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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).

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Table 1
Rates of mood-switching from unipolar major depression to mania, hypomania, or mixed-states.

Study (year)	Design	Initial ages	Diagnostic criteria	Initial status	Treatments	Exposure (yrs)	Outcome	Switch-risk			Predictive factors
								Cases (n)	Subjects (N)	%	
Perris (1968)	Pros	Adult	Clin	MDD (hosp)	Clin	10.0	M	18	138	13.0	Psychosis
Prien et al. (1973)[a]	Pros	Adult	DSM2	MDD (hosp)	IMI ± Li	1.00	M	9	78	11.5	Treatments
Winokur and Morrison (1973)	Pros	Adult	RDC	MDD (hosp)	Clin	5.50	M	9	225	4.00	–
Rao and Nammalvar (1977)	Retro	Adult	Clin	MDD (hosp)	Clin	4.00	M	42	122	34.4	–
Angst et al. (1978)	Pros	Adult	ICD8	MDD (hosp)	Clin	2.00	M[a]	20	159	12.6	Recurrences
Van Scheyen and van Kammen (1979)[a,b,]	Pros	Adult	Clin	MDD (hosp)	TCAs	0.16	M	7	50	14.0	Older age
De Wilde and Doogan (1982)[a]	Pros	Adult	Feighner	MDD (amb)	TCA/SRI	0.08	M or m	0	21	0.00	–
Himmelhoch et al. (1982)[a]	Pros	Adult	RDC	MDD (amb)	MAOI	0.12	M or m	0	19	0.00	–
Kane et al. (1982)[a]	Pros	Adult	RDC	MDD (amb)	IMI ± Li	1.42	M or m	1	27	3.70	–
Strober and Carlson (1982)	Pros	13–16	RDC	MDD (hosp)	Clin	0.17	M	2	56	3.57	FH, retard., psychosis
Akiskal et al. (1983)	Pros	Adult	DSM3	MDD (amb)	Clin	6.50	m	18	82	22.0	FH, retard., psychosis
Prien et al. (1984)[a]	Pros	Adult	RDC	MDD (amb)	TCAs	1.25	M or Mx	5	77	6.49	–
Angst (1987)[a,c]	Pros	Adult	Clin	MDD (hosp)	Clin	1.00	M or m	29	787	3.68	–
Winokur and Wesner (1987) [d]	Pros	Adult	Clin	MDD (hosp)	Clin	2.00	M or m	29	342	8.48	hosps., retardation
Garber et al. (1988)	Pros	12–18	DSM3	Dep (hosp) [e]	Clin	4.10	M or m	2	11	18.2	–
Kupfer et al. (1988)[a]	Retro	Adult	DSM3	MDD (amb)	IMI	0.75	M or m	5	197	2.54	–
Harrington et al. (1990)	Retro	6–16	Clin+RDC	Depressed	Clin	9.25	M or m	5	52	9.62	–
Johnstone et al. (1990)[a]	Pros	Adult	DSM3	MDD	AMI ± Li	1.75	M or m	0	27	0.00	–
McCauley et al. (1993)	Pros	12–18	RDC	Dep (hosp+amb) [f]	Clin	1.50	M or m	4	65	6.15	–
Menchon et al. (1993)	Pros	Adult	RDC	MDD (melancholic)	TCA/MAOI	0.50	m	26	116	22.4	Early onset
Strober et al. (1993)	Pros	12–18	RDC	MDD (hosp)	Clin	1.00	M or m	5	58	8.62	Psychosis
Geller et al., 1994	Pros	6–12	DSM3	MDD (amb)	Clin	1.75	M or m	25	79	31.6	FH, severity
Kovacs et al., 1994	Pros	8–14	DSM3	MDD+Dys	Clin	5.00	M or m	25	115	21.7	–
Peet et al. (1994)[a]	Review	Adult	Various	MDD (RCTs)	TCAs/SRIs	0.17	M	88	12962	0.68	–
Coryell et al. (1995)[g,h]	Pros	Adult	RDC	MDD (hosp+amb)	Clin	3.75	M or m	84	583	14.4	Psychosis, FH, youth
Rao et al. (1995)	Pros	12–18	RDC+DSM3	MDD (hosp+amb)	Clin	3.50	M or m	5	26	19.2	–
Tierney et al. (1995)	Retro	8–18	DSM3R	MDD	SRI	0.19	M	2	33	6.06	
Howland (1996)	Retro	Adult	Clin	MDD	Clin	0.08	M or m	9	182	4.95	–
Kovacs (1996[i]	Pros	8–13	RDC+DSM3	MDD (amb)	Clin	3.75	M or m	19	92	20.6	–
McConville et al. (1996)	Pros	12–18	DSM3R	MDD	SRI	0.23	M	1	13	7.69	–
Emslie et al. (1997)	Pros	7–17	DSM3R	MDD ± Anxiety	SRI	0.15	M	3	48	6.25	
Amsterdam (1998)[a]	Retro	Adult	DSM4	MDD	SNRI	0.12	M or m	0	42	0.00	–
Weissman et al. (1999)	Pros	6–12	RDC	MDD	Clin	1.00	M or m	5	83	6.02	FH
Goldberg et al. (2001)	Pros	Adult	DSM4	MDD (hosp)	Clin	7.50	M or m	30	74	40.5	Psychosis
Keller et al. (2001)	Pros	12–18	DSM4	MDD	TCA/SRI	0.17	m	1	188	0.53	–
Emslie et al. (2002)	Pros	8–18	DSM4	MDD	SRI	0.17	m	1	109	0.92	–
Ghaemi et al. (2004)[a]	Pros	Adult	DSM4	MDD	Clin	1.00	M or m	0	37	0.00	–
Martin et al. (2004)[a]	Retro	5–29	ICD9	MDD (amb)	TCAs/SRIs	0.79	M or m	6918	73511	9.41	Youth

Table 1 (*continued*)

Study (year)	Design	Initial ages	Diagnostic criteria	Initial status	Treatments	Exposure (yrs)	Outcome	Switch-risk			Predictive factors
								Cases (n)	Subjects (N)	%	
Angst et al. (2005)[j]	Pros	Adult	RDC	MDD (hosp)	Clin	11.7	M or m	121	309	39.2	Early onset
Dunner et al. (2005)[a]	Retro	Adult	DSM4	MDD (amb)	SNRIs	0.16	m	2	1139	0.18	–
Kochman et al. (2005)	Pros	7–17	DSM4	MDD (hosp)	Clin	1.11	M or m	35	80	43.8	Soft hypomania
Shirazi and Alaghband-Rad (2005)	Pros	8–17	DSM4	MDD ± Anxiety	SRI	0.12	M	5	30	16.7	–
Emslie et al. (2006)	Pros	12–17	DSM4	MDD	SRI	0.23	M or m	5	216	2.31	–
Wada et al. (2006)	Retro	Adult	DSM4	MDD	Clin	3.00	M or m	37	282	13.1	FH
Grof (2007)	Retro	Adult	DSM4	Depression	Clin	1.00	M or m	–	–	18.5	–
Brent et al. (2008)	Pros	12–18	DSM4	MDD	SRI/SNRI	0.23	m	1	334	0.30	–
Beesdo et al. (2009)[k]	Pros	14–24	DSM4	Hx of MDD	Clin	5.00	M or m	26	649	4.01	Early onset
Zimmerman et al. (2009)[l]	Pros	14–24	DSM4	Hx of MDD	Clin	5.00	M or m	35	470	7.45	Soft hypomania
Bechdolf et al. (2010)	Retro	15–24	DSM4	MDD	Clin	0.79	M or m	6	173	3.47	–
Fiedorowicz et al. (2012)	Pros	Adult	DSM4	Hx of MDD	Clin	9.95	M or m	108	550	19.6	Soft hypomania
Tondo et al. (2012)[m]	Pros	Adult	DSM4	Initial MDD (amb)	Clin	0.25	M or m	4	668	0.60	Antidepressants
Totals/means (*n*=51) –			–	**Initial MDD**	**Antidepressants**	**2.39 ± 2.99 [1.55–3.23]**	**M/Mx/m**	**7837**	**95,786**	**8.18 [8.00–8.36]**	–

In these 51 studies, the 95,786 subjects were considered initially to have unipolar major depressive disorder (MDD). Individual reported rates are not adjusted for exposure-times, the weighted-average of which was 2.39 years. The overall risk of mood-switching was 8.18% (7837/95,786); the mean across studies was 10.9 ± 11.4, and the approximate observed rate was 3.42 %/year (7837/95,786/2.39; [CI: 3.34–3.50]).

Abbreviations: *amb*, ambulatory; *AMI*, amitriptyline; *BD*, bipolar disorder type I or II; *Clin*, clinical; *DSM3* or *DSM4*, APA Diagnostic and Statistical Manual (editions III or IV); *Dys*, dysthymia; FH, Family history;*Hosp*, initially hospitalized for depression or more or longer subsequent hospitalizations; *Hx*, history of; *IMI*, imipramine; *Li*, lithium carbonate; *M*, mania; *m*, hypomania; *MDD*, major depressive disorder; *MAOI*, monoamine oxidase inhibitor; Mx, mixed-state; *Pros*, prospective; *Retard*, psychomotor retardation, often with hypersomnia; *RDC*, Research Diagnostic Criteria; *Retro*, retrospective; *SNRI, serotonin-norepinephrine reuptrate inhibitor; SRI*, serotonin-reuptake inhibitor; *TCA*, tricyclic antidepressant.

Notable factors associated with emergence of mania or hypomania included: family history of bipolar disorder; younger at illness-onset; initial or previous mild hypomanic symptoms; initial psychotic features; initial psychomotor retardation.

[a] Studies (n=14) on unipolar MDD patients included in review by Tondo et al. (2010a).

[b] 12/159 (7.55%) changed to schizoaffective diagnoses.

[c] Exposure-times are for BD as well as unipolar patients. There was a nonsignificant increased risk (2.66%–4.67%; p=0.08) following introduction of antidepressants (since 1960). Similar results were reported later for the same database (Angst (1985)).

[d] Report includes 225 cases also reported by Winokur and Morrison (1973).

[e] Includes depression with other pediatric disorders, including conduct and adjustment, as well as MDD.

[f] Includes depression with other pediatric disorders.

[g] Similar results from the same database were reported later (Akiskal et al., 1995).

[h] Rate of conversion of BD-II–BD-I: 12.8%.

[i] Also reviews other published reports reviewed above.

[j] Of initially BD-II cases, 41.2% converted to BD-I.

[k] All conversions occurred within 6 months.

[l] Subjects drawn from large German community sample; depression before age 17 had 2.2-times greater risk of later BD; conversion rate=2.5%/year × 5 years, then c.a. 0.5%/year thereafter; half of the risk was by 2.5 years.

[m] The rate of diagnostic conversion was 19/2328 (0.82%) over 16.7 years of risk-exposure; currently agitated depressed patients were not given ADs to minimize switch-risk.

Table 2
Rates of diagnostic conversion from unipolar major depressive disorder. to bipolar I or II disorder.

Study	Age groups	Newly bipolar	Total subjects	Years	Rate (%/year)
Akiskal et al. (1983)	Adults	23	206	13.0	0.86
Akiskal et al. (1995)	Adults	70	559	11.0	1.14
Coryell et al. (1995)	Adults	39	381	10.0	1.02
Martin et al. (2004)	Age 5–29	934	50,610	5.00	0.37
Angst et al. (2005)	Adults	121	309	20.4	1.92
Holma et al. (2008)	Adults	29	248	5.00	2.34
Kamat et al. (2008)	Adults	94	1360	3.00	2.30
Biederman et al. (2009)	Juveniles	29	105	7.00	3.95
Dudek et al. (2012)	Adults	40	122	9.30	3.52
Fiedorowicz et al. (2012)	Adults	96	550	19.9	0.88
Li et al. (2012)	Adults	451	3944	6.50	1.76
Tondo (2012)	Adults	2	288	0.50	1.39
Totals/means [95% CI]	–	**1928**	**58,682**	**9.22 ± 6.18 [5.2913.1]**	**1.79 ± 1.09 [1.10–2.48]**

In these 12 studies, the overall conversion (uncorrected for exposure-time) was 3.29% (1928/58,682; [CI: 3.14–3.43). Mean exposure time weighted by numbers of subjects is 5.38 years, so that the weighted conversion rate is 1928/58,682/5.38=0.61 (CI: 0.58–0.64) % per year. There may be some shared subject-sampling in the reports by Akiskal et al. 1995, Coryell et al. 1995, and Fiedorowicz et al. 2012, although their reported rates differed. In addition, Salvatore et al. (2012) have found a high rate of diagnostic conversions within 2 years of first hospitalization for a major depressive episode with psychotic features.

4. Discussion

We found new mania-like reactions (“mood-switches”) during AD-treatment among patients diagnosed with unipolar MDD, at an average frequency of 8.18% of cases, or approximately 3.42 %/year of treatment (Table 1). Rates of new diagnoses of BPD among patients diagnosed with MDD averaged 3.29%, or 0.61 %/year (Table 2). These findings indicate 2.5–5.6-fold excess of mood-switches to re-diagnoses, although reported rates of both AD-associated mood-switches and of changed diagnoses to BPD are both vulnerable to ascertainment biases. In particular, it is likely that many instances of relatively mild mood-elevation or behavioral activation are not considered manic, hypomanic, or mixed-states and so not counted as mood-switches (Offidani et al., 2012). Accordingly, the ratio of excessive mood-elevation during AD-treatment to changed diagnoses may be even greater than we estimated.

There was no secular change in switch-rates over the years encountered (1968–2012) nor was risk lower since 1990, before which tricyclic ADs, with a relatively high risk of inducing mania, were more widely used (Koszewska and Rybakowski, 2009; Tondo et al., 2010a). As expected, risk of mood-switching was higher (by 3.0-times) in uncontrolled than controlled trials, possibly because of longer observation. Switch-risk increased significantly within the initial, nominal 2 years of AD-treatment, but not thereafter (up to 4.6 years), consistent with evidence that most AD-associated manic reactions occur within the initial months of treatment (Angst, 1987; Menchon et al., 1993; Post et al., 2003; Lim et al., 2005; Fiedorowicz et al., 2012; Offidani et al., 2012; Tondo et al., 2012). However, lack of reported details concerning the timing of observed mood-changes limits estimation of switch-rates at specific times.

The observed ratio of mood-switching among depressed patients exposed to ADs was 2.6-times greater in juveniles than in adults (9.33%/3.66%). Corresponding ratios for diagnostic change versus age-groups could not be estimated adequately from the available data (Table 2). Information on age-related mood-switching is important since many cases of BPD in young patients are first detected or suspected from reactions to treatment with ADs or other mood-elevating drugs that are commonly employed in the treatment of juvenile psychiatric patients (Martin et al., 2004; Offidani et al., 2012). The observed age-difference in switching-risk versus age, may in part reflect a sampling artifact, in that juvenile patients are less likely than adults to have been diagnosed with BPD; moreover, diagnosis of BPD is less straightforward among juveniles (Martin et al., 2004; Offidani et al., 2012). Alternatively, earlier onset-age may identify a unique subgroup of patients eventually diagnosed with BPD, with higher rates of familial mood-disorders and possibly other psychobiological characteristics that may contribute to risk of treatment-associated as well as spontaneous mood-elevations (Baldessarini et al., 2012a).

In addition to the early onset-age, other factors that may be associated with mood-switching include a family history of mood disorders, psychotic features, severe depression with hospitalization, psychomotor retardation, and mild hypomanic symptoms (Table 1), as noted previously (Strober and Carlson, 1982; Akiskal et al., 1983; Perlis et al., 2010; Salvatore et al., 2012; Valentí et al., 2012).

An important, unresolved question is of the significance of AD-associated mood-switching. Two plausible possibilities are: [a] responses reflecting the presence of BPD, or [b] a direct pharmacological effect of mood-elevating treatments that may be transient, relatively rapidly reversible, and not followed by a change in diagnosis (Reichart and Nolen, 2004; Lim et al., 2005; Joseph et al., 2009; Offidani et al., 2012). The several-fold higher proportion of patients with mood-switches among unipolar MDD patients than the rate of later re-diagnoses of BPD is consistent with the possibility that some AD-associated mood-switches may represent pharmacologic reactions (AD-induced mania). It is also likely that AD-associated risk will be greater than spontaneous mood-elevations regardless of cause. It is important to note that the reported rates of re-diagnosis to BPD may be somewhat *over*-estimated if some cases involve drug-related mood-elevation and not only spontaneous mania–hypomania. That is the ratio of AD-associated mood-elevations to new diagnoses of BPD may actually be even higher than we found. A specific question remaining is whether AD-associated mania requires a diagnosis of BPD, or if some patients may become manic–hypomanic only with mood-elevating treatments but not spontaneously.

To address such questions, it would be of interest to follow large samples of depressed patients who become manic or hypomanic during treatment with a mood-elevating agent to determine their risk of later spontaneous mood-elevations requiring re-diagnosis of BPD. However, such studies are rare. One study found that 18% of 60 depressed adolescents later re-diagnosed with BPD had previous antidepressant-associated hypomania (Strober and Carlson, 1982). In another study,

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diagnostic change to BPD was observed in 44% of 41 patients considered initially to have MDD with treatment-associated hypomania, compared to none without such previous reactions (Akiskal et al., 1983). These observations leave uncertain the risk of re-diagnosis as BPD among depressed patients who experience mood-switching with AD-treatment.

Limitations of the present study include varied definitions and rates of mood-switching with ADs, and only average or maximum exposure-times. Moreover, there was little information on a putative predictive association between mood-switches and later diagnosis of BPD among patients initially diagnosed with unipolar MDD, and specifically as a function of current or onset-age. In general, the predictive value of treatment-associated mood-switching to later diagnosis of BPD remains uncertain, as are contributions to mood-switching of direct pharmacological effects versus a manifestation of BPD.

The occurrence of treatment-associated mood-switching has implications for diagnosis of BPD as well as for clinical management. That is, a single episode of AD-associated mood-switch has an uncertain relationship to the risk of future spontaneous mood-elevations or the need to diagnose BPD. Moreover, a single instance of AD-associated mood-switching (and probably even a single episode of spontaneous mania) does not seem an adequate basis for recommending indefinitely continued mood-stabilizing treatment (Zarin and Pass, 1987; Baldessarini, 2013).

In conclusion, AD-associated mood-switching into mania-like states was not rare among patients diagnosed with unipolar major depressive disorder, was especially likely among juveniles, and was much more frequent than changes of diagnosis to bipolar disorder. It remains uncertain when such reactions require re-diagnosis to bipolar disorder and corresponding, long-term mood-stabilizing treatment.

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