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Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks

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Abstract

Objective—Long-term antidepressant (AD) treatment for depression in bipolar disorder (BPD) patients is highly prevalent, but its benefits and risks remain uncertain, encouraging this meta-analysis of available research.

Method—We reviewed randomized controlled trials for BPD involving ≥6 months of treatment with AD ± mood stabilizer (MS) vs. placebo ± MS, using meta-analyses to compare reported risks of new depression vs. mania.

Results—In seven trials (350 BPD patients) involving 12 contrasts, long-term treatments that included ADs yielded 27% lower risk of new depression vs. MS-only or no treatment [pooled relative risk, RR = 0.73; 95%CI 0.55–0.97; number-needed-to-treat (NNT) = 11], but 72% greater risk for new mania [RR = 1.72; 95% CI 1.23–2.41; number-needed-to-harm (NNH) = 7]. Compared with giving an MS-alone, adding an AD yielded neither major protection from depression (RR = 0.84; 95% CI 0.56–1.27; NNT = 16) nor substantial increase in risk of mania (RR = 1.37; 95% CI 0.81–2.33; NNH = 16).

Conclusion—Long-term adjunctive AD treatment was not superior to MS-alone in BPD, further encouraging reliance on MSs as the cornerstone of prophylaxis.

Keywords

bipolar disorder; antidepressants; depression; mania; meta-analysis; maintenance treatment; mood stabilizers; review of the literature

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Declaration of interest

Dr Ghaemi currently receives research grants from Pfizer Corporation, and serves on speakers' bureaus of Glaxo-SmithKline, Astra Zeneca, Pfizer and Abbott Laboratories, and has served on advisory boards of GSK, Janssen, Pfizer, Shire and Abbott Corporations. Neither he nor any family member holds equity positions in pharmaceutical corporations. Dr Wingo and Ms. Filkowski have no disclosures of potential conflicts of interest. Dr Baldessarini is a consultant to, research collaborator with, or has received research support from the following corporations: Alkermes, AstraZeneca, Auritec, Biotrofix, IFI, Janssen, JDS-Noven, Luitpold, Lilly, Merck, NeuroHealing, Novartis and Solvay Corporations, is not a member of any speakers' bureaus, but neither he nor any family member holds equity positions in pharmaceutical or biotechnology corporations.

Depressive episodes in bipolar disorders (BPD), untreated, are longer on average than manic episodes and, with dysthymia and dysphoria, account for the majority of long-term morbidity, even during treatment (1–5). Moreover, BP depression is associated with disability, substance abuse and higher mortality (1,6,7), and typically is more difficult to treat than mania or hypomania (1,8,9). Despite the major clinical and public-health importance of depression in BPD, its treatment has been studied far less than mania or non-bipolar major depressive disorder (2,10,11).

Recent randomized controlled trials (RCTs) indicate that lamotrigine can reduce long-term risk of depressive recurrences in BPD (12,13), olanzapine combined with fluoxetine (14), as well as quetiapine (15,16) are effective short-term in acute BP depression and quetiapine appears to be helpful long-term (16). In addition, lithium has long-term beneficial effects in all phases of BPD (1,2,17) and appears to have unique and substantial anti-suicide effects (18,19). Remarkably, however, antidepressants (ADs) lack specific regulatory approval for use in BP depression, and their clinical value and safety in BPD, particularly with modern agents and type II BPD, remain uncertain and strikingly little studied (20). Several trials of ADs in acute depressive phases of BPD indicate some short-term benefit vs. placebo (21), although two comparisons with mood stabilizers (MSs)-alone did not find superior short-term efficacy (22, 23). Benefits of AD treatment in BPD also may be inferior and less sustained than in non-bipolar major depression (24). Compared with these limited short-term studies, there are even fewer *long-term* studies of ADs in BPD (25). Nevertheless, in the US currently, they are the most frequently prescribed, and among the longest sustained, of all psychotropic agents for BPD patients of all types (26–28).

Aims of the study

Given the importance of effective treatments for the depressive phase of BPD and evident disparity between the broad empirical clinical use of ADs for this purpose and the supporting evidence, we carried out a systematic review and meta-analysis of the effectiveness and behavioural safety of ADs in BPD in long-term, controlled treatment trials.

Summations

- Available research suggests an unfavorable risk / benefit relationship for long-term antidepressant treatment in type-I bipolar disorder.
- Adding an antidepressant to a mood stabilizer has yielded little gain in protection from recurrences of bipolar depression.
- Antidepressant-alone, without a mood stabilizer, may diminish depressive relapse, but carries larger risks of manic or hypomania relapses.

Considerations

- Research pertaining to long-term effects of antidepressants in bipolar disorder patients is severely limited to few controlled trials, small patient samples and mainly older drugs.
- Studies of modern antidepressants and mood stabilizers, alone, and in various combinations, are urgently needed in bipolar disorders.
- Therapeutic research with mainly depressive, type II bipolar disorder patients is needed to guide practice.

Material and methods

Data acquisition

We carried out computerized literature searches for English or foreign-language reports of controlled, long-term use of ADs in BPD (*key words*: 'antidepressant, long-term, maintenance, prevention, or prophylaxis' in 'bipolar or manic-depressive disorder, controlled, and randomized' in various combinations), using the *Medline, HealthStar, Current Contents, PsychInfo, CINAHL, National Library of Medicine, EMBASE, DARE, and Cochrane Library* databases, considering reports from 1960 to May 2008. We also hand-searched: i) bibliographies of reports initially identified by computer searching, ii) reviews on the treatment of BPD (1,10,11,20,29,30) and iii) used computerized and hand searching for abstracts or poster presentations from regular meetings (in 2000–2007) of the American Psychiatric Association, American College of Neuropsychop-harm- acology, International Society for Bipolar Disorders, the Stanley Foundation, the NIH New Clinical Drug Evaluation Unit and of the Collegium Internationale Neuropsychopharmacologicum. We also contacted expert colleagues and major funding agencies involved in therapeutics research on BPD to identify accessible data from unpublished trials and verified uncertain details of trials with the authors when necessary.

Selection criteria

Search results were reviewed independently by two reviewers (SNG, APW) to identify and evaluate potentially suitable trials. Inclusion criteria were i) involving patients diagnosed with type I or II BPD, based on modern criteria (DSM-III or IV, ICD-9 or 10, or RDC); ii) treatment based on randomization to any type of AD vs. a non-AD or placebo comparison treatment, with or without control of doses or co-treatment with MSs; iii) treatment intended for continuation for ≥6 months; iv) outcomes based on quantified assessment of mood states, recurrences, or latency to either recurrence or worsening of major depressive and other episodes. Exclusion criteria were limited to i) non-randomized treatment, ii) diagnosis of non-bipolar major depression or samples including BP and other types of clinical depression, unless data for BPD patients were quantified separately and iii) reports that did not permit analysis of risk of BP depression separate from other types of illness episodes. Two reviewers (MAF and SNG) independently assessed the methodological quality of identified trials based on Jadad scores (31), as recommended by experts in meta-analysis (32,33).

Data extraction and analysis

Data extraction was performed independently by two investigators (SNG and APW); discrepancies were resolved by consensus of all authors. Data acquired included patient characteristics, trial design features and values of quantitative outcome measures, as summarized below. As reported data were insufficient to support analyses based on time-to-relapse, we limited such outcome measures to secondary analyses and relied primarily on incidence of depressive or manic relapses or recurrences based on criteria applied to all treatment arms in each study, without adjusting for duration of treatment exposure. By separate random effect meta-analyses, we compared pooled rates of recurrences of depression or mania between AD and control arms within-trials to determine an observed rate ratio (RR) and its 95% confidence interval (CI) for each trial, as well as a pooled RR and its CI, across all included trials, weighted by the size and average variance in each trial (34). Based on random effect meta-analyses of rate differences (RD), we also estimated number-needed-to-treat (NNT; to reduce risk of depression) or number-needed-to-harm (NNH; to increase risk of mania) and their CIs. To determine if meta-analysis was unduly influenced by a single study or treatment type, we carried out sensitivity analyses based on recomputing pooled RR values after deleting individual studies serially, as provided by REVIEW MANAGER (version 4.2; Nordic Cochrane Centre, Copenhagen, Denmark) software employed for all analyses. Systematic bias (35) was assessed

by visual inspection of funnel plots (36). We also carried out planned, secondary, subgroup analyses for trials employing similar outcome measures (for AD ± MS vs. placebo or MS alone), and considered selected characteristics for meta-regression vs. computed RR values.

Results

Study sample

Of 169 reports initially screened, all but seven (37–43) were excluded (Fig. 1). One involved unpublished findings by Ghaemi et al. (43). No other accessible unpublished datasets met our inclusion criteria. The seven trials analyzed (37–43) had a moderately high average quality score of 3.1, a total of 350 BPD patients (4–42 participants/study treatment arm) of average age 40.6 years, with approximately 13 years of illness (Table 1). Drop-out rates ranged from 0 to 69% (mean 19%). BP-II cases were reported separately in only two trials (39,42). Only three trials involved placebo controls (37,39,42). All but two trials (42,43) involved tricyclic ADs (TCAs) and lithium as MS. One trial was not blinded, but was randomized (43). As there were multiple treatment arms in three (37,39,40) of the seven included trials, there were 12 contrasts involving AD-alone or with an MS vs. placebo or MS-alone to support assessment of risks of new depression (Table 2) and new mania (Table 3). Six of the seven included trials (37–40,42,43) involved ‘enrichment’ of treatment effects, requiring initial benefits of AD or MS treatment in acute BP episodes before patients entered long-term, continuation treatment.

Effects of antidepressant treatment on depression

There was an overall indication of moderate reduction in risk of depressive recurrences with AD included in long-term treatment regimens vs. either MS-alone or no treatment (RR = 0.73; 95% CI 0.55–0.97; $z = 2.16$, $P = 0.03$), suggesting sparing of new depression by approximately 27% (Fig. 2a). Only one of the 12 comparisons (38[a]) individually yielded statistical superiority of AD treatment, which involved a small comparison of imipramine-alone ($n = 13$) vs. placebo ($n = 13$), with a 60% sparing of new depressive episodes within 2 years (Table 2).

In additional meta-analyses involving subgroups (Table 4), three studies (38[a],40[a],43; note that letters refer to treatment arms of studies cited in Table 2–4 and in References) with 50 participants that compared AD-alone vs. no treatment yielded a significant, 54% lower risk of new depression (RR = 0.46; 95% CI 0.27–0.80). However, when AD ± MS was compared with MS-alone in eight contrasts (38[b],39,40[b,d],41[a,b],42,44) involving 346 patients, there was very little difference in risk of new depression (RR = 0.89; 95% CI 0.64–1.25). Five other studies (39,40[d],41[b],42,44) involving 246 patients compared AD + MS with MS-alone and found little benefit with an AD added (RR = 0.84; 95% CI 0.56–1.27). In addition, there was no difference in risk of new depression with AD-alone vs. MS-alone (RR = 1.00; CI 0.57–1.75) in three trials involving 118 patients (38[b],40[b],41[a]).

Although not derived from the same trials, and so involving unmatched but separately randomized samples, data from Table 2 pooled from the six treatment arms involving MS-alone yielded a similar recurrence rate for depression (43/148 = 29.1%) to that found by pooling data from the five arms with AD added to MS (26/116 = 22.4%) (RR = 1.29; 95% CI 0.85–1.98).

Effects of antidepressant treatment on risk of mania

There were 74 new cases of mania and seven cases of hypomania. The pooled risk of new hypomanic or manic episodes was 72% greater in association with long-term use of ADs than without such treatment (RR = 1.72; 95% CI 1.23–2.41; $z = 3.15$, $P = 0.002$; Fig. 2b). Specifically, three comparisons (40[d],42,43) involving only 4–8 participants per treatment arm found no cases of mania or hypomania with or without AD treatment within approximately

12 months of exposure (Table 3), and two of these involved only BP-II patients (40[d],43). However, two of the nine remaining comparisons individually found significantly increased risk of mania (not including hypomania) with ADs; both involved comparisons of imipramine-alone to lithium-alone (38[b],41[a]). Among the seven remaining trials, five found increased risk of mania with ADs (38[a],39,40[a,b],44) and two did not (40[c],41[b]).

We also carried out additional meta-analyses involving subgroup effects regarding risk of new mania (Table 4). When AD was used with or without an MS in eight studies involving 364 participants, risk of new mania was significantly increased compared with use of MS-alone (RR = 1.80; 95% CI 1.22–2.65) (38[b],39,40[b,d], 41[a,b],42,44). When AD was used alone in three other trials (38[a],40[b],41[a]) involving 118 patients, there was a significant 2.4-fold increase in risk of mania compared with use of MS-alone (RR = 2.37; 95% CI 1.38–4.05). When AD was combined with MS in five comparisons (39,40[d], 41[b],42,44) involving 246 patients, risk of mania was 37%, but non-significantly, greater than with MS-alone (RR = 1.37; 95% CI 0.81–2.33).

In addition, we pooled data from unmatched (i.e. not derived from the same trials) but separately randomized samples and found that risk of new mania was half as great among BPD patients given an AD with an MS (25/116 = 21.6%) vs. an AD-alone (28/62 = 45.2%) (RR = 0.48; 95% CI 0.31–0.74; Table 3), suggesting a protective effect of co-treatment with an MS. In a similar analysis, risk of new mania was substantially (51%), but non-significantly, greater when an AD was added to an MS (26/116 = 21.6%) than during treatment with an MS-alone (22/148 = 14.9%) (RR = 1.51; 95% CI 0.90–2.51).

Meta-analyses based on risk-difference, with NNT and NNH

We also carried out complimentary meta-analyses of effects of AD treatment, based on RD rather than RR, to retain some comparisons without adjustment for zero numerators in single treatment arms, and to obtain estimates of the NNT so as to reduce risk of new depression by one case and the NNH by increasing risk of new mania by one case. Consistent with the preceding RR findings, the pooled meta-analytic RD in 12 comparisons, risk of new depression decreased by 10% [RD = −0.90 (95% CI −0.17 to −0.01; $z = 2.15$, $P = 0.032$] and mania increased by 14% [RD = 0.14 (95% CI 0.06–0.22; $z = 3.42$, $P = 0.001$; not shown].

Based on reciprocals of computed RDs, reducing risk by one new episode of BP depression is estimated to require a NNT of 11.1 (95% CI 5.82–128) patients, whereas increasing risk of mania by one episode required a NNH of only 7.18 (95% CI 4.59–16.5) patients, when AD ± MS was compared with MS-only or no treatment. These values accord closely with estimates based on the difference between the pooled response rates for reducing risk of new depression [NNT = 1/(0.253–0.355) = 10; Table 2) and for increasing risk of new mania [NNH = 1/(0.298–0.157) = 7; Table 3). Of note, the estimated NNH when an AD was added to an MS vs. treatment with an MS-alone (NNH = 16) was greater than in the overall contrast of AD being present vs. absent (NNH = 7), again suggesting a substantial protective effect of MSs vs. new mania. These NNT and NNH estimates support the conclusion that beneficial, depression-avoiding effects of adding ADs were limited, that risk of inducing mania was substantially increased, and that the apparent ‘risk/benefit’ ratio was <1.0 or unfavorable (NNH /NNT = 7.18 / 11.1 = 0.65). The findings further suggest that the presence of an MS, even with an AD added, limited risk of mania, as expected.

Sensitivity analysis, publication bias and meta-regression

No individual trial appeared to bias the reported conclusions substantially, based on sensitivity analysis involving eliminating one trial at a time, serially, from the meta-analysis (not shown). Also, systematic bias appeared to be unlikely based on visual inspection of funnel plots of

standard-error-of-RR vs. RR for depression ($n = 12$ comparisons) or mania ($n = 9$ comparisons; not shown). Also, information concerning types of ADs, source of funding, diagnostic subgroups and sex was too limited to support credible meta-regression analyses for associations of outcomes with subgroups. Despite limited power, we considered potential effects of trial-quality ratings and completion rates on meta-regression analyses for sparing of new depressive episodes or increases of new manic episodes, and found no significant relationships (not shown).

Discussion

Available research on *long-term* use of ADs to treat patients diagnosed with BPD is not adequate to support their extraordinarily widespread, off-label, empirical use in clinical practice (20,27,28). On balance, the research reviewed here suggests an *unfavorable* risk / benefit relationship for long-term AD treatment in BPD, especially BP-I disorder, in that adding an AD to an MS yielded little reduction in risk of BP depression beyond that achieved with MSs-alone (Table 2 and Table 4). Particularly when given alone, ADs were associated with considerable added risk of mania (Fig. 2b; Table 3 and Table 4).

Trials available for these analyses of long-term effects of ADs in BPD patients (Table 1) are few in number, typically involve small sample sizes and rarely consider BP-II patients (39, 42,43) or modern drugs (42,43). Recurrence rates usually were not reported as a function of precise treatment-exposure times, and their analyses required reliance on crude and not necessarily directly comparable proportions of participants with recurrences. Moreover, bias may be introduced by using the same data in more than one comparison in multi-arm trials, of which we had three (37,39,40). Enrichment trial designs, with which patients in an acute episode were treated openly with a study drug to short-term recovery, and then randomly assigned to different long-term treatment-arms, without necessarily being in remission (44), were encountered in 6 / 7 trials analyzed (37–40,42,43), and may limit generalization of observed effects to those in less selective, clinical circumstances. Moreover, the range of specific treatments compared was very limited, and most trials involved agents used less commonly now than formerly, including TCAs and lithium (28). Only 2 / 7 studies (42,43) included serotonin reuptake inhibitors (SRIs), precluding meaningful comparisons by AD-type. Indeed, a main conclusion of this review is that the information available from RCTs involving BPD patients, with which to evaluate long-term maintenance treatment involving ADs is simply insufficient to guide rational practice with modern medications. This limited body of information is at striking disparity with the widespread and long-sustained use of modern ADs, with or without a growing range of agents with apparent mood-stabilizing properties, in current American clinical practice (27,28).

Despite their limitations, when the available data were pooled, there was a minor beneficial effect of including an AD, with about 27% lower overall risk of long-term recurrences of depression (Fig. 2a). On the other hand, there was a 72% increase of risk of new episodes of mania (including hypomania and mixed states; Fig. 2b). The observed switch risk is higher than had been noted in many previous studies, especially those involving low doses of a modern antidepressant combined with an MS (45), potentially because of three main factors. First, most of the reviewed studies (10 / 12 contrasts; Table 3) used a TCA, which has a relatively higher risk of treatment-emergent mania in adults compared with SRIs and some other modern ADs (45–47). Second, a TCA was used *without* an MS in 5 / 10 contrasts (Table 3). Third, switching risk appears to be greater with longer-term follow-up (48), potentially because of rapid cycling as part of the natural course of some cases of BPD or in association with AD treatment (49). Furthermore, the apparent benefits and risks of including an AD were both smaller when added to an MS, compared with MS-alone (Table 4). There was insufficient information to compare outcomes with specific types of ADs or MSs, BPI vs. BP-II patients or men vs. women. These

findings complement a recent review of 12 *short-term* RCTs of ADs in BP depression, which found moderate benefits in acute BP-depression compared with no treatment or with a placebo, and limited risk of inducing mania when exposure was brief and an MS was present (21). However, such short-term AD efficacy did not exceed that associated with lithium monotherapy (22). Recently, the largest randomized trial (N = 366 patients) of adding an AD (bupropion or paroxetine) to MSs in acute BP depression for less than 6 months found neither AD benefit nor more mania, compared with treatment with an MS-alone (23).

In conclusion, the available research findings pertaining to long-term effects of AD treatment in BPD do not necessarily reflect current experience and are far from adequate to guide rational therapeutics. Clearly, the long-term value and risks of ADs in BPD patients require further study. Nevertheless, we recommend caution in the long-term clinical use of ADs aimed at limiting recurrences of BP depression, and encourage increased reliance on MSs as the cornerstone of maintenance treatment of BPD patients, especially in type-I BPD, with its risk of potentially dangerous manic or mixed states. We also strongly encourage additional research on long-term comparisons of currently widely employed, modern treatments for both types I and II BPD, with particular attention to the depressive, dysthymic, mixed-state phases of the illness, which continue to represent the largest proportion of unresolved treated morbidity, and major sources of disability and excess mortality (1,3,5).

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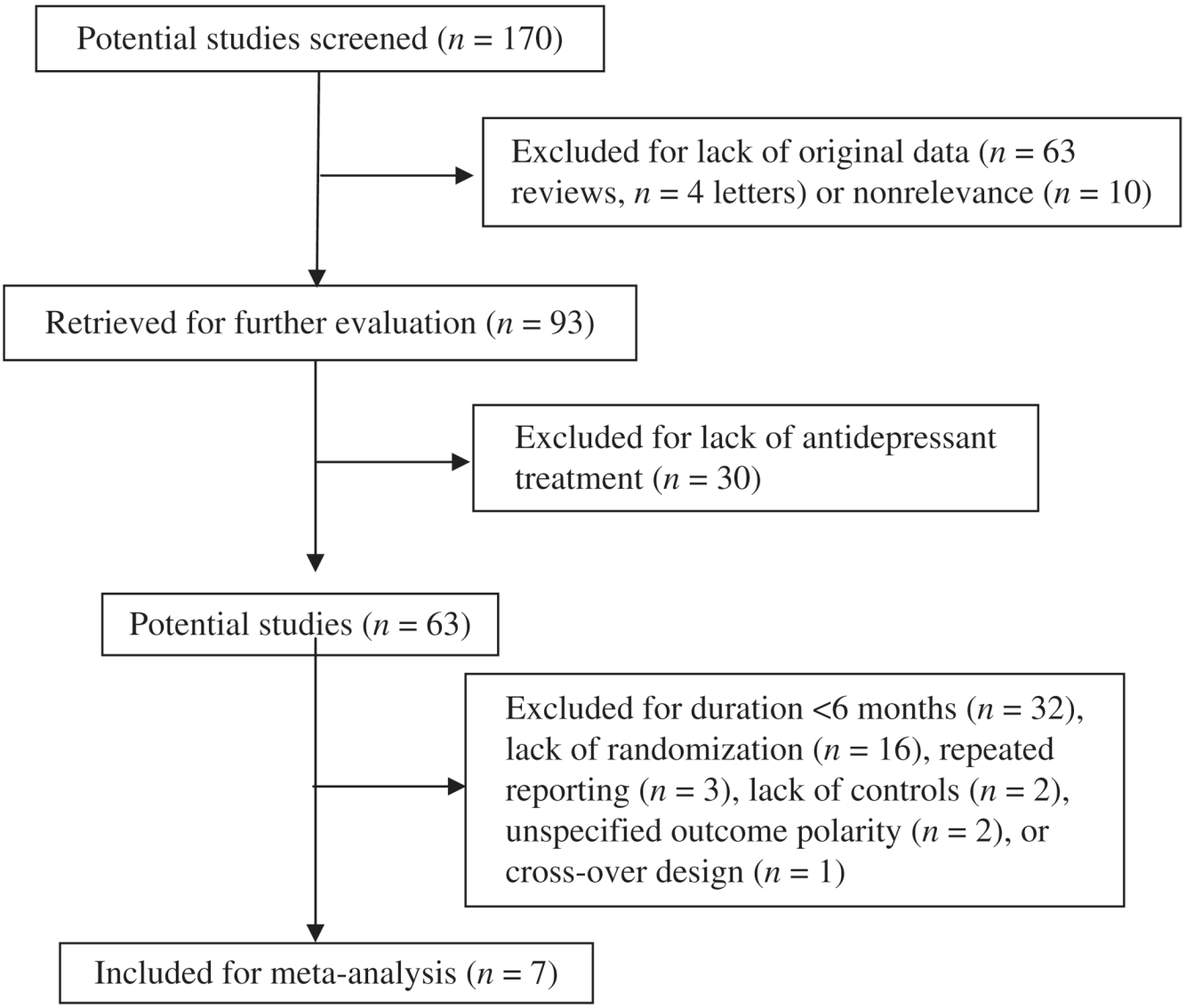

Fig. 1.
Selection of trials for meta-analysis, starting from 170 reports screened, and only seven, supporting 12 comparisons, accepted (37–43).

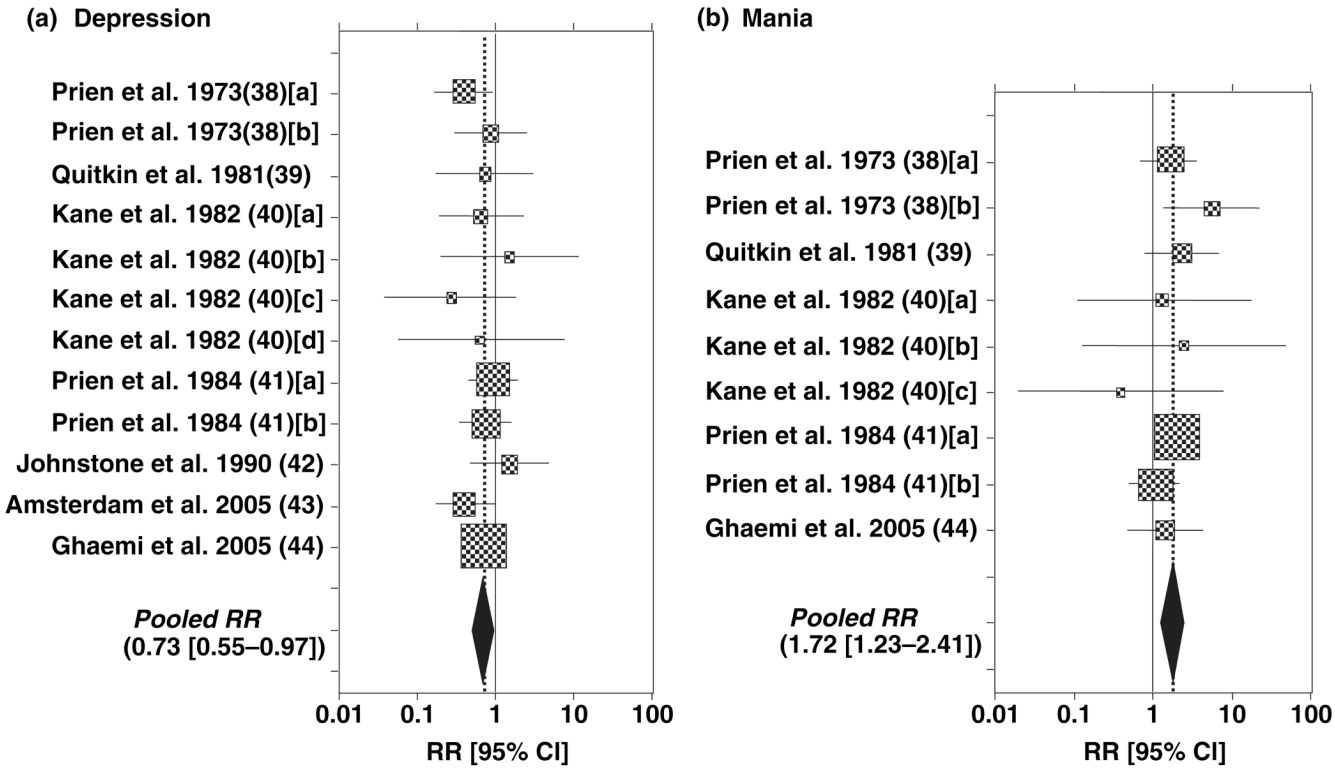

Fig. 2.

Meta-analysis of rates of (a) new depression [12 paired comparisons yielding crude rates of 50 / 202 (24.8%) with vs. 77 / 225 (34.2%) without an antidepressant] or (b) new mania [nine paired comparisons; crude rates: 62 / 202 (30.7%) vs. 40 / 225 (17.8%)] during randomized treatments comparing an antidepressant with or without a mood stabilizer vs. placebo or a mood stabilizer alone. Data are relative rates (RR) with their 95% CI (horizontal lines) for up to 12 comparisons in seven reports (Table 1; 37–43); symbol (square) size reflects weighting by patient count (*N*) and a computed variance estimate. Each diamond is pooled RR (its width = 95% CI): (a) 0.73 (95% CI 0.55–0.97); (b) 1.72 (95% CI 1.23–2.41), indicated by vertical dotted line. Note that only 1 / 12 (a) or 2 /9 (b) comparisons separates statistically significantly from the null value of 1.0 (vertical solid line), and that 4 / 12 (a) vs. 1 / 9 comparisons (b) showed no difference from the null or an effect opposite to that expected.

Table 1

Characteristics of long-term controlled trials of antidepressant treatment in bipolar disorder

Study	Funding	Quality	Dx	*N*	Index episode	% men	Age (years)	Illness severity	Treatments (dose)	Trial (months) *	Outcomes	Drop-outs (%)
Prien et al. (37)	Fed	4	BP-I	44	D	77	43.3 ± 11.9	Onset 29 ± 11 years; 1.8 ± 0.9 hosp ≤2 years	IMI (125 [50–200]) Li (1250 [500–2250]; 0.5–1.4) Pbo	24 (−)	New D or M (hospital or new Rx)	68.6
Quitkin et al. (38)	NS	4	BP-I	75	NS	48	36.8 ± 13.1	Prior M: 1 (26%), 2–3 (23%), ≥4 (23%); D: 1(13%), 2–3 (32%), ≥5 (28%); hosp (60%)	Li + IMI (100–150) Li (0.8–1.2)	24 (18.5)	New D or M (RDC)	5.3
Kane et al. (39)	Fnd	3	BP-II	22	D	23	48.7	Onset: 29 years; ≥4 prior D (86%)	IMI + Li (0.8–1.2) IMI (100–150) Pbo	19 (11)	New D or M (RDC)	45.5
Prien et al. (40)	Fed	4	BP	114	D or M	42	38.1 ± 12.4	Onset 25 ± 11 years; 7.0 prior epis; 42% hosp; 47% M/mixed	Li + IMI (132 [75–150]) Li (0.75 [0.45–1.1])	24 (−)	New D or M (RDC), or poor response	0.9
Johnstone et al. (41)	Pharma	2	BP	13	D	31	50.5 ± 9.5	Onset 37 ± 11 years; prior: 1.8 ± 0.8 M, 4.8 ± 2.9 D	Li + AMI (88 [50–124]) Li (0.5–0.9)	36 (9.6)	New D or M (DSM-IIIR)	46.0
Amsterdam et al. (42)	Fnd + Pharma	2	BP-II and NOS	12	D	25	38.0 ± 14.2	Ill 20 ± 16 years; 5.9 ± 8.3 hypo-M; D 9.6 ± 14.8 months; baseline: HDRS 7.4 ± 2.6, YMRS 1.6 ± 1.4	FLX (20) Pbo	8 (−)	New D (DSM-IV)	0.0
Ghaemi et al. (43)	Fed	3	BP-I and II	70	D	46	43.2 ± 13.2	Onset 19 ± 10 years; prior: SUD 50%, psychosis 25%, RC 25%	ADs + MS MS (std Rxs)	36 (−)	New D or M (DSM-IV), or new Rx	20.3
Total/mean	Varied	3.1	BPD	350	Usually D	46.3	40.6	Onset 27.3 years	MSs ± Ads	≤24.1	New D or M	18.7

AD, antidepressant; BP, bipolar disorder, types I, II or NOS; DSM, APA Diagnostic & Statistical Manual criteria; Dx, diagnosis; epi, episode; HDRS, 17-item Hamilton Depression Rating Scale; Fed, federal (NIH) grant; Fnd, foundation grant; hosp, hospitalization; MS, mood stabilizer; *N*, total participants; Pharma, pharmaceutical support; Qual, Jadad quality rating scale score; RC, rapid cycling

(≥4 episodes in a year); RDC, research diagnostic criteria; Rx, treatment or treated; std, standard; SUD, substance use disorder; D, major depression; M, mania; NS, not stated. In two 'enriched' trials, patients were initially treated to euthymia with lithium (38) or with IMI (39).

Treatments: ADs, various antidepressants; AMI, amitriptyline; FLX, fluoxetine; IMI, imipramine; Li, lithium carbonate; MS, mood stabilizer; Pbo, placebo; duration is in months, as nominal and [*] actual average (in parentheses).

Doses: Antidepressants (mg/day; median and range); Li (serum mEq/l; median and range); doses for combinations are for each agent. Note that several trials provide 2–4 contrasts (37,39,40).

Table 2

Rates of new *depression* with long-term treatments for bipolar disorder

Study	Antidepressants (%)	Controls (%)	RR [95% CI]
Prien et al. (38[a])	IMI: 4/13 (30.8)	Pbo: 10/13 (76.9)	0.40 [0.17–0.95]*
Prien et al. (38[b])	IMI: 4/13 (30.8)	Li: 6/18 (33.3)	0.92 [0.32–2.62]
Quitkin et al. (38)	IMI + Li: 3/37 (8.1)	Li: 4/38 (10.5)	0.77 [0.18–3.21]
Kane et al. (40[a])	IMI: 2/5 (40.0)	Pbo: 4/7 (57.1)	0.70 [0.20–2.44]
Kane et al. (40[b])	IMI: 2/5 (40.0)	Li: 1/4 (25.0)	1.60 [0.21–11.9]
Kane et al. (40[c])	IMI + Li: 1/6 (16.7)	Pbo: 4/7 (57.1)	0.29 [0.04–1.95]
Kane et al. (40[d])	IMI + Li: 1/6 (16.7)	Li: 1/4 (25.0)	0.67 [0.06–7.85]
Prien et al. (41[a])	IMI: 10/36 (27.8)	Li: 12/42 (28.6)	0.97 [0.48–1.98]
Prien et al. (41[b])	IMI + Li: 8/36 (22.2)	Li: 12/42 (28.6)	0.78 [0.36–1.69]
Johnstone et al. (41)	AMI + Li: 3/5 (60.0)	Li: 3/8 (37.5)	1.60 [0.51–5.03]
Amsterdam et al. (42)	FLX: 3/8 (37.5)	Pbo: 4/4 (100.0)	0.38 [0.15–0.92]*
Ghaemi et al. (43)	ADs + MSs: 11/32 (34.4)	MSs: 17/38 (44.7)	0.77 [0.42–1.39]
Totals	ADs ± MSs: 45/178 (25.3%)	MSs or Pbo: 61/172 (35.5%)	0.726 [0.547–0.962]*

ADs, antidepressants; AMI, amitriptyline; FLX, fluoxetine; IMI, imipramine; Li, lithium carbonate; MS, mood stabilizer; Pbo, placebo.

Total $N = 350$ patients (repeated arms counted only once). Note that 10 / 12 comparisons indicate *lower* risk of new depression with long-term antidepressant, of which only 2 / 12 risk ratios (RR) as well as the pooled RR are statistically <1.0 (*), based on random-effects meta-analysis.

Different treatment arms in the same study are distinguished by alphabetical letters.

Table 3

Rates of new *mania* with long-term treatments for bipolar disorder

Study	Antidepressants (%)	Controls (%)	RR [95% CI]
Prien et al. (38[a])	IMI: 8/13 (61.5)	Pbo: 5/13 (38.5)	1.60 [0.71–3.60]
Prien et al. (38[b])	IMI: 8/13 (61.5)	Li: 2/18 (11.1)	5.54 [1.40–21.9]*
Quitkin et al. (38)	IMI + Li: 9/37 (24.3)	Li: 4/38 (10.5)	2.31 [0.78–6.85]
Kane et al. (40[a])	IMI: 1/5 (20.0)	Pbo: 1/7 (14.3)	1.40 [0.11–17.5]
Kane et al. (40[b])	IMI: 1/5 (40.0)	Li: 0/4 (0.0)	2.50 [0.13–48.8]
Kane et al. (40[c])	IMI + Li: 0/6 (0.0)	Pbo: 1/7 (14.3)	0.38 [0.02–7.93]
Kane et al. (40[d])	IMI + Li: 0/6 (0.0)	Li: 0/4 (0.0)	——
Prien et al. (41[a])	IMI: 19/36 (52.8)	Li: 11/42 (26.2)	2.02 [1.11–3.65]*
Prien et al. (41[b])	IMI + Li: 10/36 (27.8)	Li: 11/42 (26.2)	1.06 [0.51–2.20]
Johnstone et al. (41)	AMI + Li: 0/5 (0.0)	Li: 0/8 (0.0)	——
Amsterdam et al. (42)	FLX: 0/8 (0.0)	Pbo: 0/4 (0.0)	——
Ghaemi et al. (43)	ADs + MSs: 6/32 (18.8)	MSs: 5/38 (13.2)	1.42 [0.48–4.24]
Totals	ADs ± MSs: 53/178 (29.8%)	MSs or Pbo: 28/172 (16.3%)	1.72 [1.23–2.41]*

Abbreviations as for Table 2.

Total $N = 350$ trial participants (repeated arms counted only once). Note that 8/12 comparisons indicate *greater* risk of mania with long-term antidepressant, of which only 2/12 risk ratios (RR) and the pooled RR are statistically >1.0 (*), based on random-effects meta-analysis.

Alphabetical letters are used to indicate different treatment arms within a study, as similarly noted for Table 2.

Table 4

Meta-analyses of subgroup effects

Subgroups	Studies	Risk of new depression			Risk of new mania		
		Comparisons	Cases	RR [95% CI	Comparisons	Cases	RR [95% CI]
AD-only vs. Pbo-only	(38[a],40[a],43)	3	50	0.46 [0.27–0.80]	3	50	1.58 [0.73–3.42]
AD ± MS vs. MS-only	38[b], 39, 40[b,d],41 [a,b],42,44)	8	346	0.89 [0.64–1.25]	8	364	1.80 [1.22–2.65]
AD + MS vs. MS-only	(39, 40[d], 41[b], 42,44)	5	246	0.84 [0.56–1.27]	5	246	1.37 [0.81–2.33]
AD-only vs. MS-only	(38[b], 40[b], 41[a])	3	118	1.00 [0.57–1.75]	3	118	2.37 [1.38–4.05]

AD, antidepressants; MS, mood stabilizer; Pbo, placebo.

Contrasts are derived from subgroups reported in Table 2 and Table 3.

Different treatment arms in the same study are distinguished by alphabetical letters, as similarly noted for Table 2 and Table 3.