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Excessive Mood Elevation and Behavioral Activation with Antidepressant Treatment of Juvenile Depressive and Anxiety Disorders: A Systematic Review

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Key Words

Adolescents · Children · Antidepressants · Anxiety · Bipolar disorder · Depression · Mania · Adverse events

Abstract

Background: The prevalence, characteristics and implications of excessive arousal-activation in children and adolescents treated with antidepressants for specific illnesses have not been systematically examined. ***Methods:*** We compared reports of antidepressant trials (n = 6,767 subjects) in juvenile depressive (n = 17) and anxiety disorders (n = 25) for consensus-based indications of psychopathological mood elevation or behavioral activation. ***Results:*** Rates of excessive arousal-activation during treatment with antidepressants were at least as high in juvenile anxiety (13.8%) as depressive (9.79%) disorders, and much lower with placebos (5.22 vs. 1.10%, respectively; both $p < 0.0001$). The antidepressant/placebo risk ratio for such reactions in paired comparisons was 3.50 (12.9/3.69%), and the meta-analytically pooled rate ratio was 1.7 (95% confidence interval: 1.2–2.2; both $p \leq 0.001$). Overall rates for 'mania or hypomania', specifically, were 8.19% with and 0.17% without antidepressant treatment, with large drug/placebo risk ratios among depressive (10.4/0.45%) and anxiety (1.98/0.00%) disorder patients. ***Conclusions:*** Risks of excessive mood elevation during antidepressant treatment, including mania-hypomania, were much greater than with placebo, and similar in juvenile anxiety and depressive disorders. Excessive arousal-activation in children or adolescents treated with antidepressants for anxiety as well as depressive disorders calls for particular caution and monitoring for potential risk of future bipolar disorder.

Introduction

Treatment with antidepressants (ADs) has been associated with a range of excessive emotional arousal or behavioral activation in adult [1–3] as well as juvenile [4, 5] mood disorder patients, particularly among those diagnosed with unipolar depression. Such responses may reflect unrecognized bipolar disorder (BPD), especially among young persons who have not previously become manic or hypomanic spontaneously. Alternative possibilities include adverse drug effects or perhaps even de novo induction of BPD by mood-elevating treatments [6–11]. Risks of pathological mood elevation may be greater in association with treatment with older tricyclic ADs than with modern, second-generation agents in adults [3, 9, 12], but serotonin reuptake inhibitors have been impli-

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cated at ages below mid-adolescence [4, 13, 14]. These risks need to be balanced against evidence that the responsiveness of depression to AD treatment may be less in juveniles (and rarely studied separately in children) compared to adults [3, 15–17]. In addition, the use of ADs to treat a broad range of disorders has increased severalfold in both adults and children following the introduction of modern ADs since the late 1980s, even for patients with known or suspected BPD [18, 19].

International cross-sectional and longitudinal studies of the relationship between rates of AD prescriptions and incidence of BPD have found more apparent BPD in AD-treated samples of all ages [7, 20]. Clinical studies also indicate major secular increases in the apparent prevalence of patients diagnosed with BPD between the 1990s and 2000s, ranging from 2-fold in adults to approximately 40-fold in juveniles [21]. In contrast, community-based epidemiological estimates indicate little change in the prevalence of BPD in recent decades [22]. The marked increase of diagnoses of BPD among juveniles may reflect greater clinical interest and more effective, or possibly exaggerated, case identification [23]. Broad acceptance and wider use of modern ADs throughout clinical medicine itself may also be a contributing factor [20, 24].

Several case series have reported on associations of AD treatment with new-onset episodes of mania or hypomania in children and adolescents [4, 25–27]. However, risks of more broadly defined excessive arousal-activation have not been systematically evaluated in findings from prospective, controlled clinical trials, particularly to compare risks with specific drugs versus a placebo or other control conditions. There are even fewer comparisons of risks by indications for AD treatment, particularly juvenile depressive versus anxiety disorders, for which ADs are commonly used in clinical settings [3]. Symptoms of excessive arousal and even mania have been associated with AD treatment of juvenile anxiety disorder patients, though rarely in adults [6]. For both depressive and anxiety disorder patients, questions remain as to whether such effects represent adverse drug reactions or if anxiety syndromes as well as depression may sometimes precede spontaneous BPD, especially in juveniles [28–31]. Much of the available information about risks involved has relied on passively and incidentally identified adverse events in treatment trials rather than on direct investigation of defined responses as a specified research outcome measure, as noted in recent reviews [8, 11].

Given the remaining uncertainties concerning excessive activation-arousal in young patients treated with ADs, and the potential clinical, public health, and conceptual-scientific significance of such reactions, we carried out a comprehensive review of the available research literature on associations of AD treatment with the emergence of a range of symptoms of apparently excessive emotional arousal or behavioral activation, as well as mania-hypomania, among children and adolescents with mood or anxiety disorders, based on findings from clinical trials of AD treatment.

Methods

We followed PRISMA guidelines for systematic searching for reports pertaining to a range of symptoms of clinically excessive arousal or activation arising during treatment of juvenile patients with ADs up to March 2012 [32]. Key words were: 'child,' 'adolescent,' 'antidepressant,' 'hypomania,' 'mania,' 'manic,' 'bipolar,' 'adverse,' and 'switching.' To increase identification of studies involving anxiety disorders, we expanded the search terms to include: 'anxiety,' 'obsessive-compulsive,' 'OCD,' 'generalized anxiety,' 'GAD,' 'phobia,' and 'social phobia.' Searching and ratings of target responses were carried out independently by two investigators (E.O. and E.T.); disagreements were resolved by consensus among these primary raters and a senior investigator (G.A.F.). Electronic research-literature databases searched included CINAHL, the Cochrane Library MedLine, PsychInfo, PubMed and Web-of-Science. In addition, bibliographies of initially identified reports were searched manually. Owing to the infrequency of required investigations, we included studies of varied designs (randomized controlled trials, retrospective studies, reviews and meta-analyses, but not single case reports) in addition to randomized, placebo-controlled trials. We sought studies involving juveniles with an average age <18 years, diagnosis of broadly defined depressive or anxiety disorders, and treatment with ADs. Studies were screened to identify reports of new onset of behavioral events involving arousal or activation considered psychopathological or adverse events [33].

Statistical analyses included comparisons of continuous measures by ANOVA methods (t tests) or paired t tests, as well as random-effects meta-analytic and metaregression modeling. Pooled proportions (affected/all exposed subjects) were also compared by contingency tables (c^2). Data are reported as means with standard deviations (SD) or with 95% confidence intervals (CI). Computations used standard commercial computer programs (Statview.5; SAS Institute, Cary, N.C., USA and STATA.8; StataCorp, College Station, Tex., USA).

Results

Searching initially identified 354 reports of studies involving children and adolescents treated with an AD or a psychostimulant; we excluded 312 reports not meeting study criteria, leaving 42 studies involving a total of 6,767 subjects to analyze (fig. 1). They included 17 studies re-

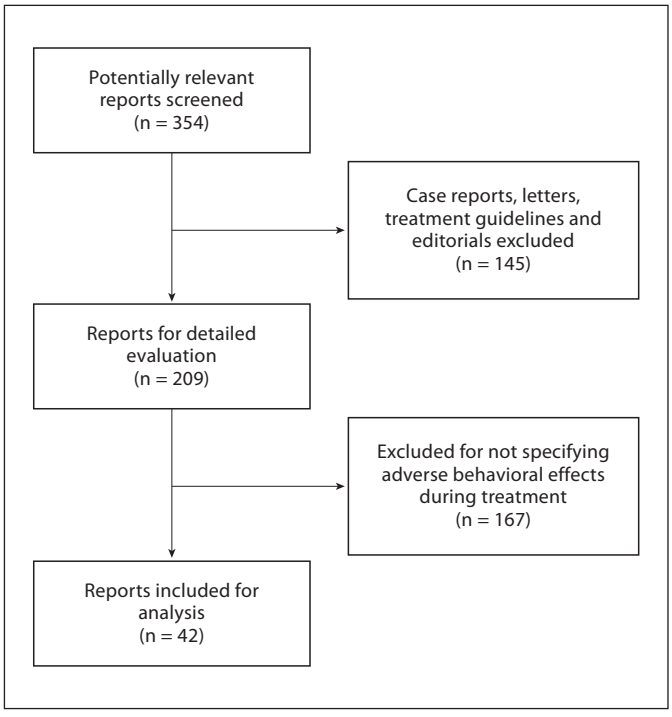

Fig. 1. Summary of report selection. Excluded from n = 354 initial potential reports were 146 of inappropriate type (73 letters, editorials or treatment guidelines, 62 case reports and 11 reviews), and 165 lacking information on rates of adverse behavioral changes. The final 42 reports included were from trials in depressed patients (n = 17 with 2,637 cases) or for anxiety disorders (n = 25 with 4,130 cases), or a total of 6,767 juvenile patients-subjects (5,294 given ADs, 1,473 controls).

garding AD trials in juvenile depressive disorders, with or without other psychiatric disorders (n = 2,637 subjects, 2,083 given an AD and 554 controls), 16 of which provided quantitative estimates of behavior outcomes considered as adverse events (see online supplementary table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000345316) [34–50]; 25 studies involved AD trials in juvenile anxiety disorders, with or without other psychiatric disorders (n = 4,130 subjects, 3,211 given an AD and 919 controls; online suppl. table 2) [51–76]. It is important to emphasize that interpretation of the findings is limited by the variety of types of patients and ages represented, and the range of behavioral outcomes considered to represent excessive arousal. A total of 19 studies involved a placebo or another no-treatment control-comparison condition, and were suitable for meta-analysis. As studies referred to a primary diagnosis, we considered separately trials involving depressive (online suppl. table 1) and anxiety-related disorders (online suppl. table 2) and compared their findings.

Depression

We identified 17 reports of trials involving ADs or stimulants alone or with other psychotropic agents (most often mood stabilizers or antipsychotics) in various types of juvenile depressive disorders, with or without other comorbidities (online suppl. table 1). Subject ages varied from 3 to 22 (mean 12.5) years in trials involving 13–439 subjects. A majority of the 2,637 depressed subjects (54.3%) were boys. Exposure times varied from 6 to 40 weeks, and latency to identified excessive mood elevation averaged 4.8 ± 4.3 weeks among reports including such information (online suppl. table 1). Study designs included prospective randomization and blinding (usually with a placebo control) in 6/17 trials. Methods of assessing adverse behavioral manifestations involved more or less systematic assessments in 11/17 trials; in 4 others, noteworthy behavioral responses were identified in spontaneous reporting of apparent adverse events (online suppl. table 1).

The depression studies analyzed reported various types and levels of behavioral activation considered in each report to be psychopathological. These responses ranged from insomnia, various manifestations of behavioral activation and overarousal, restlessness, agitation, irritability or sustained anger, as well as hypomania, 'manic symptoms,' and mania that may or may not have met formal contemporary diagnostic criteria, especially pertaining to duration; such events were sometimes associated with discontinuing from trials (online suppl. table 1). Three studies included currently depressed juveniles who were suspected of having BPD but did not include a control condition to indicate risk of spontaneous behavioral changes [40, 44, 46]. The range of responses considered precludes confident estimates of occurrence rates, which ranged from 0.3% for reactions considered to represent hypomania in a recent, large, prospective treatment trial involving treatment-resistant depressed, mainly adolescent, patients [50] to 50% for 'manic symptoms' in a small retrospective study [46]. Nevertheless, 5 of the studies involved comparisons of AD-treated versus placebo-control cases of juvenile depression [36, 38, 39, 42, 47]; in all of these, the rates were much lower with placebo treatment (online suppl. table 1).

Observed, crude mean rates of apparent mood shifting were 20.5 times higher with ADs (16.8 ± 14.6%) than placebo (0.82 ± 0.86%) when all available trials and data pertaining to juvenile depressed patients were included (t = 2.40, p = 0.027). Rates adjusted for approximate or nomi-

Table 1. Rates of excessive arousal-activation with antidepressant versus placebo treatment for depressive or anxiety disorders in juvenile patients

Conditions	Mood-shifting rates (n/N, %)		RR	χ^2	p value
	antidepressant	placebo			
Depression					
All data	205/1,826 (11.2)	6/554 (1.10)	10.2	53.0	<0.0001
Paired data	34/861 (3.95)	6/544 (1.10)	3.59	9.76	0.0018
Mania-hypomania	122/1,173 (10.4)	1/222 (0.45)	23.1	23.0	<0.0001
Anxiety					
All data	482/3,501 (13.8)	48/919 (5.22)	2.64	50.4	<0.0001
Paired data	154/1,317 (11.7)	48/919 (5.22)	2.24	27.6	<0.0001
Mania-hypomania	8/414 (1.98)	0/377 (0.00)	>2	7.35	0.0067
All cases					
All data	687/5,327 (12.9)	54/1,463 (3.69)	3.49	100	<0.0001
Paired data	188/2,178 (8.63)	54/1,463 (3.69)	2.34	34.4	<0.0001
Mania-hypomania	130/1,587 (8.19)	1/599 (0.17)	48.2	49.7	<0.0001
Mania-hypomania paired	123/1,541 (7.98)	1/599 (0.17)	46.9	48.3	<0.0001

Data are pooled ratios of subjects with mood shifting (n) to all subjects (N) treated with antidepressants or placebo for juvenile depressive or anxiety disorders, based on findings in online tables 1 and 2.

Comparisons include all available outcomes or hypomania-mania specifically, as well as paired comparisons with antidepressants vs. placebo. The findings indicate large antidepressant > placebo risk differences in risks of mood shifting, and similar risks with anxiety and depressive disorders.

nal exposure times (not precisely associated with outcomes) were 1.16 ± 1.25% per week with ADs and 0.084 ± 0.091% per week with placebo (a 13.8-fold difference). However, a probably more secure comparison found drug-associated rates to be 3.66 times greater with ADs than placebo in controlled studies with paired comparisons [3.95% (34/861) vs. 1.08% (6/554); $c^2 = 9.76$, $p = 0.0018$].

Anxiety Disorders

We also identified 25 other, similarly heterogeneous studies of juvenile cases of anxiety-related disorders with or without other psychiatric comorbidities, involving varied study designs and methods of defining behavioral outcomes (online suppl. table 2). Notably, however, cotreatment with mood stabilizers and antipsychotics was rare compared to the studies involving depression (see online supp. materials). The anxiety disorder studies involved a total of 4,130 young patients, of whom 57.5% were boys with an average age of 12 (range 3–18) years. AD exposure times varied from 8 to 104 (mean 17.6) weeks. Of these studies, 16/25 involved prospective, randomized comparisons of outcomes during treatment with ADs versus a placebo. Methods of assessing observed behavioral responses appeared to be systematic in only 12/25 studies; 2 did not define this aspect of methods, and the other 11 seemed to involve spontaneous reporting of adverse effects, so as to limit confidence in the validity of reported outcomes. As in trials involving depression, outcomes ranged through insomnia, agitation or either subjective or objective physical restlessness, excitement or disinhibition, hypomania, or mania. Rates of such behavioral outcomes with AD treatment ranged from 0.7 to 2.4% for mania in 4 reports [56, 65, 66, 68] to as high as 45–55% for insomnia, restlessness, agitation or irritability [52, 57, 59], and even 83% in 1 study reporting on unspecified behavioral reactions [73]. Reported latency to such reactions averaged 5.0 ± 3.0 weeks (online suppl. table 2), which was similar to that with depressive disorders.

Observed mean rates of apparent arousal-activation responses among juveniles with anxiety-related illnesses (online suppl. table 2) were 3.13-fold higher with ADs (22.6 ± 20.3%) than placebo (7.23 ± 7.45%; $t = 2.89$, $p = 0.006$). Rates of mood change adjusted for nominal exposure times differed by 2.94-fold between AD and placebo treatment (2.10 ± 2.22% vs. 0.714 ± 0.820% per week). Moreover, in controlled trials, paired AD-associated versus placebo-associated rates differed by 2.24-fold [11.7% (154/1,317) vs. 5.22% (48/919); $c^2 = 27.6$, $p < 0.0001$].

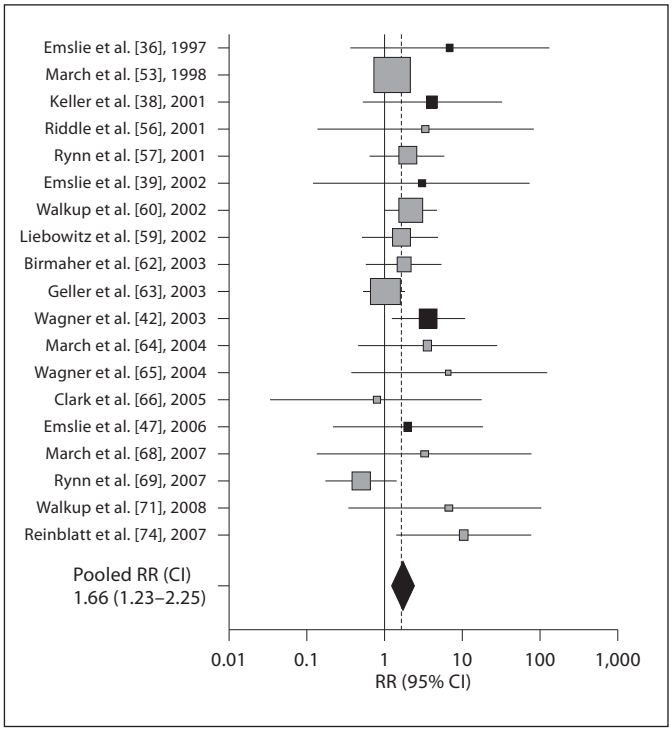

Fig. 2. Meta-analysis of rates of excessive mood elevation with ADs vs. placebo in controlled trials (n = 19) involving depressive (black boxes; n = 5) or anxiety-related disorders (gray boxes; n = 14; box size is proportional to study size). There was a highly significant overall drug/placebo difference (z = 3.33, p = 0.001) as indicated by the pooled RR of 1.66 (95% CI: 1.23–2.25; black diamond and vertical dotted line) compared to the null value of 1.0 (vertical solid line). The meta-analytically computed NNT is 36 (22–110). The pooled RR for juvenile depression was 3.61 (1.60–8.10; z = 3.10, p = 0.002), and for anxiety, 1.49 (1.08–2.06; z = 2.42, p = 0.016), a 2.4-fold but nonsignificant difference (t = 0.616, p = 0.546), with similar NNT estimates for depression and anxiety (37 vs. 32).

Comparisons of Outcomes and Diagnostic Groups

We further summarized proportions of patients showing excessive arousal or activation with AD versus placebo treatment in several ways, based on overall proportions, comparing risks of excessive activation with AD versus placebo and comparing all available data (data limited to controlled trials for direct comparisons), as well as risks specifically for outcomes reported as mania-hypomania. These comparisons were for both diagnoses as well as for depressive and anxiety disorder subjects (table 1).

Overall risk with AD treatment, regardless of primary diagnosis or outcome type, was 12.9% (687/5,327), and with placebo, 3.69% (54/1,463) – a highly significant 3.49-fold difference (table 1). For drug-placebo paired observations, the overall risks were 8.63% (188/2,178) versus 3.69% (54/1,463), another highly significant 2.34-fold difference. For mania-hypomania specifically, the drug-associated versus placebo-associated risks were 8.19% (130/1,587) versus 0.17% (1/599) overall, and for such outcomes in paired comparisons, 7.98% (123/1,541) versus 0.17% (1/599). These risks for both mania and hypomania were more than 45 times greater with than without AD treatment (both $c^2 \geq 46$, both $p < 0.0001$; table 1).

We also compared outcomes by diagnosis (table 1). With paired data, risk of excessive arousal was 2.96 times greater (11.7 vs. 3.95%) during AD treatment with anxiety than with depressive disorders ($c^2 = 39.6$, $p < 0.0001$). Similarly, with placebo, risk of spontaneous increases in mood or behavior was 4.74 times greater in anxiety disorders (5.22 vs. 1.10%; $c^2 = 16.3$, $p < 0.0001$). These observations suggest that risk of excessive arousal-activation was at least as large in anxiety as depressive disorders in children and adolescents.

For manias and hypomanias specifically, the risk (weighted by subject counts) with AD versus controls in depressive disorders was 10.4% (122/1,173) versus 0.45% (1/222; $c^2 = 23.0$, $p < 0.0001$); for anxiety disorders, the respective rates were 1.98% (8/414) versus 0.00% (0/377; $c^2 = 7.35$, $p = 0.0067$; table 1). These pooled risks of mania or hypomania during AD treatment, therefore, were 5.25 times greater in depressive (10.4%) than anxiety disorders (1.98%; $c^2 = 29.2$, $p < 0.0001$). However, risk of spontaneous mania-hypomania during placebo treatment was low in depression (0.45%) and did not occur with anxiety disorders (0.00%).

Meta-Analytic Modeling

Finally, we carried out a meta-analysis of pairs of mood-elevating responses with ADs versus placebo available in reports of 19 controlled trials (fig. 2). This analysis resulted in an overall drug/placebo risk ratio (RR) of 1.66-fold (95% CI: 1.23–2.25; p = 0.001). Meta-analysis for studies of depression (3.61; 1.60–8.10) and for anxiety disorders (1.49; 1.08–2.06) yielded somewhat greater drug/control RR values for depression, but with overlapping CIs. Estimates of the number-needed-to-treat (NNT) to obtain an excess of 1 case of excessive arousal with an AD versus placebo, based on the reciprocal of meta-analytic mean differences in rates (1/RD) yielded an overall NNT of 36 (95% CI: 22–110), with estimated NNT values of 37 for depression and 32 for anxiety – all consistent with the relative infrequency of such reactions. Metaregression modeling found diagnosis, year of reporting, total subject number, mean age, percentage males, and duration of treatment exposure all to be unrelated to outcomes (not shown).

Discussion

This review provides information concerning apparently excessive emotional arousal and behavioral activation in children and adolescents in association with AD treatments for depressive and anxiety disorders, and considered by the investigators of the trials as reportable adverse events. Overall rates of excessive arousal-activation during AD treatment were substantial in both depressive (11.2%) and anxiety (13.8%) disorders, and 3–10 times higher than with placebo (table 1). Moreover, in paired comparisons, overall risks (weighted by subject count) of outcomes considered 'mania or hypomania,' with versus without AD treatment, was 7.98 versus 0.17%. Also, a 1.7-fold overall difference with/without ADs was sustained by meta-analytic modeling of studies that compared risks with and without AD treatment (fig. 2). Such rates are only moderately lower than rates of new mania or hypomania among depressed adults with BPD treated with an AD (15.3%; with or without a mood-stabilizing drug) [3], but involve a range of levels of overarousal. More specifically, the overall risk of mania or hypomania during treatment with an AD was similar to, or somewhat higher than, the rate in AD-treated adults diagnosed with unipolar major depressive disorder (5.97%; 95% CI: 5.88–6.04) [5]. Owing to the limited incidence of excessive arousal-activation in the present juvenile studies, the estimated NNT to encounter more risk with an AD than with placebo was quite high, at 36 (95% CI: 32–110).

These findings support the conclusion that the broadly defined excessive arousal responses considered were strongly associated with AD treatment, and sustained even when reactions were limited to those considered as mania or hypomania. Moreover, the risks were similar or even greater among young patients considered to have an anxiety disorder versus depression (table 1). These findings require consideration of possible mechanisms involved.

An important possibility is that the excessive arousal-activation observed represented responses to AD treatment in cases of previously undiagnosed BPD. Such activation responses have often been reported in association with AD treatment, and may be particularly likely among juvenile depressed patients who have not yet experienced a spontaneous episode of mania or hypomania, and are a clinically important basis of initially recognizing BPD in previously depressed patients [3, 4, 8, 11, 13, 14, 77, 78]. The relatively high rates of excessive arousal-activation encountered seem inconsistent with typical exclusion of patients with known BPD from most AD trials [79], but are consistent with the view that BPD is not easily diagnosed in juveniles [59, 60, 80, 81–83].

Even though such responses do not necessarily prove the presence of previously undiagnosed BPD, it is important to note that continued use of ADs in cases of unrecognized BPD can lead to sustained mood instability [2, 79, 82, 84]. This consideration underscores the potential significance of even moderately excessive arousal-activation in guiding to future clinical management to monitor for similar future responses and for possible BPD, while considering the use of mood-stabilizing treatments judiciously.

An alternative potential basis for the observed high risk of excessive mood-elevating effects are directly AD-associated reactions that may be particularly likely among children and adolescents, as a pharmacological effect. Putatively drug-induced states of excessive arousal may or may not be followed by spontaneous mood elevations that would support a diagnosis of BPD. The similar or greater risks of excessive arousal-activation in AD-treated juvenile anxiety disorders, rather than selectively in depression (table 1), might be taken as evidence in support of this possibility. Alternatively, anxiety disorders may increase the risk of excessive behavioral activation such as through increased reactivity to the social environment [85]. A further possibility is that anxiety disorders in juveniles, in addition to depression, may represent a significant pathway to developing BPD. Less relevant to the current short-term treatment exposures, physiological adaptations to long-term AD treatment might also increase risks of developing BPD [7, 8, 11, 83, 86].

In order to clarify the mechanistic and prognostic significance of excessive arousal-activation or even of hypomania-mania associated with AD treatment in children, it would be helpful to have information based on long-term follow-up of persons experiencing such reactions. Factors to be considered in such studies would include the course and subsequent consequences of drug-associated hyperarousal responses, their relationship to risks of spontaneous mania-hypomania, and effects of drug type, dose, duration of exposure, and the latency from arousal reactions to the diagnosis of BPD. Some information of this kind has been reported. Strober and Carlson [87] followed 60 adolescents diagnosed with major depression for up to 4 years that included treatment with various ADs and antipsychotics: 20% were rediagnosed with BPD, as predicted by having experienced hypomania-mania during AD treatment, as well as having psychotic features or a family history of mood disorders. Similarly, Akiskal et al. [88] followed 206 adolescents and adults

diagnosed with unipolar depression for approximately 3 years; 8.7% experienced hypomania during treatment with an AD, all of whom were later rediagnosed with BPD. More recently, Martin et al. [4] found evidence of mania-hypomania in 5.4% of over 87,000 mostly depressed young patients aged 5–29 years during treatment with an AD, and 3 times lower risks without such treatment. Risks were highest at ages 15–19 years and with tricyclic ADs after age 15, but with serotonin reuptake inhibitors among younger children [4, 13].

Contrary to expectation, risk of excessive arousal-activation during AD treatment was at least as high among juveniles with anxiety disorders as with depression (table 1). Although depression commonly precedes manifestations of mania or hypomania in patients diagnosed with BPD [3, 79, 82], anxiety disorders or anxious depression may also be antecedents of later BPD, as well as being common comorbidities with BPD [6, 28, 30, 89–95]. As we found (table 1; online suppl. table 2), risks of new-onset mania or hypomania during AD treatment of young anxiety disorder patients have been reported to be several times higher than without anxiety disorders, particularly among boys [28]. In striking contrast, risk of overarousal or mood switching is much less common among adults with anxiety disorders treated with ADs [6]. It is also noteworthy that the risk of spontaneous mood activation among the juvenile anxiety disorder patients in the present study *not* treated with ADs (9.27%) was nearly 5 times greater than in depressive disorder cases (table 1). This finding is also consistent with an association between anxiety disorders and BPD in juveniles.

This systematic review involves several notable limitations. In most reports considered, the occurrence of symptoms of excessive emotional arousal or behavioral activation was not a systematic and explicit outcome based on consistently defined criteria. Many studies were not randomized, blinded or controlled, and none involved long-term follow-up assessments. Few studies even employed systematic checklists to evaluate the onset of treatment-emergent behavioral or other adverse events, but instead used spontaneously reported adverse events typical of many treatment trials [96]. Furthermore, reported frequencies of excessive arousal-activation (see online supp. materials) varied greatly among children treated with ADs, depending on definitions and severity criteria involved. Nevertheless, there were enough controlled data, with matched pairs of outcomes among patients randomized to treatment with an AD or not, as to indicate major drug-placebo differences in both types of disorders (fig. 2; table 1).

Despite methodological limitations imposed by the available data, a substantial likelihood of excessive arousal or activation, and even hypomania or mania, was clear in children and adolescents during AD treatment. The incidence of such responses, even those considered specifically to represent mania or hypomania, were much higher than in comparable reports involving anxious adults and similar to those reported among depressed adults, all treated with an AD. A notable and unexpected finding was that the risk of excessive arousal-activation, or even of hypomania or mania, was at least as high during AD treatment for anxiety as for depression. Additional follow-up studies are required to clarify the proportion of young patients experiencing such responses to AD treatment who later develop spontaneous mania-hypomania so as to support a diagnosis of BPD. Also of interest is the proportion of subjects who do not experience spontaneous mood elevations and may represent adverse pharmacological effects of ADs.

In spite of uncertainties regarding the interpretation of the excessive mood-elevating effects reported, the findings appear to have clinical implications. Notably, we recommend special caution and close monitoring in the use of ADs to treat depression or anxiety in juvenile patients in whom the risk of excessive mood elevation or the presence of undiagnosed BPD is likely to be underestimated. Those who experience pathological mood elevation or activation during AD treatment need especially close monitoring for similar future responses and for development of BPD. We also encourage avoidance of unnecessary and potentially burdensome or risky, indefinite, long-term use of mood-stabilizing treatments following single mood-elevating responses to AD treatment [95] and consideration of effective and safe nonpharmacological interventions, such as psychotherapy, for anxiety disorders [97].

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