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Review

Mania associated with antidepressant treatment: comprehensive meta-analytic review

Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review.

Objective: To review available data pertaining to risk of mania–hypomania among bipolar (BPD) and major depressive disorder (MDD) patients with vs. without exposure to antidepressant drugs (ADs) and consider effects of mood stabilizers.
Method: Computerized searching yielded 73 reports (109 trials, 114 521 adult patients); 35 were suitable for random effects meta-analysis, and multivariate-regression modeling included all available trials to test for effects of trial design, AD type, and mood-stabilizer use.
Results: The overall risk of mania with/without ADs averaged 12.5%/7.5%. The AD-associated mania was more frequent in BPD than MDD patients, but *increased more* in MDD cases. Tricyclic antidepressants were riskier than serotonin-reuptake inhibitors (SRIs); data for other types of ADs were inconclusive. Mood stabilizers had minor effects probably confounded by their preferential use in mania-prone patients.
Conclusion: Use of ADs in adults with BPD or MDD was highly prevalent and moderately increased the risk of mania overall, with little protection by mood stabilizers.

L. Tondo[1,2], G. Vázquez[3], R. J. Baldessarini[1]

[1]Department of Psychiatry and Neuroscience Program, Harvard Medical School and McLean Division of Massachusetts General Hospital, Boston, MA, USA, [2]Department of Psychology, University of Cagliari, and Lucio Bini Mood Disorders Research Center, Cagliari, Sardinia, Italy and [3]Department of Neurosciences, University of Palermo, Buenos Aires, Argentina

Key words: antidepressants; bipolar disorder; major depression; mania; meta-analysis

Leonardo Tondo, MRC 3, McLean Hospital, 115 Mill Street, Belmont, MA 02178-9106, USA.
E-mail: ltondo@mclean.harvard.edu

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Summations

- Antidepressant drugs (AD) treatment of bipolar disorder (BPD) and major depressive disorder (MDD) patients approximately doubled moderate spontaneous risk of mania–hypomania.
- A small proportion of adults initially diagnosed with MDD emerged as probable BPD cases during AD-treatment.
- Tricyclic antidepressants carried a higher risk of new mania–hypomania than serotonin reuptake inhibitors.
- Mood stabilizers had little preventive effect against mood elevation during AD treatment.

Considerations

- These meta-analytic findings should be viewed cautiously because of heterogeneity of studies included.
- Clinically, we recommend use of mood-stabilizers in BPD patients, especially when exposed to ADs, despite limited support in this study.

Introduction

Occurrence of mania or other forms of abnormally elevated mood ('mood switch') in association with antidepressant (AD) treatment, has been recognized since the earliest use of imipramine in the late 1950s (1–6). However, it remains unclear to what extent such mood switching arises naturally in the course of major affective illnesses, or is actually caused by AD treatment (7–13). Mood elevation

associated with AD treatment might indicate: efficacy of the treatment, an adverse pharmacological effect, misdiagnosis of previously unrecognized bipolar disorder (BPD), or actual conversion from major depressive disorder (MDD) to BPD. It is also likely that ADs increase occurrence of abnormally elevated mood in some vulnerable patients, regardless of clinical diagnosis (14–17). The importance of this topic includes not only inconsistencies and gaps in previous research, continued uncertainty about the scientific and clinical significance of manic reactions during AD treatment, and their legal implications if harm results, but also the paucity of comprehensive and quantitative analyses of available data, with comparisons of MDD and BPD patients, or assessment of effects of simultaneously administered mood stabilizers (18, 19).

A widely held assumption is that mood elevation during AD treatment indicates the presence of BPD, which sometimes is first recognized during such treatment, particularly in young depressed patients (20, 21). Risk factors for mood switching (as well as diagnostic confusion) during exposure to an AD may include the presence of previous mixed manic-depressive states, especially agitation during a treated depressive episode (21–23), as well as relatively early age-at-onset (20, 24), and a cyclothymic (25) or hyperthymic temperament (26). All ADs have been associated with mania, although they may vary by type, dose, and latency to occurrence (10, 27–30).

Aims of the study

To address the several remaining questions about effects of antidepressant drugs (ADs) on risk of new psychopathological excited states, we comprehensively reviewed all available controlled and open trials since the dawn of the AD era in the late 1950s, pertaining to the topic or involving mania as a planned or incidental finding, considering all reported AD drugs and major mood disorders, as well as effects of co-administering putative mood-stabilizing agents.

Material and methods

We considered all reports of original data on AD treatment of BPD or MDD, and occurrence of new episodes of mania, mixed-states, or hypomania (here, all termed 'mania'). Potential studies were identified by searching computed literature (*PubMed*® database, using 'mania,' or 'hypomania,' and 'antidepressant' as search terms) through December 2008, supplemented with references cited in publications identified by searching. To obtain as complete a survey as possible, we considered blinded, randomized, controlled trials (RCTs) as well as unblinded and only partially controlled clinical cohort trials to obtain rates of mania in both AD-treated and AD-untreated or placebo-treated patients, in the same trials. For meta-analysis, we included only non-duplicative data from studies with ≥2 arms in which at least eight treated and untreated patients were compared. Data were verified directly with authors when not clear from publications (31, 32). Since case–control and case report studies preclude estimates of actual rates of mania (events/persons-at-risk), they were not included. We also excluded studies reporting only on episodes or rates of mania, rather than persons who became manic among those at-risk. New episodes of mania were expressed as the proportion (%) of patients becoming manic during observation, or as rates (% of patients/month). Given the rarity of reporting precise exposure times per person, we relied on nominal average treatment exposures (months) reported for each study treatment arm, or on conservative estimates based on information reported; average exposure was ≤24 months in all trials.

We rated *study quality* by giving one point each for: i) blinded RCT design with parallel groups; ii) ≥50 subjects/arm; and iii) follow-up observation for 2–24 months (maximum score = 3.0). For meta-analysis of studies having a study arm with no mood-elevation episodes, we used a common continuity-adjustment method (adding 0.5% to paired samples with and without AD exposure) in computations of pooled rate ratios (RR), and also estimated pooled risk difference [RD, which tolerates zero values in one study arm and is used to estimate numbers needed to harm (NNH = 1/RD)]; all pooled RR or NNH values are reported with their 95% confidence intervals (CI) (33). Studies with no mood switches, with *and* without AD, were excluded from meta-analysis as uninformative. We also examined the potential influence of unusually large studies on pooled RRs by serially excluding them singly from meta-analyses (influence or sensitivity analysis).

In separate meta-analyses, we also compared studies: i) involving MDD vs. BPD patients [unspecified forms of major affective disorder (MAD) were excluded]; ii) using RCT vs. open designs; iii) with *old* [tricyclic ADs (TCAs) or monoamine oxidase inhibitors (MAOIs)] vs. *modern* ADs [mostly serotonin reuptake inhibitors (SRIs); occasionally serotonin–norepinephrine

reuptake inhibitors (SNRIs) or the atypical agent bupropion]; and iv) with vs. without concomitant use of mood stabilizers (lithium, certain anticonvulsants, or unspecified agents, with too few studies of antipsychotic agents with putative mood-stabilizing effects), including studies with at least some patients treated with a mood stabilizer.

There was insufficient information to allow separate analyses of types I vs. II BPD patients or of specific types of mood elevation (mania, hypomania, mixed-state). In addition, we considered whether pooled RR values were altered by covariates specified below, including use of meta-regression analysis that considered: publication year, months of treatment exposure, and quality rating. We also carried out multivariate linear regression analyses, with the proportion of patients becoming manic in each study as the outcome variable, and independent variables including: diagnosis (BPD vs. MDD) study design (RCT vs. cohort-comparison studies), use of a mood stabilizer, type of AD, quality rating, duration of follow-up, current age, and year of publication. Timing of mania (months from onset of AD exposure) was not stated in most studies, obviating use of survival analysis.

Statistical analyses used commercial microcomputer programs (STATA 8.0®; Stata Corporation, College Station, TX, USA: STATVIEW-5®; SAS Institute, Cary, NC, USA). Means are shown with standard deviation (SD), and other computed values are shown with 95% CI. Comparisons with two-tailed $P > 0.05$, at stated degrees of freedom (df), were considered not significant.

Results

Studies and population sample

We identified 73 studies [39 (53.4%) RCTs and 34 or 46.6% open trials] with data pertaining to new episodes of hypomania or mania during 109 treatments with ADs (1–6, 14, 16, 18, 20, 27, 29, 31, 32, 34–92), divided by type of study design, diagnosis, type of AD, and use of a mood stabilizer. The 73 studies included a total of 114 521 adult patients (56 212 given ADs, and 58 309 not; 7915 with BPD, 102 501 with MDD, and 4105 with an unspecified MAD), aged 4l.7 (SD = 7.20) years, and exposed for an average of 5.32 (SD = 6.09) months (Table 1). Of these studies, 35 provided information suitable for meta-analysis, in that they reported numbers of subjects with mania during AD treatment or without it *and* total numbers of subjects treated and not treated.

Table 1. Characteristics of studies and patients reviewed

Factors	Measures
Number of reports reviewed	73
Number of comparisons	109
Design types: per cent RCTs	53.4
Current age, years: mean (SD)	41.7 (7.20)
Approximate exposure time, months: mean (SD)	
All trials	5.32 (6.09)
Open trials	6.62 (5.06)
RCTs	4.76 (6.44)
Subjects, *n* (%)	
Overall	114 521
MDD	102 501
BPD	7915
Major affective disorder (unspecified)	4105
Given antidepressants	56 212
Not given antidepressants	58 309
Proportions of patients with mania, % (CI)	
Given antidepressants	
Overall	12.5 (12.4–12.6)
BPD: all cases	15.3 (14.5–16.1)
BPD: no mood stabilizer	13.8 (8.31–19.3)
BPD: with mood stabilizer	15.9 (11.7–20.1)
MDD: all cases	5.97 (5.88–6.04)
MDD: no mood stabilizer	6.16 (3.35–8.97)
MDD: with mood stabilizer	4.49 (–1.25; 10.2)
Not given antidepressants	
Overall	7.46 (7.36–7.56)
BPD: all cases	13.8 (12.2–15.3)
BPD: no mood stabilizer	16.5 (4.96–28.0)
BPD: with mood stabilizer	11.2 (6.41–16.0)
MDD: all cases	1.24 (1.22–1.26)
MDD: no mood stabilizer	1.03 (0.00–2.05)
MDD: with mood stabilizer	2.38 (–1.58; 6.34)
Risk difference: (treated minus untreated)	
Overall	5.04
BPD	1.50
MDD	4.73
Rates of new mania (%/month)	
With antidepressants	4.96 (4.88–5.04)
Without antidepressants	1.50 (1.47–1.52)

AD, antidepressant drugs; BPD, bipolar disorder; MDD, major depressive disorder; RCT, randomized controlled trial.

Patients in an unusually large study by Martin et al. 2004 (20) numbered 81 036; however, rates of new mania without this study yielded rates of 12.5% with, vs. 7.67% without AD treatment, based on averages per study, and so were very similar to the reported overall values above. Moreover, follow-up times for BPD (5.2 months) vs. MDD patients (6.1 months) were similar.

Risk of manic episodes

Proportions (%) of patients experiencing new episodes of mania-like excitation during trials are summarized in Table 1, divided into those exposed vs. not exposed to an AD, separated by BPD vs. MDD, diagnoses, and those given a mood stabilizer or not. Overall proportions of manias, with/without an AD, averaged 12.5%/7.46% (1.7-times greater with ADs [paired-t (df = 53) = 2.09, $P = 0.04$], with an overall RD of 5.04% across exposure times averaging 5.32 (SD = 6.09) months, or an increase of about 1%/month (Table 1). As expected, rates of new-mania were

much greater among BPD patients [with and without ADs: 15.3% and 13.8%; ratio = 1.1; paired-t (df = 26) = 0.20, P = 0.84] than in MDD patients [with/without ADs: 5.97%/1.24%; ratio = 4.8; paired-t (df = 24) = 4.02 P = 0.0005], with much greater *relative* increases with ADs among MDD patients. These comparisons indicate greater base- and AD-associated risks among BPD patients, as expected in this mania-prone subgroup, but a remarkable relative increase by nearly five times among MDD patients given an AD. Estimated *rates* (%/month) of mania with vs. without AD treatment were 5.0 vs. 1.5, or 3.3-fold higher with ADs. Among patients diagnosed with BPD vs. MDD, these rates, averaging 6.23 (SD = 13.6) and 4.01 (SD = 6.86), respectively, did not differ significantly [F (df = 40) = 0.46; P = 0.50].

Risk factors

We tested selected variables for association with risk for mania in a multivariable, linear-regression model (Table 2). Among patients *given ADs*, rates of new mania were independently and significantly higher (in descending order of significance) among: i) patients with BPD vs. MDD; ii) longer reported average follow-up; iii) younger average current age; and iv) clinical cohorts vs. RCTs. *Without ADs*, factors associated with mania were: i) diagnosis [BPD > MDD (Fig. 1)]; ii) longer follow-up; and iii) younger age (Table 2). Other factors not associated with risk of mania (with or without ADs) in such multivariate modeling were: year of publication, study design (RCT vs. clinical) and quality rating, type of AD given, and use of a mood stabilizer.

Table 2. Factors associated with percent of patients experiencing mania or hypomania with vs. without antidepressants

Factors	β-Coefficient (95% CI)	t-score	P-value
With antidepressants			
BPD vs. MDD	13.8 (7.78–19.8)	4.60	<0.0001
Longer follow-up	0.68 (0.27–1.08)	3.35	0.001
Younger current age	0.49 (0.10–0.88)	2.51	0.015
Open trials vs. RCTs	6.16 (0.72–11.6)	2.26	0.027
Without antidepressants			
BPD vs. MDD	11.2 (4.60–17.8)	3.53	0.002
Longer follow-up	0.46 (0.07–0.86)	2.42	0.025
Younger current age	0.35 (0.02–0.73)	1.95	0.065

BPD, bipolar disorder; MDD, major depressive disorder; RCT, randomized controlled trial.

Based on multivariate, linear regression modeling. Factors found to be unrelated to the outcome in both groups, included study quality (based on RCT design, ≥50 subjects in each study-arm, and ≥2 months of exposure to treatment), year of publication, type of antidepressant given, use of a mood stabilizer; and design (open vs. RCT) without AD treatment.

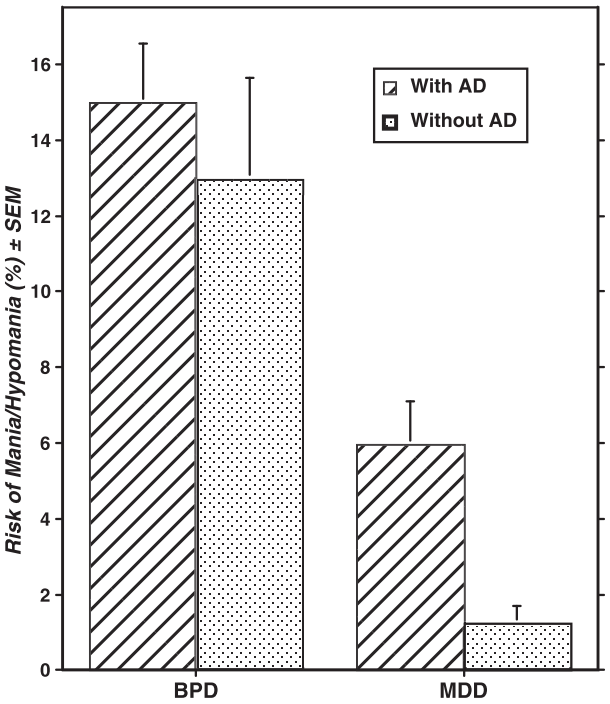

Fig. 1. Risk (%) of mania or hypomania (with SEM) associated with and without antidepressant drug treatment for bipolar disorder (n = 29 studies) and major depressive disorder patients (n = 25 studies).

Mania vs. antidepressant type

Crude proportions (%) of patients becoming manic during exposure to particular types of ADs ranked: TCAs > modern agents [mainly SRIs plus a few trials involving an SNRI (duloxetine, venlafaxine) or bupropion] > MAOIs (Table 3). However, TCAs did not differ from modern ADs [SRIs + SNRIs + bupropion; (df = 71), F = 2.43; P = 0.123], nor did MAOIs differ significantly from modern ADs: [(df = 39) F = 1.57; P =

Table 3. Antidepressant type and risk of mania or hypomania

Drug type	Trials	Subjects	Patients with new mania (% CI)
Mixed	22	3878	22.1 (21.6–22.5)
TCAs	46	10 187	12.7 (12.4–12.9)
SRIs	18	38 612	8.71 (8.59–8.83)
SNRIs	6	1361	7.77 (7.22–8.33)
Bupropion	3	69	7.63 (6.04–9.21)
MAOI	14	2179	4.58 (4.38–4.77)
All ADs	111	56 212	12.5 (12.4–12.6)

AD, antidepressant drugs; MAOI, monoamine oxidase inhibitors; TCA, tricyclic ADs; SRI, serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors.

Statistical comparisons were by paired tests comparing mania risk with vs. without ADs for each AD type. 'Mixed' drugs are not defined in reports, other to note that 'ADs' were given. For comparison (see Table 1), untreated patients with presumably spontaneous mania were included in 45 trials involving 58 309 subjects, yielding a rate of 7.46% (95% CI: 7.36–7.56) mania or hypomania.

0.217], although TCAs were associated with more risk than MAOIs [(df = 58) $F = 6.38$; $P = 0.014$].

Meta-analytic modeling of factors associated with mania

Based on random effects meta-analyses, there was a highly significant difference of mania risk with vs. without AD exposure (RR = 1.76, $P < 0.0001$, with an estimated NNH of 27 persons; Table 4). Risk assessed with meta-analyses also was associated significantly and similarly with: i) AD treatment in studies involving both RCTs and clinical cohort designs; ii) in MDD but not BPD; iii) with TCAs but not modern ADs or MAOIs (Fig. 2); and iv) with little difference in apparent risk with vs. without mood stabilizers; Table 4).

In patients given ADs, risk with/without a mood stabilizer was: for BPD, 15.9%/13.8%; for MDD, 4.49%/6.16%; without an AD, the corresponding pooled ratios of risks were: BPD: 11.2%/16.5%, MDD: 2.38%/1.03%, and none of these contrasts with/without a mood stabilizer in diagnostic or treatment subgroups was statistically significant (Table 1). The preceding findings, in contrast to computations of crude risks of mania (Table 3), excluded studies with no mania events with or without AD treatment (notably with MAOI studies, 5/6 of which found no cases of new mania), possibly accounting for somewhat different impressions, notably including a lack of important differences in risk with particular types of ADs, based on meta-analyses (Table 4).

Applying an influence or sensitivity analysis to the meta-analytic results (eliminating one study at a time) indicated that only one study appeared to be an outlier; this was an unusually large trial by Martin and colleagues reported in 2004 (20) that involved AD treated vs. untreated MDD patients. Even excluding this study from meta-analytic modeling, the association of AD treatment with risk of mania remained highly significant (RR = 1.65, and NNH = 30, $P = 0.005$). In addition, with meta-regression modeling, we found that no factor (trial design, study quality, diagnosis, AD type, mood-stabilizer use, year of publication, or duration of AD exposure) was independently and significantly associated with risk of mania (Table 4).

Discussion

Among mood-disordered subjects overall, we found an increase of risk (RD) of pathological mania like mood elevation with AD exposure of 5.04% (12.5% with, 7.46% without ADs, or 1.68-fold). This risk was much higher among BPD vs. MDD patients, without AD-treatment (13.8%/1.24%, or 11.1-fold), as well as with such treatment (15.3/5.97%, or 2.6-fold; Table 1), again as expected. Notably, in addition to the expected and substantial risks of new mania in BPD, some patients initially diagnosed with unipolar MDD also carried a finite risk of mania, hypomania, or mixed states ('mania'), which averaged 5.97% with, and 1.24% without AD exposure (Table 1). Overall, the present findings indicate a gradient of rates of new mania, ranking: BPD with ADs > BPD without ADs > MDD with ADs > MDD without ADs (Table 1), in agreement with clinical experience. Diagnosis (BPD vs. MDD) also was a highly significant and independent risk factor for new mania in multivariate modeling (Table 2). For comparison, reported rates of new manias for BPD patients are 15–50%, and among patients diagnosed with MDD, 3–10% (11, 93, 94). However, the *relative* risk due to AD exposure vs. spontaneous risk in BPD (only 1.11-fold) was far less than in MDD cases (4.81-fold). This conclusion is supported not only in crude estimates (Table 1),

Table 4. Summary of results of meta-analyses for proportion of patients with new mania/hypomania

Measure	Contrast	Studies (*n*)	RR (95%CI)	*z*	*P*-value	NNH (95%CI)
Overall meta-analysis	AD effect	48	1.76 (1.33–2.33)	3.94	<0.0001	27.2 (16.7–75.3)
Trial design	RCTs	30	1.43 (1.10–1.86)	2.66	<0.008	28.7 (18.2–69.2)
	Open trials	18	1.95 (1.37–2.78)	3.71	<0.0001	28.9 (13.8–∞)
Diagnosis	BPD	25	1.13 (0.90–1.42)	1.08	0.282	41.7 (18.5–∞)
	MDD	22	3.76 (2.77–5.09)	8.56	<0.0001	22.8 (13.2–85.4)
AD type	MAOIs	6	2.83 (0.79–10.2)	1.60	0.110	31.3 (14.6–∞)
	TCAs	30	1.93 (1.13–3.30)	2.41	0.016	18.5 (8.65–∞)
	SRIs + SNRIs	9	1.70 (0.87–3.32)	1.56	0.119	90.9 (16.9–∞)
Mood stabilizers	Without	33	1.76 (1.27–2.44)	3.41	0.001	58.7 (37.9–131)
	With	15	1.73 (1.18–2.54)	2.81	0.005	27.2 (15.3–125)

Data are relative risk (RR) with/without AD treatment, and its 95% confidence interval (CI), and number needed to harm (NNH) estimates based on reciprocals of pooled mean differences in risks with vs. without antidepressant (AD) treatment. Moreover, in separate meta-regression analysis, these factors plus the publication year and months of treatment exposure were not independently associated with occurrence of mania.

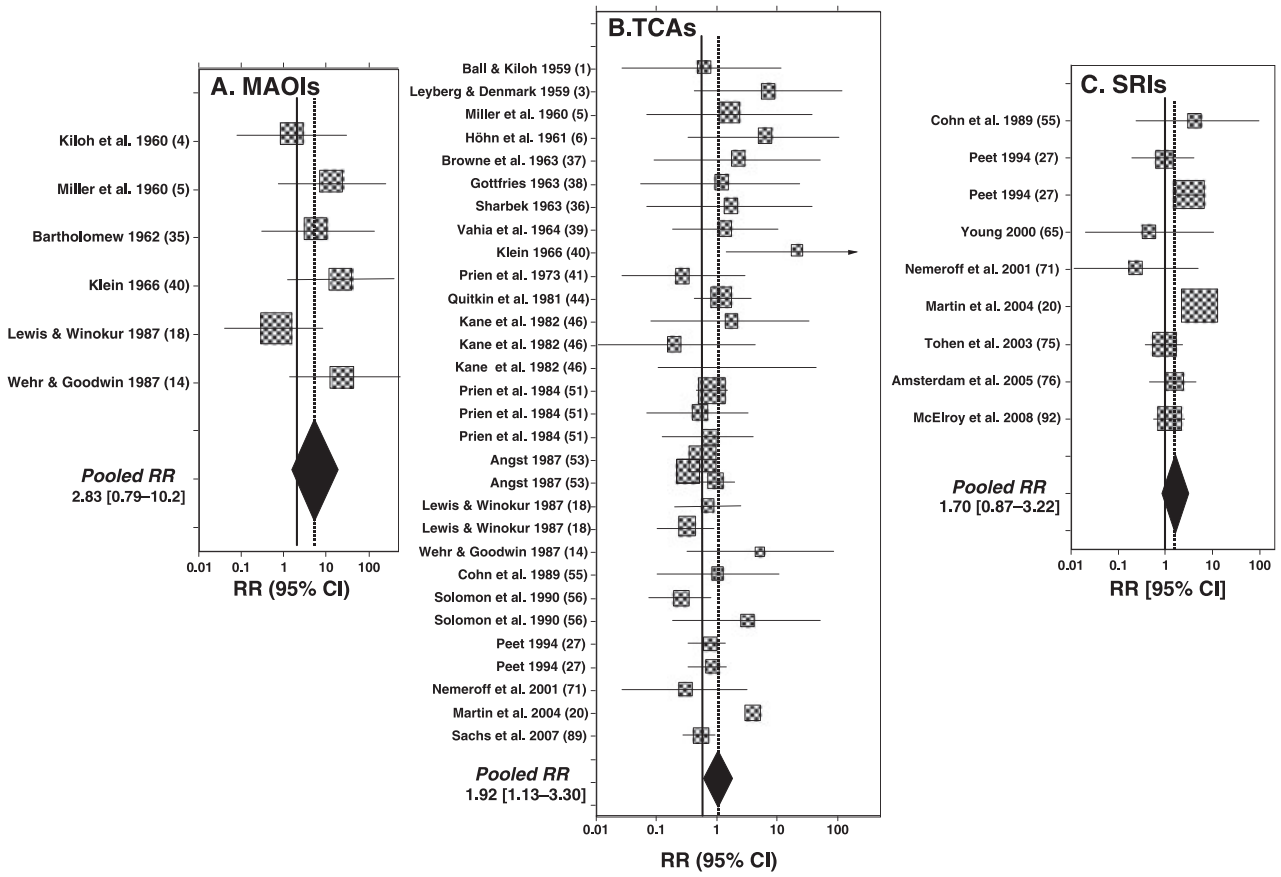

Fig. 2. Forest plots [for individual trials (gray boxes reflecting study size and measurement variance) vs. computed rate ratios (RR) with 95% CI, with pooled RR and CI values (vertical dotted lines and black diamonds)] for a total of 45 trials yielding pooled RR values (with 95% CIs) computed by random effects meta-analyses for three major antidepressant drug groups, with null value of RR = 0.0 (as vertical solid lines) and computed pooled RR in descending order of apparent effect on manifestation of new mania, for: (a) monoamine oxidase inhibitors [MAOIs, six trials; pooled RR = 2.83 (CI: 0.79–10.2); $z = 1.60$, $P = 0.110$], (b) tricyclic antidepressants [TCAs, 30 trials; pooled RR = 1.92 (CI: 1.13–3.30); $z = 2.41$, $P = 0.016$), and (c) serotonin-reuptake inhibitors [SRIs, nine trials; pooled RR = 1.70 (CI: 0.87–3.32); $z = 1.56$, $P = 0.12$], indicating that TCAs alone, were probably riskier than SRIs, but with overlapping CIs. In addition, we estimated number needed to harm [NNH as reciprocals of random effects meta-analyses of risk differences (RD), as: (a) MAOIs: NNH = 31.3 (CI: 14.6–infinity); (b) TCAs: NNH = 18.5 (CI: 8.65–infinity)]; (c) SRIs: NNH = 90.9 (CI: 17.0–infinity); these results suggest that MAOIs and TCAs may carry indistinguishable risks, and when results from RCTs of these first generation antidepressants pooled, NNH = 21.7 (CI: 10.3–infinity), a value that is 5.4-times lower (greater risk) with older agents than with modern SRIs, whose NNH = 117 (CI: 15.7–infinity). Note that many of these results are marginally or not statistically significant, and only 4/45 studies considered showed significantly higher risk with ADs. References to studies cited are provided in parentheses (some studies included more than one treatment condition).

but also by meta-analysis (the relative increase in mania with ADs in BPD/MDD was 1.13/3.76), and was statistically significant only among the MDD patients (Table 4). This seemingly paradoxical outcome reflects the relatively high rate of spontaneous mania among BPD patients that was little increased (by only 1.13%) during AD exposures averaging 5 months.

The surprisingly high *relative* increase of new mania-like states associated with AD treatment among MDD patients (ratio of drug-associated vs. spontaneous risk) raises several possibilities. AD treatment itself may induce a manic, hypomanic, or mixed state in some patients previously considered to have MDD (14, 15, 95), with a relatively large gain in risk of nearly five-fold among MDD treated vs. not treated with ADs (Table 1). This interpretation is further supported by the low rate (1.0–2.3%) of spontaneous states of abnormal excitation among MDD patients without AD treatment (96, 97), again reflecting clinical experience. However, induction of mania in MDD patients may indicate current limitations to differentially diagnosing BPD vs. MDD, and uncertainties about how to classify presumed MDD patients who later become manic, especially only with exposure to ADs. Patients considered to have MDD, but who become pathologically excited when exposed to an AD, sometimes are considered 'misdiagnosed BPD' patients. Others (sometimes

considered 'type-III' BPD (98), or as 'BPD not otherwise specified' in DSM-IV) may truly be cases of MDD, vulnerable to transient, pharmacologically induced excitement during AD treatment without evidence of spontaneous mania or hypomania. Yet another hypothetical possibility is that AD treatment itself may induce BPD in formerly MDD patients (14, 15, 93). Differentiating among these possibilities can be facilitated by following such patients clinically after mood elevation in association with AD treatment. Many who later develop spontaneous mania, hypomania, or mixed states would be considered as falling within a proposed 'BP spectrum' (95–97, 99–101). Aside from the uncertain significance of mania associated with AD treatment, the research literature on this topic is large, complex, and leaves unanswered questions, including medico-legal uncertainties pertaining to harm associated with unexpected, drug-associated mania, all of which encouraged the current review.

In accordance with current clinical opinions, TCA treatment was more likely to be associated with manic or other excited states than modern ADs, mainly represented by SRIs (12, 68, 89). This difference confirms findings from a previous, smaller meta-analytic study of effects of ADs in BPD patients only (10) and from a recent review of RCTs in bipolar depression (102). The present review indicated minor differences in risk among modern ADs as a group, including SRIs and very few studies of SNRIs or of the atypical agent bupropion (Table 3). There are insufficient numbers of trials involving specific ADs to support meta-analyses comparing risks between AD types. However, like the TCAs, venlafaxine, especially when given at high doses, has a reputation for producing more mania than other modern ADs (28, 72). The present data pertaining to this agent or duloxetine, another SNRI, showed no difference in rates of new manias with the other modern ADs but were too limited to support separate meta-analytic comparisons.

Risk factors associated with newly emerging mania, aside from diagnosis and treatment, included currently younger age, at least among BPD patients (Table 2). We also found that study design was significantly associated with risk of mania, in that clinical cohort trials yielded higher risks of new manic episodes than RCTs. This observation may reflect the relatively brief AD exposures in most RCTs (4.76 vs. 6.62 months in RCTs vs. open trials; Table 1), exclusion of obviously mania-prone subjects entering RCTs involving risk of being given an AD, and the lack of blinded treatment in the cohort studies, that may risk inflating estimates of new mania. Even the observed average exposure of 5.3 months may be insufficient to capture episodes of emerging, especially spontaneous, mania and too brief to document cycle acceleration (100), but too long to exclude spontaneous mania. That is, new mania arising during a relatively brief RCT may be particularly indicative of a causal association with AD treatment. Instead, prolonged observation, with or without AD treatment, probably increases chances of observing *spontaneous* mania that may confound estimates of risks associated with AD treatment. Longer follow-up was associated with greater risk of mania in AD-treated patients in a study from the Stanley Bipolar Treatment Network, with nearly twice-higher rates of mania or hypomania when follow-up involved a year vs. only 10 weeks, but that study could not distinguish spontaneous from AD-induced mania (101). In addition, Angst and his colleagues reported that risk of new episodes of mania, or conversion from diagnoses of unipolar MDD to BPD rose continuously at about 1%/year for 50 years, during prolonged follow-up (96).

Surprisingly, mood stabilizers did not have an appreciable mania-limiting effect in the studies reviewed, with or without co-treatment with an AD (Table 1). Moreover, in a multivariate regression analysis, with or without ADs, mood-stabilizing treatment was not specifically associated with decreased risk of mania (Table 2). These unexpected observations may be confounded by bias toward giving mood stabilizers to known cases of BPD or generally sicker patients with higher rates of spontaneous or AD-induced mania, and by short average observation times (5 months of AD exposure) that may limit potentially beneficial, long-term effects of mood stabilizers. The lack of clear evidence of reduced risk of mania when ADs were given to BPD patients treated with a mood stabilizer, as found in this analysis accords with some recent controlled studies (10, 72, 88, 91, 103, 104), but not others, especially when lithium was used (30, 66, 102, 105). Interpretation of effects of combining mood stabilizers and ADs for BPD patients should also considered that a need for adjunctive AD treatment, itself, may reflect lack of effectiveness of prophylaxis with a mood stabilizer alone. Whatever its interpretation, our findings concerning mood-stabilizer co-treatment with an AD does *not* support the prevalent clinical impression that these drugs effectively limit risk of mania, at least among type I BPD patients, including many who are exposed to ADs (12, 103, 106, 107). In addition, evidence from animal studies indicates that mood stabilizers do not

prevent behavioral sensitization to ADs or other agents that may model drug-induced mania (108). Finally, modern pharmacogenomic and other biological research promise to characterize, and support prediction of patients likely to become manic when given an AD, and should be pursued (109–113).

In conclusion, in this extensive review, risk of mania or hypomania in MAD patients exposed to ADs ('switch' risk) averaged 12% overall. Despite uncertainties about interpretation of new episodes of mania or hypomania during AD treatment, we support the practice of treatment with a mood stabilizer when an AD is prescribed for BPD patients as clinically prudent, pending further study.

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Declaration of interest

Dr Tondo has collaborated in investigator-initiated research with Janssen and Eli Lilly. Dr Vázquez is a consultant with AstraZeneca, Glaxo-SmithKline, and Eli Lilly Corporations. Dr Baldessarini has been a consultant or research collaborator with: AstraZeneca, Auritec, Biotrofix, Janssen, JDS-Noven, Lilly, Luitpold, NeuroHealing, Novartis, Pfizer, and SK-BioPharmaceutical Corporations. No author is a member of pharmaceutical speakers' bureaus, nor do they or any family member hold equity positions in biomedical or pharmaceutical corporations.

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