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Brief report

Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: A review

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ABSTRACT

Objectives: Compare reported rates of mood-shifts from major depression to mania/hypomania/mixed-states during antidepressant (AD)-treatment and rates of diagnostic change from major depressive disorder (MDD) to bipolar disorder (BPD).
Methods: Searching computerized literature databases, followed by summary analyses.
Results: In 51 reports of patients diagnosed with MDD and treated with an AD, the overall risk of mood-switching was 8.18% (7837/95,786) within 2.39 ± 2.99 years of treatment, or 3.42 (95% CI: 3.34–3.50) %/year. Risk was 2.6 (CI: 2.5–2.8) times greater with/without AD-treatment by meta-analysis of 10 controlled trials. Risk increased with time up to 24 months of treatment, with no secular change (1968–2012). Incidence rates were 4.5 (CI: 4.1–4.8)-times greater among juveniles than adults (5.62/1.26 %/year; $p < 0.0001$). In 12 studies the overall rate of new BPD-diagnoses was 3.29% (1928/56,754) within 5.38 years (0.61 [0.58–0.64] %/year), or 5.6-times lower (3.42/0.61) than annualized rates of mood-switching.
Conclusions: AD-treatment was associated with new mania-like responses in 8.18% of patients diagnosed with unipolar MDD. Contributions to mood-switching due to unrecognized BPD versus mood-elevating pharmacological effects, as well as quantitative associations between switching and later diagnosis of BPD not associated with AD-treatment remain uncertain.
Limitations: Rates and definitions of mood-switching with ADs varied greatly, exposure-times rarely were precisely defined, and there was little information on predictive associations between mood-switches and BPD-diagnosis.

1. Introduction

Many cases of bipolar disorder (BPD) present in episodes of major depressive disorder (MDD), accounting for approximately half of initial episodes (Goodwin and Jamison 2007; Tondo et al., 2010b; Etain et al., 2012). Many such patients risk switching of mood from depression to disruptive and potentially dangerous manic/hypomanic, mixed, or psychotic states, sometimes in association with treatment with a mood-elevating agent, and some require re-diagnosis to BPD (Lim et al., 2005; Visser and Van der Mast, 2005; Licht et al., 2008; Tondo et al., 2010a; Li et al., 2012). Such risk may be particularly high among juvenile depressed patients, who are more likely to be treated with antidepressants (ADs) and stimulants before a diagnosis of BPD is made (Martin et al., 2004; Baldessarini et al., 2005; Lim et al., 2005; Biederman et al., 2009; Offidani et al., 2012). Moreover, patients who begin BPD with depressive or mixed episodes appear to be at increased risk for long-term morbidity, disability, and suicide (Baldessarini et al., 2010a, 2010b, 2012b). These considerations indicate the importance of quantifying the risk of excessive elevation of mood and behavioral activation during

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treatment with mood-elevating drugs, and its relationship to later diagnoses of BPD supported by spontaneous mood-elevations (Strober and Carlson, 1982; Akiskal et al., 1983). Finally, it remains unclear to what extent AD-associated mood-switches represent uncovering of potential or unrecognized BPD, or a more direct pharmacologic effect independent of diagnosis (Tondo et al., 2010a; Offidani et al., 2012).

Accordingly, we carried out a systematic review of reports on AD-associated mood-switching among patients diagnosed with MDD, as well as of reports on diagnostic conversion from MDD to BPD. We aimed to clarify the rates of each phenomenon and to seek relationships between them, as well as considering the possible significance of AD-associated mood-switching.

2. Methods

We supplemented two recent systematic literature searches (Tondo et al., 2010a; Offidani et al., 2012) for reports pertaining to manic-switching during AD-treatment and to diagnostic change to BPD in MDD patients identified in several computerized databases to September, 2012: *Best Evidence* (from 1991); *Centre for Reviews and Dissemination*; *CINAHL database*; *Cochrane Library*; *EMBASE* (from 1980); *ISI database*; *MEDLINE-PubMed* (from 1966); *PsychInfo*; *PsycLIT* (from 1967); *Thomson–Reuters*; and *Web-of-Science*. The search used combinations of the following subject headings: adolescent, adverse, antidepressant, bipolar, child, depression, diagnosis, major depression, mania, hypomania, mood-switch. We initially screened more than 2,000 on-line abstracts; reprints of 590 potentially eligible reports were obtained and duplicate data were excluded. Computerized searching was supplemented by reviewing bibliographies in reports reviewed. This process yielded an initial collection of 250 unique reports for detailed review, of which 51 pertaining to mood-switching and 12 pertaining to diagnostic conversion for subjects of any age and with any study-design, based on the occurrence of spontaneous hypomania or mania to the extent possible with reported information. Limitations of information reported precluded testing of heterogeneity of data pooled. Data were pooled and analyzed by standard statistical methods, using *Statview.5* (SAS Institute; Cary, NC) and *Stata.8* (StataCorp, College Station, TX) commercial programs.

3. Results

Rate of mood-switching with antidepressants

Reports of AD-treatment-associated mood-switching ($n=51$; Table 1) included a total of 95,786 depressed patients of a range of ages, treated and followed for times varying from 4 weeks to 23 years (mean: 2.39 ± 2.99 years; median: 1.00 [IQR: 0.20–3.75]). The overall rate of mood-switching into mania, hypomania, or mixed-states was 8.18% (7837/95,786), compared to the mean $\pm$ SD of rates from individual studies of 10.9 ± 11.4% (95% CI: 7.73–14.1). Owing to the lack of details about exposures for individuals, we did not adjust tabulated rates for the time-at-risk, which averaged 2.39 (95% CI: 1.55–3.23) years. However, an estimated annualized rate of mood-switching was 3.42 (CI: 3.35–3.50) %/year (7837/95,786/2.39 years).

Switching rate was strongly associated with longer nominal treatment-exposure times (overall $r=0.528$, $p<0.0001$). However, this association was significant only within the initial two years of AD-exposure ($r=0.401$, $p=0.031$) but not later ($r=0.156$, $p=0.489$), suggesting that most of the risk was limited to the initial months of treatment. The time-adjusted rate of switching within the first year of antidepressant-exposure averaged 1.03 ± 1.26 %/month. We found no indication of a secular trend, as switching rates were uncorrelated with the year of reporting between 1968 and 2012 ($r=0.003$, $p=0.983$). Also, rates were not higher before than during broad application of modern antidepressants since 1990 (9.32 ± 8.94% versus 11.8 ± 12.6%, respectively; $t=0.784$, $p=0.461$).

Prospective studies yielded non-significantly higher rates of AD-associated mood-switching than with retrospective designs (11.6 ± 11.7% versus 8.38 ± 10.1%, respectively; $t=0.789$, $p=0.434$) with similar average exposure-times (4.89 ± 6.23 versus 3.31 ± 5.93 years; $t=0.759$, $p=0.452$). However, AD-associated switch-rates were 3.0-times lower in placebo-controlled versus uncontrolled studies (4.20 ± 4.04% versus 12.8 ± 11.9%; $t=2.22$, $p=0.031$); controlled studies also involved significantly shorter exposure-times (9.32 ± 10.6 versus 65.6 ± 77.7 months; $t=2.27$, $p=0.028$), which may limit risk.

To verify an expectedly higher risk of manic-switching during AD-treatment, we compared the data from 10 paired assessments with versus without such treatment or with a placebo (Prien et al., 1973, 1984; Kane et al., 1982; Peet, 1994; Emslie et al., 1997, 2002, 2006; Keller et al., 2001; Martin et al., 2004; Dunner et al., 2005). Random-effects meta-analysis indicated a highly significant relative risk (RR) of 2.62 with/without ADs (95% CI: 2.48–2.77; $z=33.6$, $p<0.0001$), with an estimated number-needed-to-harm (NNH) of 21 (CI: 19–22). This relationship remained similar and highly significant with two unusually large studies (Peet, 1994; Martin et al., 2004) omitted individually or together to avoid their potentially distorting influences on the analysis (RR=2.84; CI: 2.62-3.06).

Comparison of patient-samples of adult versus juvenile ages indicated marked differences in switch-risk. The rates were 9.33% (7126/76,356) among juveniles versus 3.66% (711/19,430) in adults, with a risk-ratio (RR) of 2.55 (CI: 2.36–2.75; $p<0.0001$). Adjusted for estimated exposure-times, the corresponding juvenile versus adult incidence rates were 5.62 %/year (9.33%/1.66 years) versus 1.26 %/year (3.66%/2.90 years), for a risk-ratio of 4.46 (CI: 4.12–4.82; $p<0.0001$).

Finally, multivariate linear regression modeling found that only longer duration of treatment was significantly associated with higher switch-rates ($t=3.77$. $p<0.0001$). Other factors not significantly associated with switch-rates were: year of study, prospective versus retrospective design, randomized-controlled versus open trial, age, and total number of subjects/study (all $t \leq 1.70$; all $p \geq 0.10$).

Rates of conversion from unipolar major depression to bipolar disorders

We also identified 12 studies with information pertaining to rates of conversion of diagnoses from apparent unipolar MDD to type I or II BPD, excluding cases involving mania/hypomania associated only with mood-elevating treatments when these were identified (Table 2). Based on the ratio of cases with changed diagnoses to all subjects, the overall risk of diagnostic change was 3.29% (1928/58,682) in an average exposure time of 5.38 years for an incidence rate of 0.612 (CI: 0.580–0.640) %/year. The mean conversion rate across individual studies was 1.79 [1.10–2.48] %/year. The available data were insufficient to support assessment of effects of age on rates of diagnostic change.

We found a large excess of mood-switching associated with AD-treatments versus new diagnoses of BPD, based primarily on occurrence of spontaneous mania–hypomania. This ratio, based on weighted proportions of switching versus new diagnoses, unadjusted for exposure-times, was 2.95-fold (8.18%/3.29%; $\chi^2=1473$, $p<0.0001$). With rates adjusted for estimated exposure-times (3.42 and 5.38 years, respectively), this ratio was even greater, at 5.61 (3.42/0.61%/year; Tables 1 and 2).