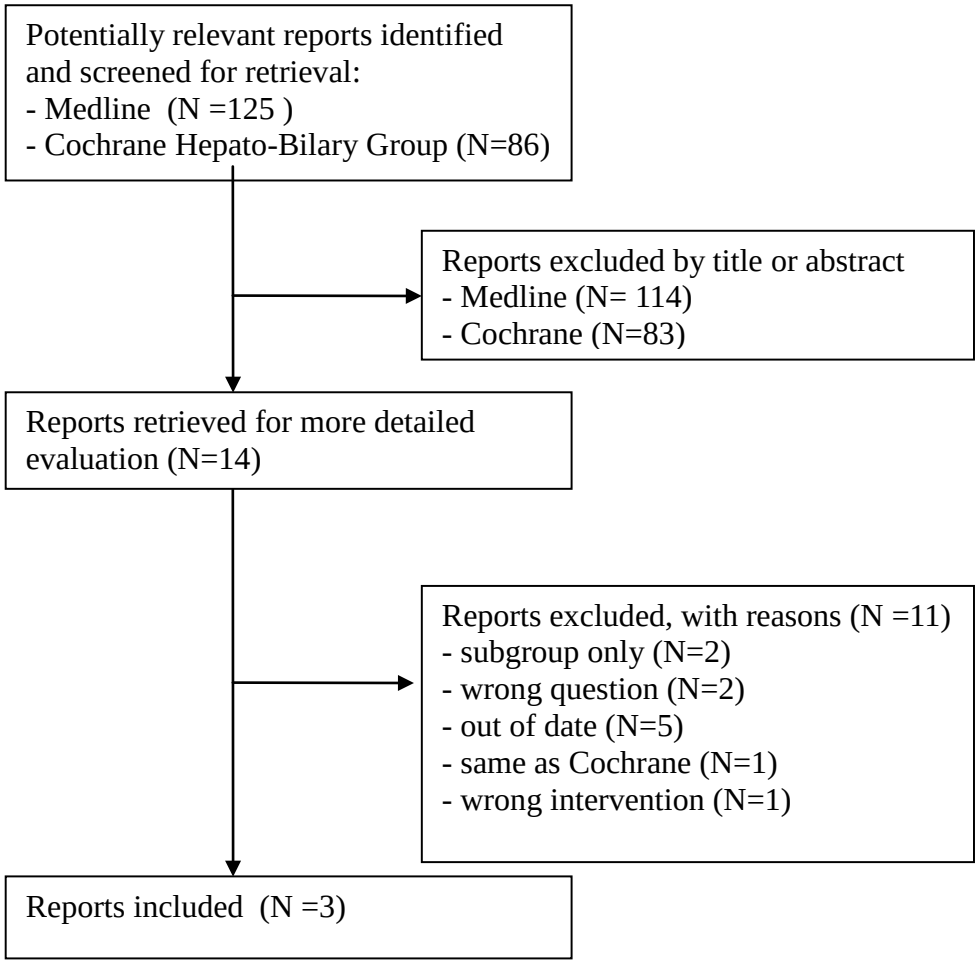


Fig. DS11: PRISMA diagram - proton pump inhibitors for esophagitis

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

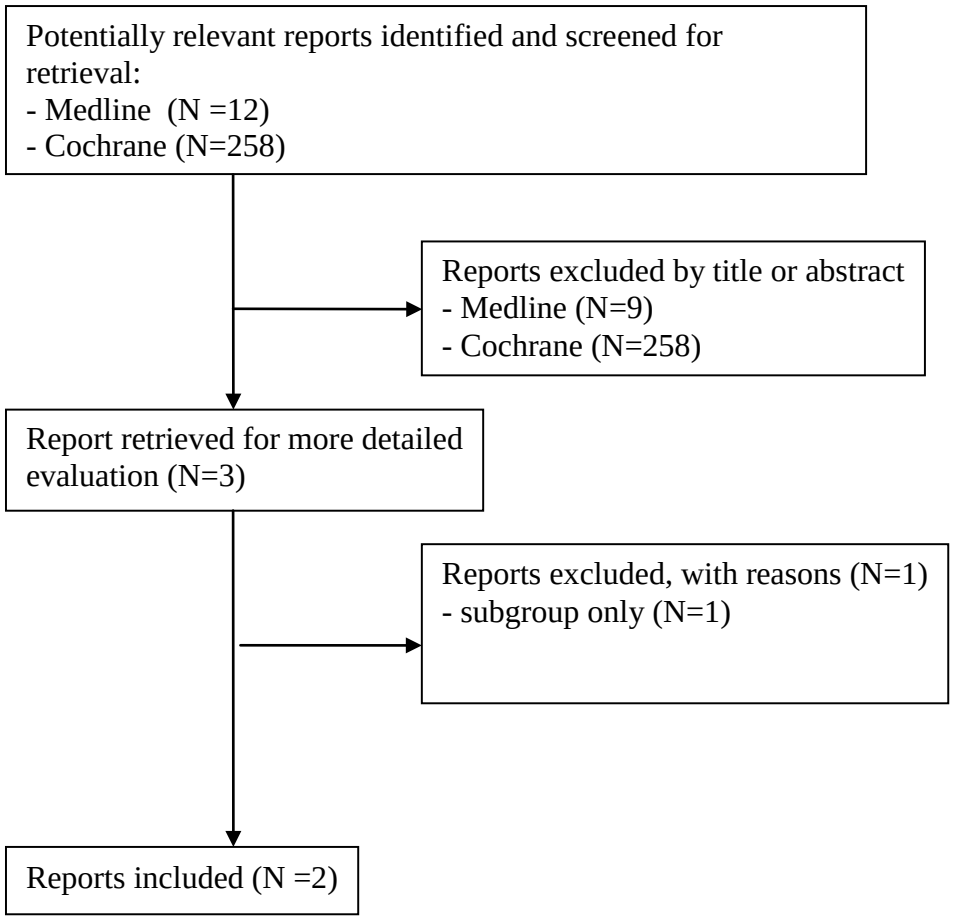


Fig. DS12: PRISMA diagram - ulcerative colitis

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

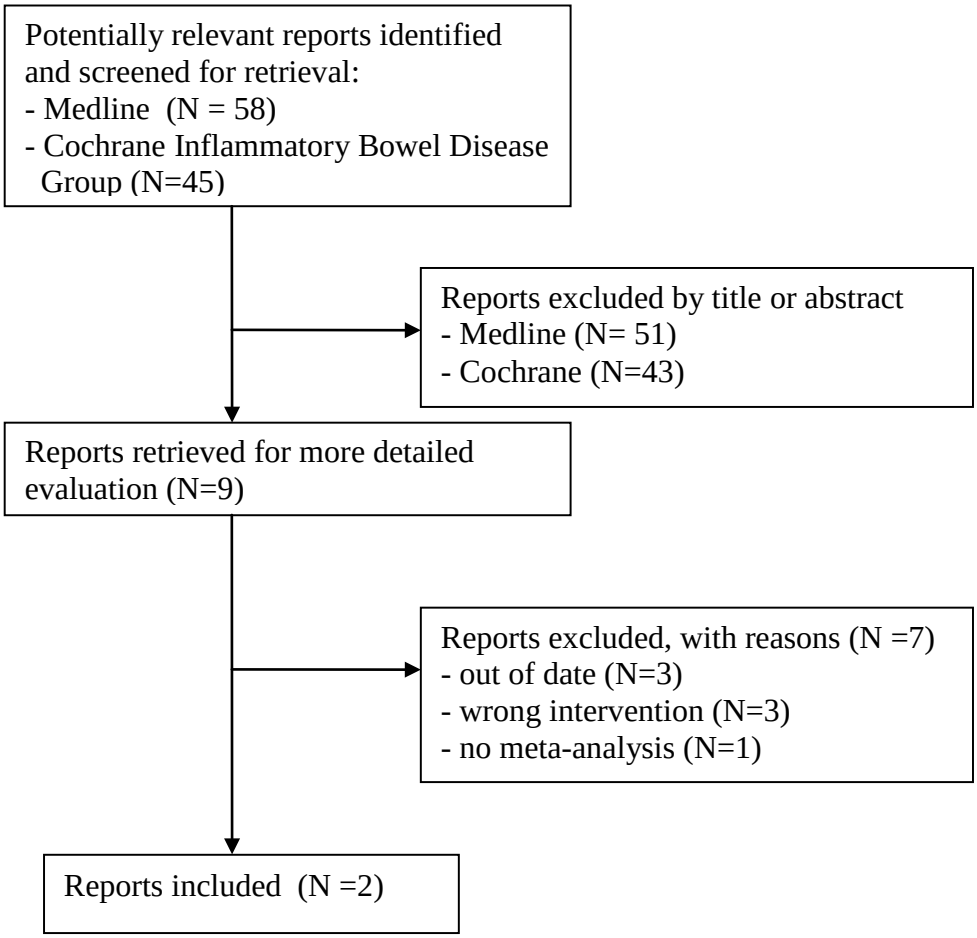


Fig. DS13: PRISMA diagram - multiple sclerosis

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

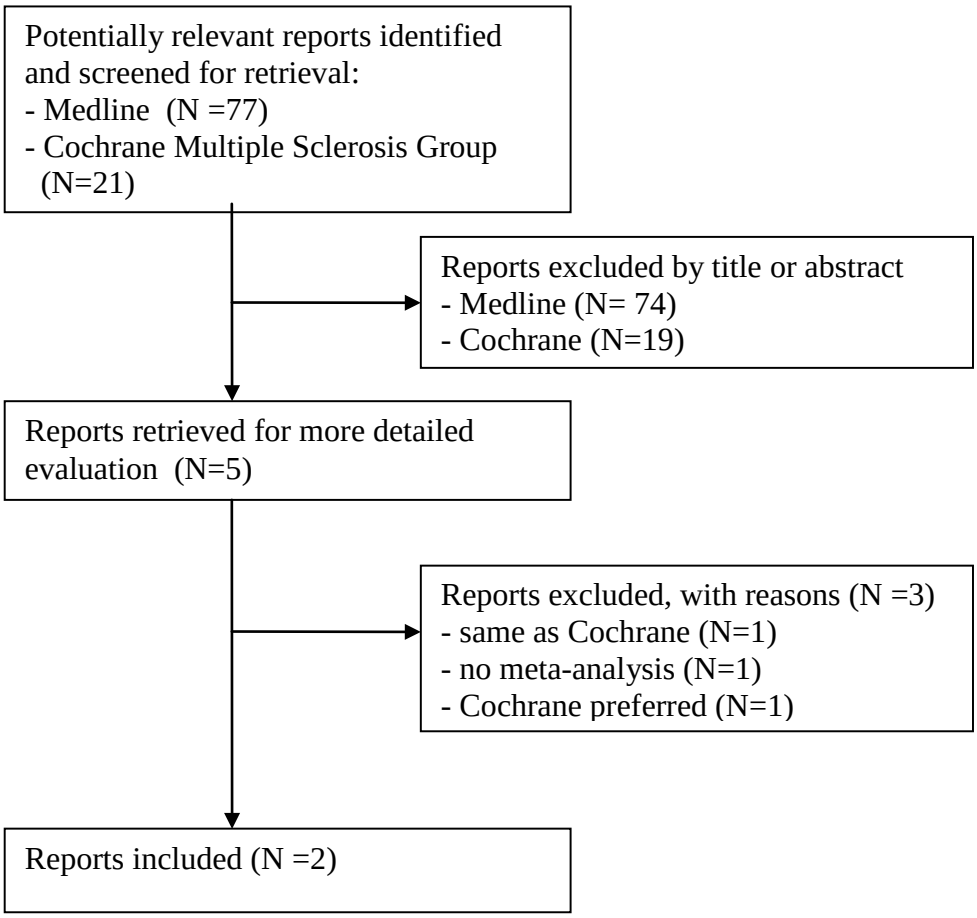


Fig. DS14: PRISMA diagram - Parkinson disease

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

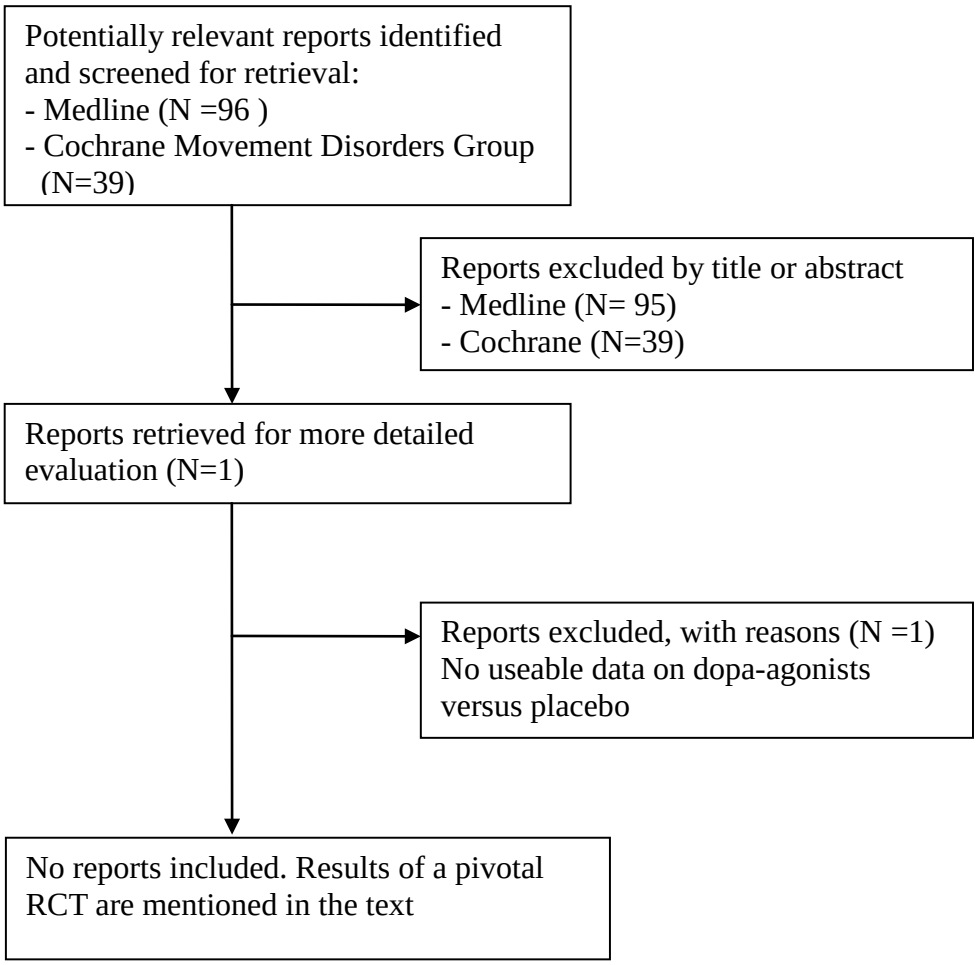


Fig. DS15: PRISMA diagram - breast cancer

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

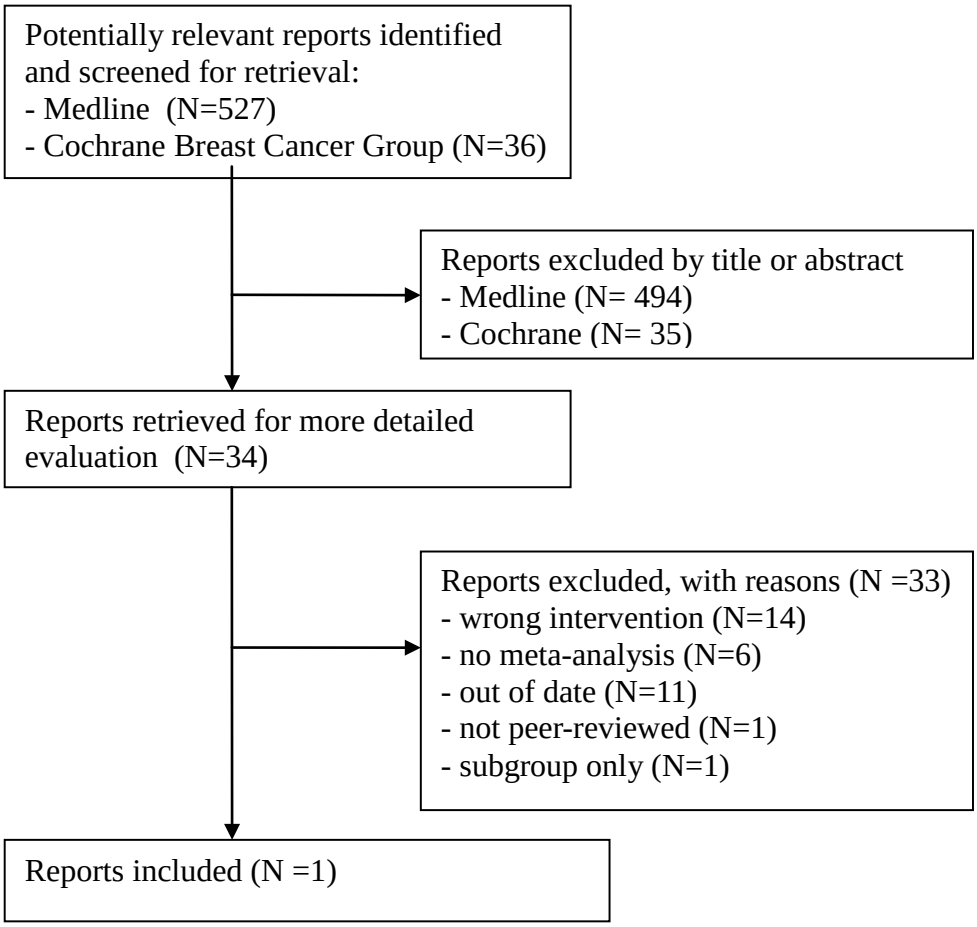


Fig. DS16: PRISMA diagram - lung cancer

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

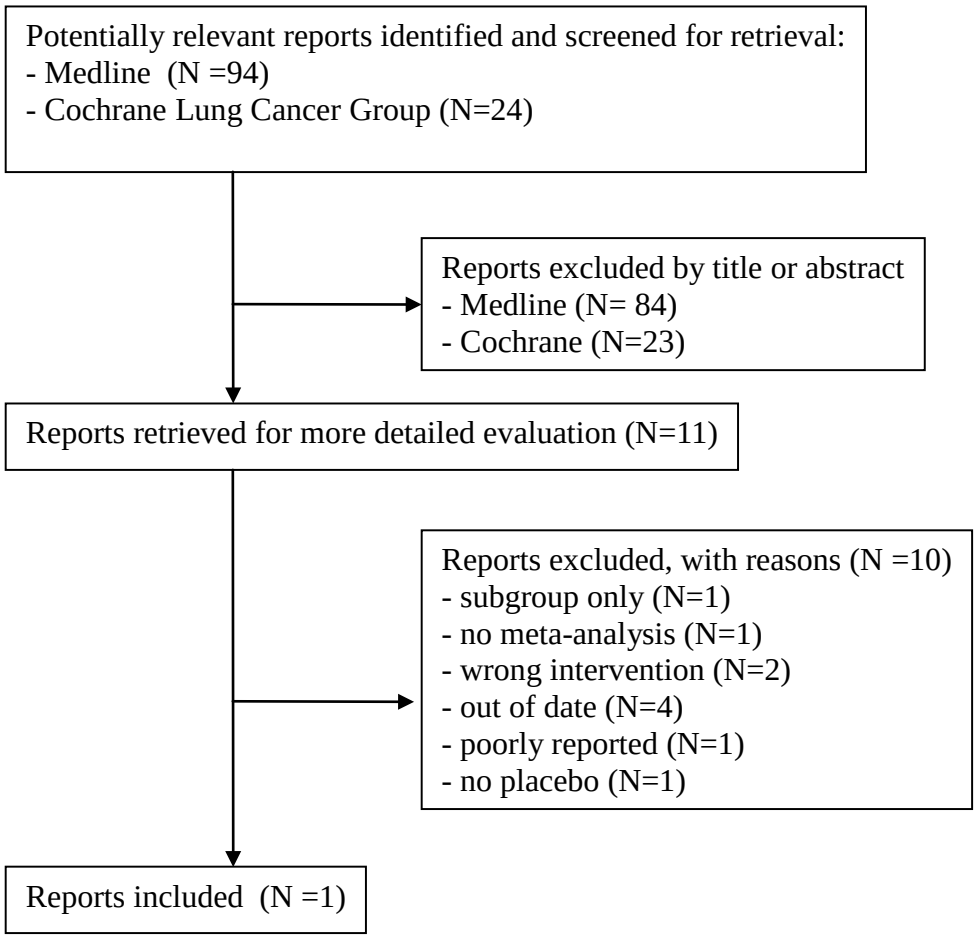


Fig. DS17: PRISMA diagram - antibiotics

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

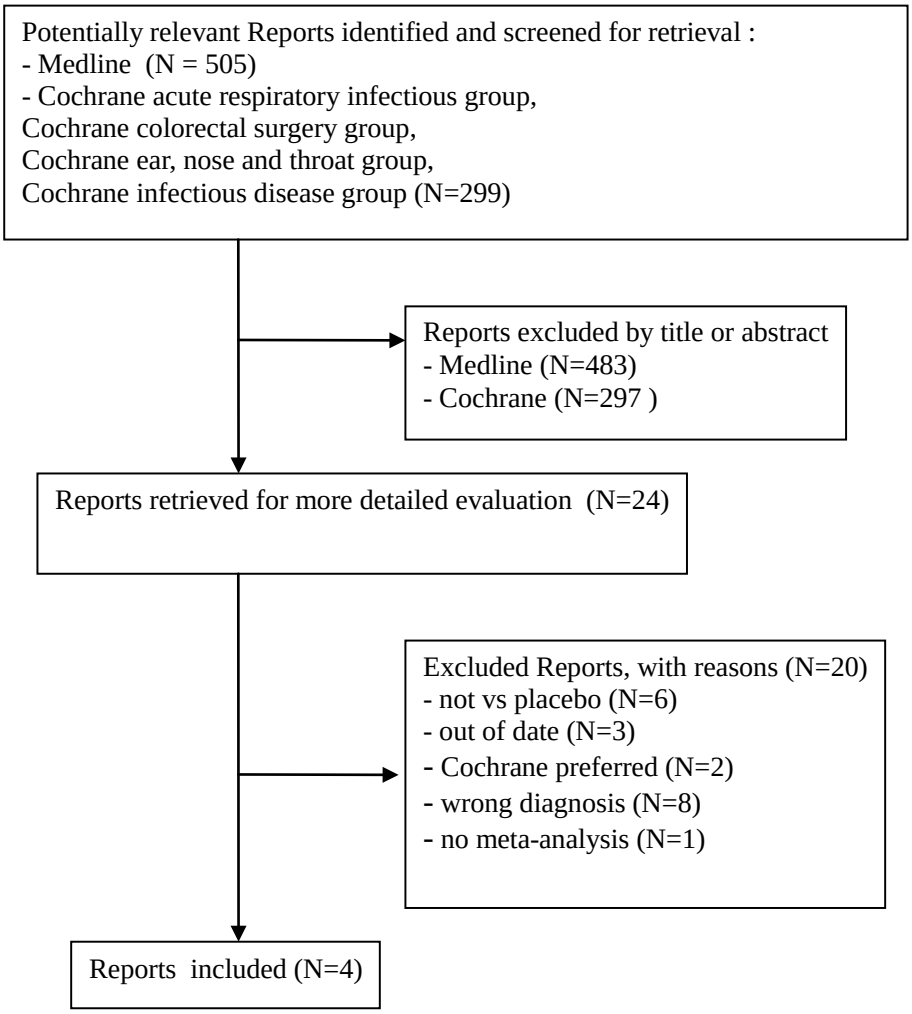


Fig. DS18: PRISMA diagram - schizophrenia

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

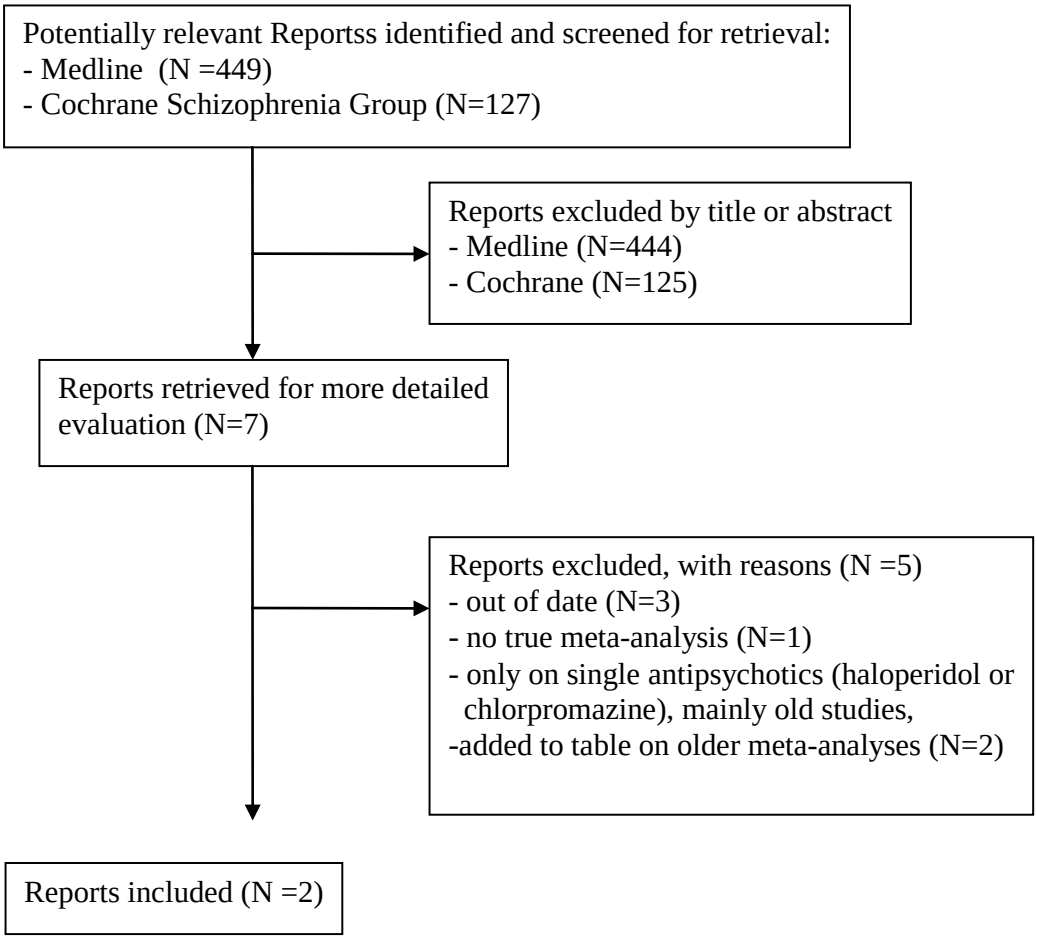


Fig. DS19: PRISMA diagram - bipolar disorder

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

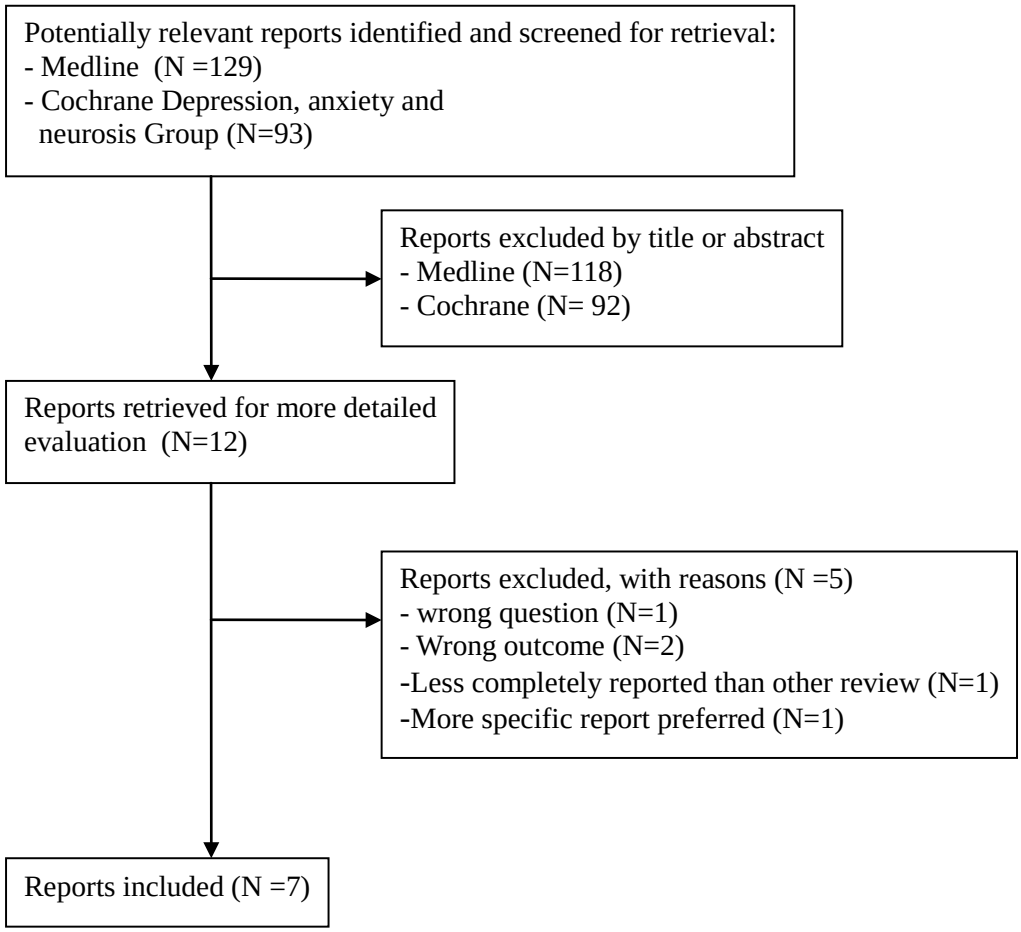


Fig. DS20: PRISMA diagram – obsessive–compulsive disorder

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

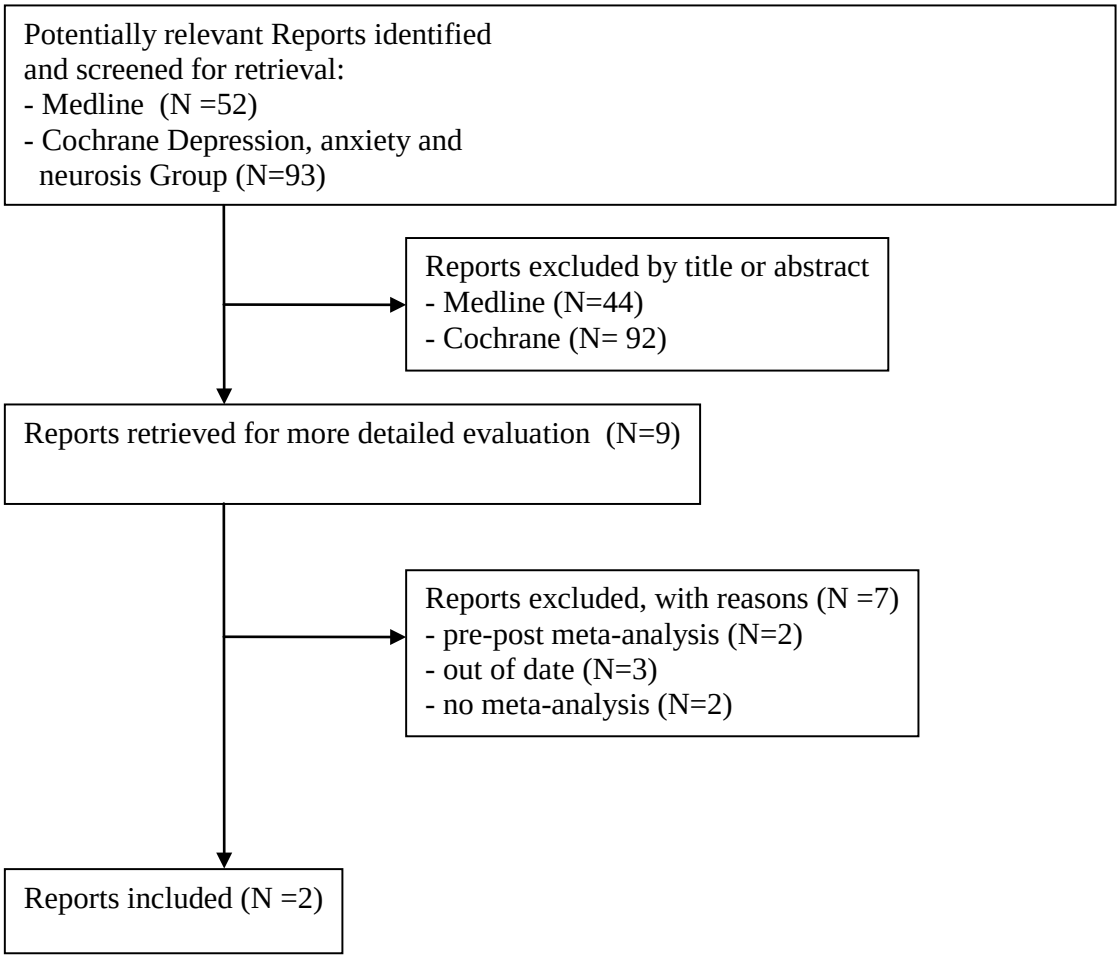


Fig. DS21: PRISMA diagram - major depressive disorder

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

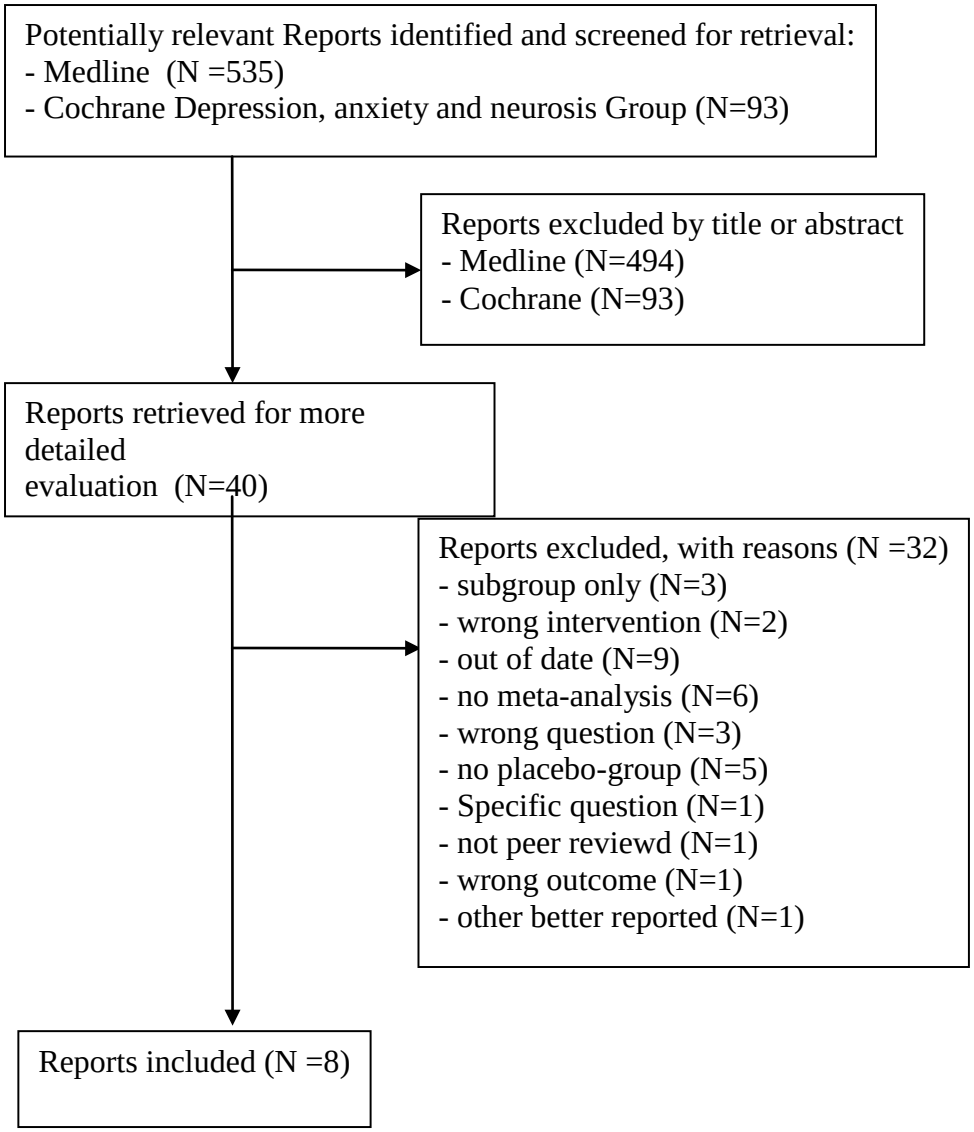


Fig. DS22: PRISMA diagram - panic disorder

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

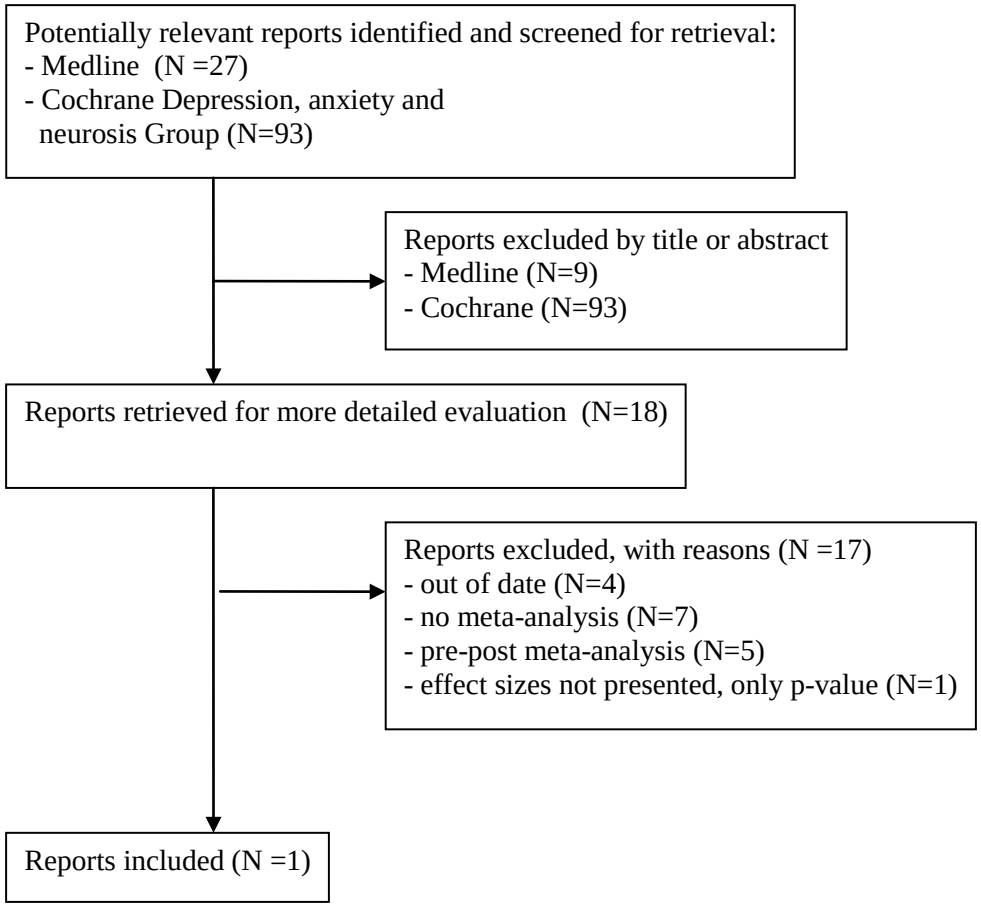


Fig. DS23: PRISMA diagram - dementia

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

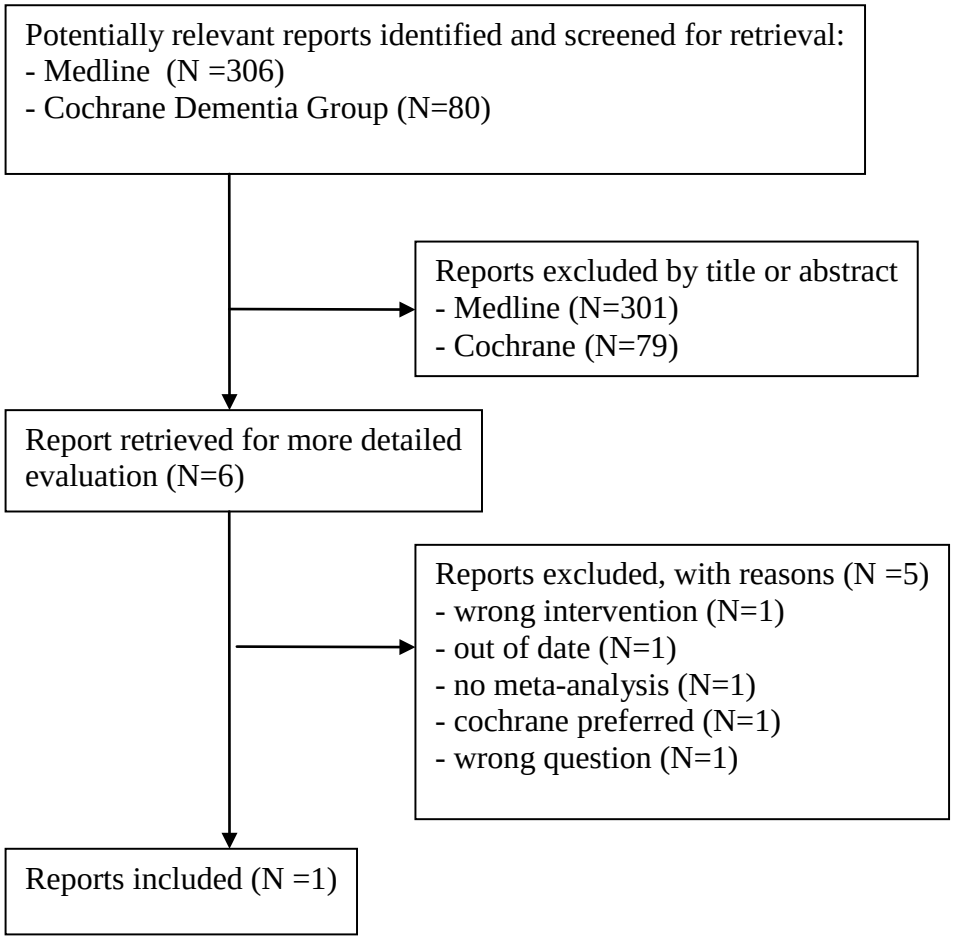


Fig. DS24: PRISMA diagram - attention-deficit hyperactivity disorder

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

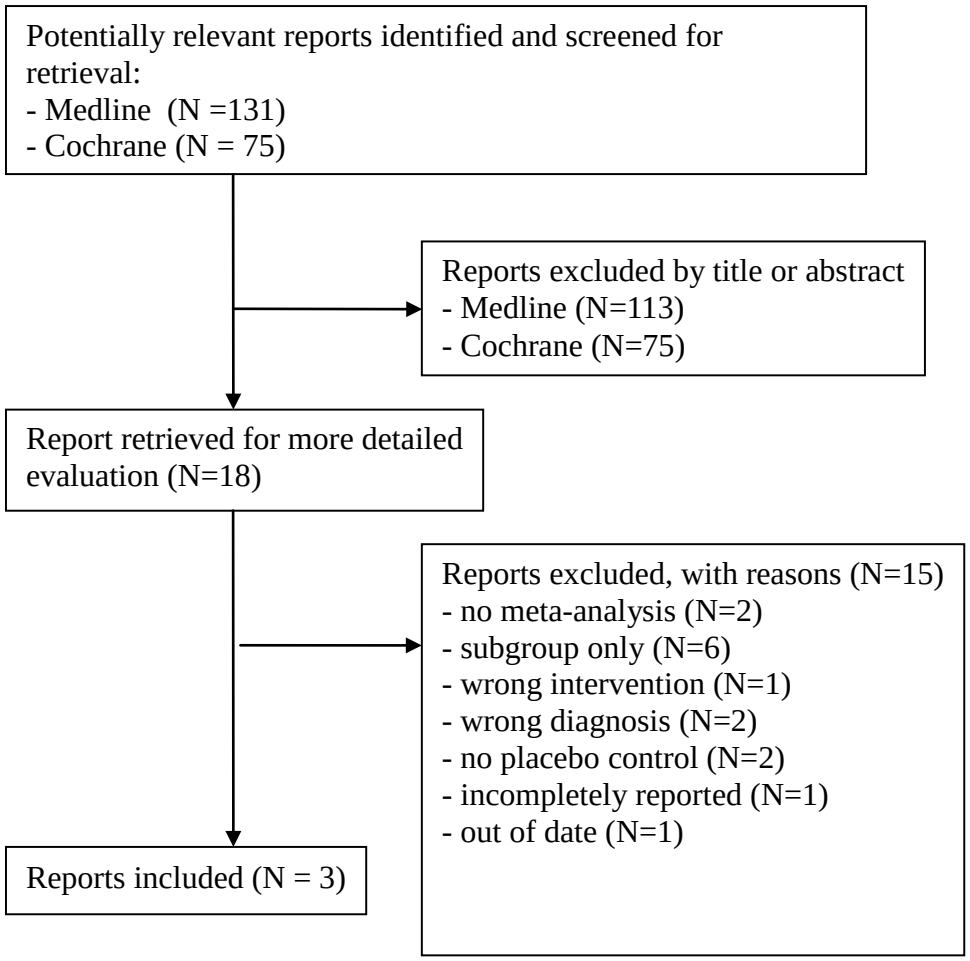


Fig. DS25 Systematic presentation of the effect sizes in Figure 1 labelled by 'Disease − Drug – Outcome. This figure presents the same results as Fig. 1 in the print version, but indicates exactly which result corresponds to which result in the text and Tables 1 and 2. To enable verification Tables 1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

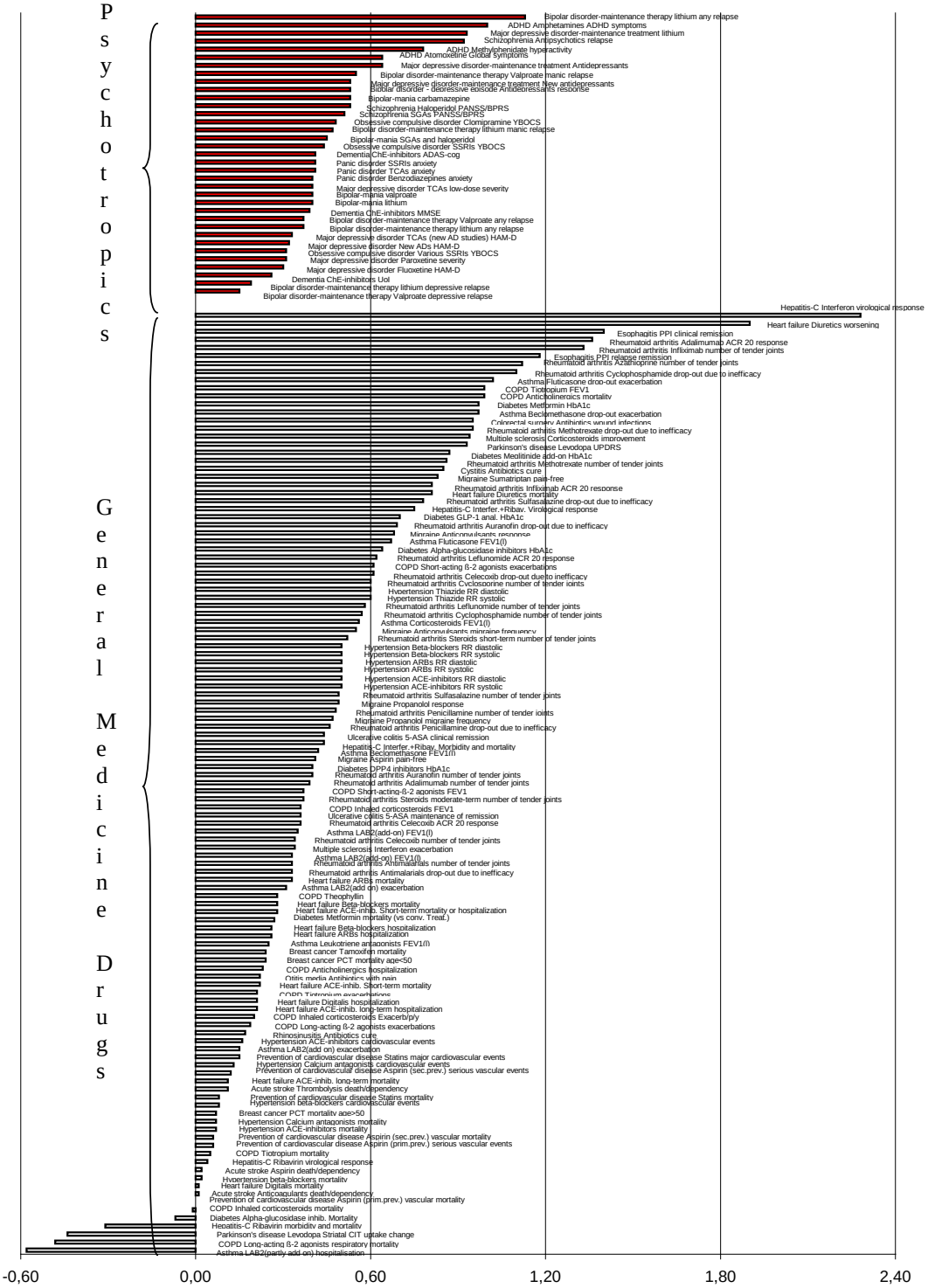


Fig. DS26 Summary of the percentage relative risk reductions/response ratios presented in Tables DS3 and DS4: dot plot. All relative risk reductions in Tables DS3 and DS4 are presented. Data on older meta-analyses from Table DS1 are not included. Effect sizes of general medicine medication are presented 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).

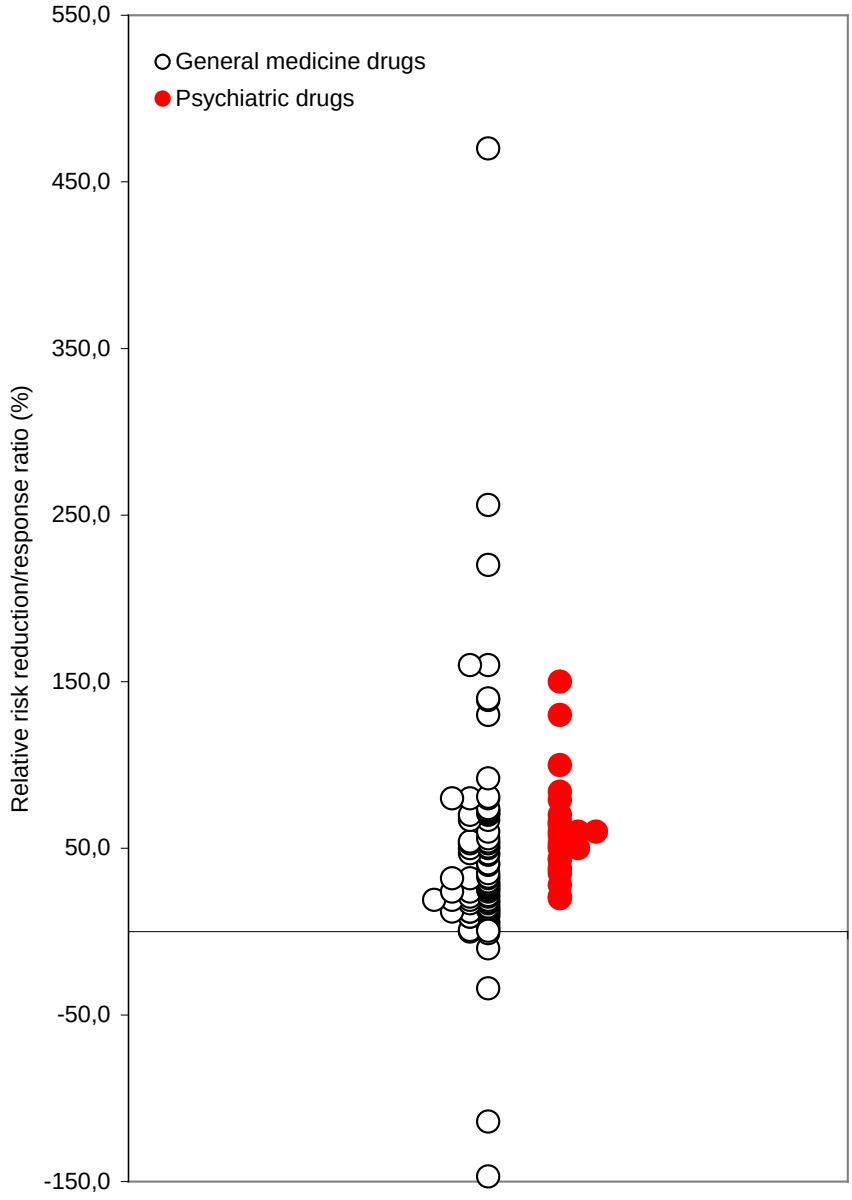


Fig. DS27 Summary of the percentage relative risk reductions/response ratios presented in Tables DS3 and DS4: bar chart. This figure presents the same results as Fig. DS26, but indicates exactly which corresponds to which result in Tables DS3 and DS4.

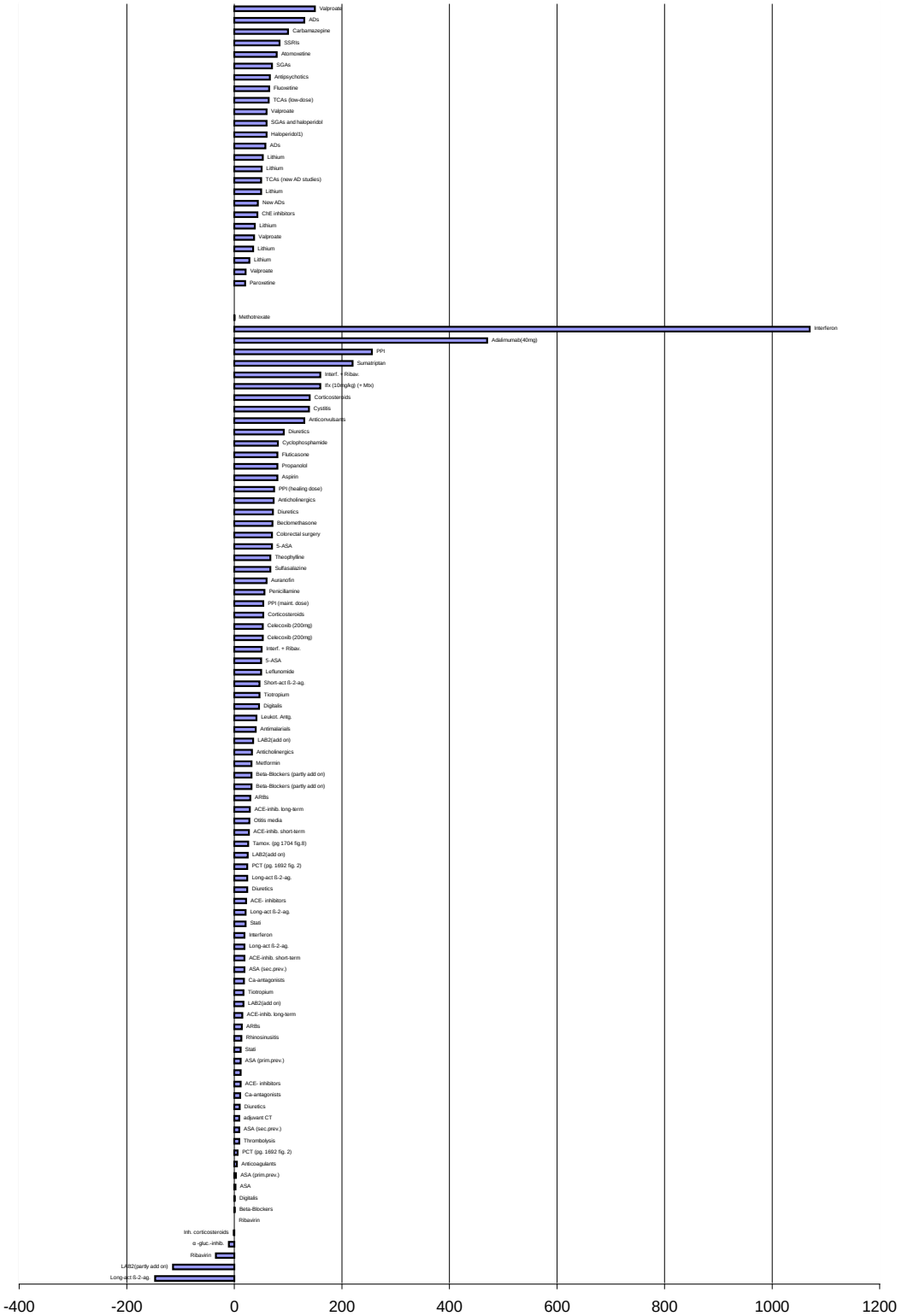


Fig. DS28 Summary of the percentage absolute risk/response differences presented in Tables DS3 and DS4: dot plot. All absolute risk/response differences in Tables DS3 and DS4 are presented. Data on older meta-analyses from Table DS1 are not included. Effect sizes of general medicine medication are presented 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.

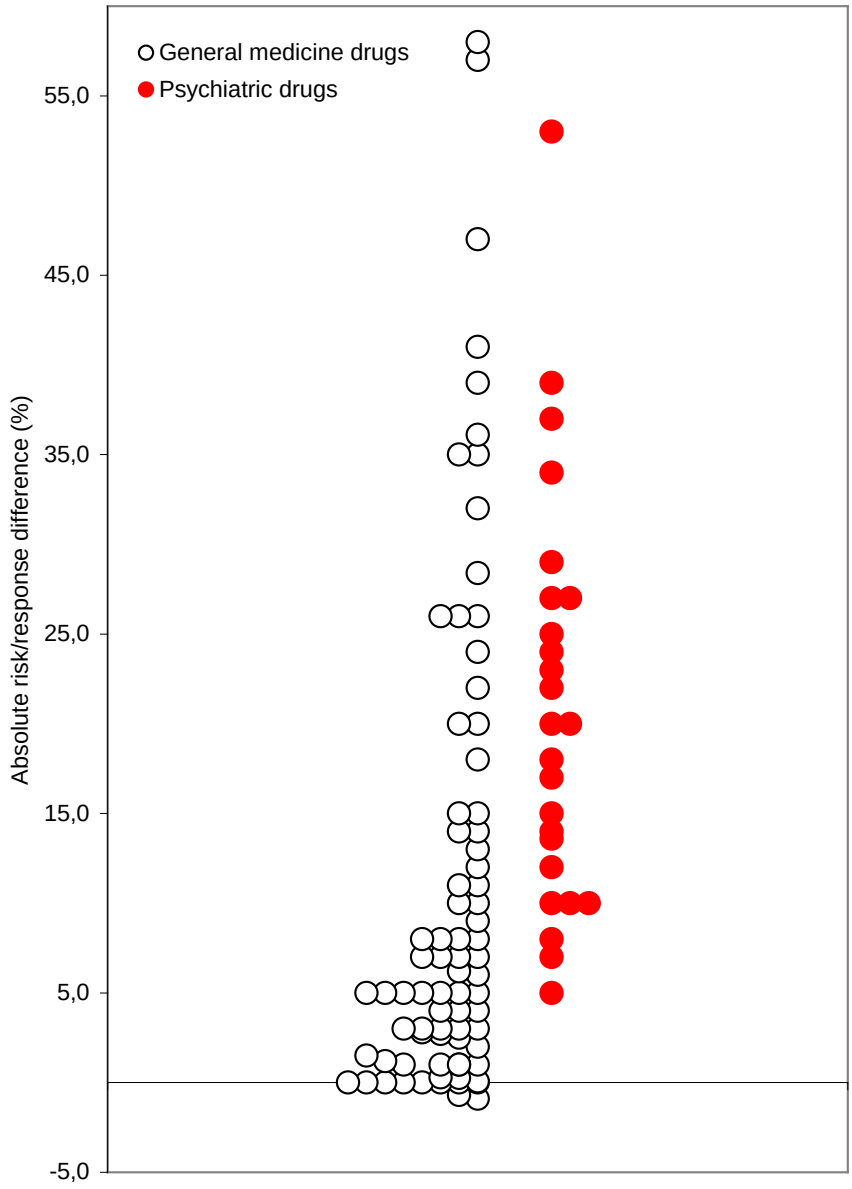
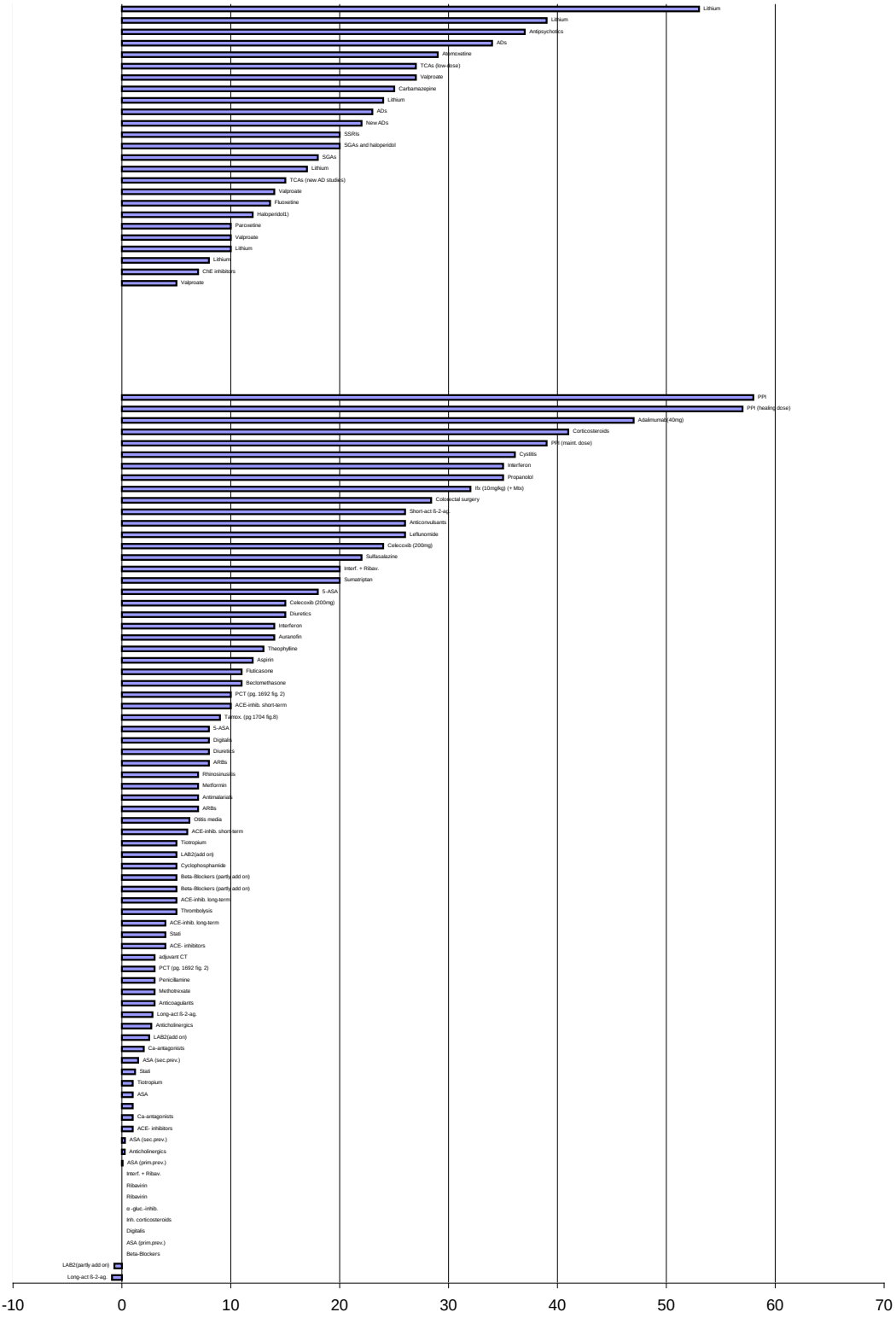


Fig. DS29 Summary of the percentage absolute risk/response differences presented in Tables DS3 and DS4: bar chart. This figure presents the same results as Fig. DS28, but it indicates exactly which corresponds to which result in Tables DS3 and DS4.



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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