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Antidepressant-coincident mania in children and adolescents treated with selective serotonin reuptake inhibitors

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Abstract

Several factors have amplified concern about the possibility that antidepressant medication may contribute to induction of pediatric mania. These include the high rate of antidepressant medication prescription, the recent surge in the rate of diagnosis of pediatric bipolar disorder in the USA, and a growing number of case reports and clinical studies showing coincidence of manic symptoms with antidepressant pharmacotherapy in both youths and adults. However, the question of how medications and manic symptoms might be related is complicated, and decisive research studies with rigorous designs for evaluating the issues have not been published. The situation makes it difficult for practitioners to make good, evidence-based decisions. The scientific literature is ambiguous, and the stakes are high. We review the extant literature, offer seven different conceptual models of how medication and mania might be related, and comment on the evidence and clinical implications of each.

Keywords

adolescents; antidepressant; children; citalopram; fluoxetine; induced hypomania; induced mania; paroxetine; sertraline; SSRI; switch; venlafaxine; youth

The increasing use of selective serotonin-reuptake inhibitors (SSRIs) to treat children and adolescents with psychiatric disorders has caused considerable controversy [1]. The use of antidepressants in youths tripled between 1987 and 1996, with rates of prescription rising from three per 1000 to ten per 1000 children and teenagers; and 21 per 1000 youths in the 15–18-year old range [2]. Although some SSRIs have demonstrated efficacy under controlled conditions in randomized clinical trials [3,4], there is evidence that many of these drugs may not be efficacious in general clinical settings [5–7]. The potential benefit of antidepressant treatment needs to be weighed against the potential costs and risks when deciding whether to prescribe [8]. Perhaps the most salient concern is the debate over whether SSRIs cause suicidal ideation or behavior in adolescents [9]. Although the relative risk of suicide when taking

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antidepressants is small, suicide is such a serious outcome that this has led to the UK restricting the use of antidepressants in children to fluoxetine in combination with cognitive-behavioral therapy [10]. An additional point of concern that has received less attention in the literature is the question of whether SSRIs may induce mania or hypomania in children and adolescents. Current evidence suggests that this is a topic worthy of further empirical study [11], as well as one of significant clinical concern [12,13]. Although mania is a less severe outcome than suicide, it may be a much more common adverse event, suggesting that the public health burden could be similar.

There are important reasons to focus on reviewing the relationship of antidepressants and mania in youths. Although there is a substantial body of literature suggesting that antidepressant treatment with SSRIs can cause an affective switch to mania or hypomania in adults [14–17], comparatively little is known about this phenomenon in children and adolescents. Importantly, epidemiological evidence suggests that there is a negative correlation between age and risk for antidepressant-induced mania [18]. Put another way, the risk of inducing mania with antidepressant medication may be especially high for children and adolescents 14 years old and younger [19]. Younger age at first treatment for bipolar disorder has also been reported as a predictor of vulnerability to antidepressant-induced cycle acceleration [20].

Several factors make it challenging to draw firm conclusions based on the literature regarding antidepressants and mania. One is the methodological shortcomings of the literature. The decisive design to evaluate the risk of antidepressant-induced mania would be to take a group of youths, randomly assign half to antidepressants and half to placebo and then follow them over a long time period to evaluate the relative risk of developing mania while taking antidepressants. Unfortunately, the available studies using random and blinded assignment have not used state of the art assessment for manic symptoms, and the studies with better assessment have used nonexperimental designs. Additionally, several limitations preclude using longitudinal randomized controlled trial (RCT) designs to examine this issue, including needing a very large (if not prohibitive) sample size for adequate power and the potential ethical dilemma of randomizing adolescents to no antidepressants for a lengthy period of time when some believe they are an effective treatment. A second issue is the complexity of the possible relationships between antidepressants and mania. Most articles have not defined *a priori* conceptual models or tested competing models against the evidence. This review will delineate seven different conceptual models – three of which involve antidepressants having an iatrogenic effect, two pertaining to the nature of bipolar disorder and two that are driven by artifacts of the assessment process. A third issue is that, in the absence of decisive data and analyses, the popularity of explanations and the choices made by practitioners are going to be driven by factors besides evidence. In the parlance of the decision-making literature, we are forced to rely on heuristics to guide our practices, and these may be biased in predictable ways such as overestimating risks [21].

This review attempts to address the three challenges by:

- Relying on explicit criteria from Evidence-Based Medicine [28] for evaluating the quality of the studies providing evidence about the potential association between antidepressants and mania;
- Providing specific conceptual models of the relationship that include potential confounds as well as harmful effects of medication as possible explanations;
- Qualitatively evaluating the evidence with regard to each model;
- Qualitatively describing the provocativeness of each model or the degree to which it might capture attention in both clinical and popular audiences for reasons besides supporting evidence;

- Illustrating a quantitative approach for weighing the likelihood of help versus harm (LHH), again borrowed from Evidence-Based Medicine [28].

The review closes with recommendations about improved assessment strategies that can help manage the risk of mania during treatment of depression, as well as informing future research in this area.

Models of the relationship between antidepressants & mania (& seven potential pitfalls & remedies for practitioners)

The following section describes seven different conceptual models of the possible relationship between antidepressant medications and manic symptoms. For each model, there is a statement about the potential associated pitfalls from the vantage of the practitioner, along with strategies to avoid or ameliorate the pitfall. Each model is also rated in terms of its 'provocativeness', conveying the degree to which the model is likely to gain attention owing to factors besides just the weight of evidence supporting it. More 'provocative' models are likely to play upon fear of causing harm (cognitive science has demonstrated that human beings give greater weight to potential risks than benefits in decision making) or a sense of scandal. More provocative models would be of concern to practitioners and would also readily attract the attention of media outlets that are perhaps first concerned with popular appeal above scientific evidence. Conversely, less provocative models may have a more difficult time capturing imaginations and gaining broad dissemination, even if they happen to be accurate. Next, we evaluate the degree to which the model in question is supported by the available evidence. The ratings attached to the provocativeness and 'likelihood' obviously include a large degree of subjectivity. We do not pretend that they are completely objective or precise and did not rely on formal coding criteria, but we intend them to be a concise and clear way of communicating our impressions based on a qualitative review of the literature. We also want to be clear that the term 'likelihood' is not intended to connote any formal statement about probability (i.e., a score of 6 does not mean that there is a 6/7 chance that the theory is correct). Finally, we present some potential research designs that could more informatively test each of the different models.

Ignition hypothesis

Uncovering a latent diathesis, turning on genes that were already present. The tinder of biological and environmental risk factors were already present and the exposure to the medication provided the spark necessary to light the bipolar 'blaze'. There has been a dramatic increase in the rate of diagnosis of bipolar disorder in the USA [22,23], leading to speculation that the higher rates may, in part, be attributable to the higher rate of medication prescription in the USA igniting a larger amount of mania in the population [24]. *Potential pitfall*: selecting an agent that is a logical choice for the presenting symptoms but destabilizes the patient. *Remedy*: careful assessment of risk factors, careful monitoring of possible switch or breakthrough mania and rapid change in pharmacology after manic symptoms emerge. *Provocativeness* (1–7, with 7 being the most provocative): 5. The Ignition hypothesis is the scenario most widely discussed at meetings and in the popular press – is there a subset of patients (those with bipolar disorder) who actually are likely to be harmed by front-line treatments for depression? European regulatory agencies and other groups are concerned that the higher rates of pediatric mania in the USA may be at least partially attributable to the high rates of exposure to medication [24]. *Likelihood based on available evidence*: 4. *Informative way to evaluate*: demonstrate gene compound interactions. This has not yet been done in psychiatry, but could be accomplished by adding genotyping to Phase III trials, or by personalized-medicine data mining approaches (comparing the genome against treatment adverse effects). For example, work in Type II diabetes has revealed genetic polymorphisms associated with edema, or fluid retention, a side effect of drug treatment [25]. Studies such as

these from branches of medicine other than psychiatry suggest that linking genetic information with medication side effects is possible. However, due to low base rates of mania as a side effect, these approaches would require huge sample sizes, though these are being built rapidly, and also more systematic coding of manic symptoms than is typically done. Ideally, any pharmacogenetic research in this area would also take into account environmental factors; however, this is difficult on a large scale and examining gene-by-medication interactions may be more feasible.

Scar hypothesis

Creating a new diathesis in the absence of prior biological risk. *Potential pitfall*: causing harm with well-intentioned and logical treatment for depression. *Remedy*: careful assessment of risk factors, intense monitoring to detect emergent mania, and a rapid switch in pharmacology. *Provocativeness: 7*. This is the scary monster lurking in the closet for prescribers. Take one brain, previously incapable of developing mania, treat it for depression and leave it permanently vulnerable to manic episodes. *Likelihood based on available evidence*: 2. There are no decisive studies refuting this possibility. However, there are many other scenarios that appear much more plausible, both as causes of manic symptoms and also because the idea that brief exposure to a compound could produce permanent deleterious change contradicts growing knowledge of the plasticity of the CNS and its tendency to survive and recover from insult. *Informative way to evaluate*: demonstrate changes in brain morphology or pathophysiology following medication exposure, and show that these predict recurrences of mania. It would be decisive if it could be demonstrated that these changes occur after exposure to the compound even in the absence of established genetic risk factors for bipolar disorder.

Side effect hypothesis

Temporary deleterious effect of the drug, but not a true manifestation of a bipolar illness. *Potential pitfall*: the error would be in attributing the symptoms to a disease instead of the imperfect drug. *Remedy*: avoid labeling people with manic symptoms occurring while taking antidepressants as having ‘bipolar disorder’. At present, the Diagnostic and Statistical Manual of Mental Disorders-IV – Text Revision (DSM-IV-TR) indicates that these events should be coded as ‘substance-induced mania’ rather than a form of bipolar disorder [26] because of the possibility that the symptoms are a side effect rather than an unmasking of a bipolar diathesis. The clinical management typically would involve changing pharmacotherapy and using intensive assessment to evaluate whether mood symptoms persist at a problematic level. *Provocativeness*: 3. The Side effect argument motivated some high-profile lawsuits back when compounds were first introduced, but this scenario has definitely been eclipsed by the Ignition and Scar hypotheses in recent discussions. The ‘side effect’ model is less frightening because it posits that the harmful effects of the compound are limited in duration (or else it transforms into the Scar Hypothesis). *Likelihood based on available evidence*: 4. *Informative way to evaluate*: A–B–A–B design, also known as a challenge–withdrawal–rechallenge study, to demonstrate that side effects only happen when exposed to the agent. The Side effect hypothesis would also be substantiated by either showing that manic symptoms occur in the absence of genetic risk for bipolar disorder, or by showing that the pathophysiology of side effects is different from the pathophysiology of bipolar disorder.

Vigilance hypothesis

Increased monitoring for the illness, but no actual change in risk. The Vigilance hypothesis is a variant of ‘verification bias’, which plagues medical assessment and represents a serious threat to the validity of any studies without blinded evaluation and a stringently defined comparison group (ideally based on random assignment) [27,28]. *Potential pitfall*: confusing heightened monitoring with increased risk. Falling victim to a cognitive heuristic and

remembering the cases where mania occurred, but discounting the cases where it did not occur while using antidepressants. *Remedy*: evaluate all patients on antidepressants for possible emergence of manic symptoms – avoid 'work-up' bias. The US FDA now recommends evaluation for possible bipolar disorder when prescribing antidepressant medications, although the suggested language currently falls short of a 'black box' warning [101]. Practitioners can find review articles and RCTs and learn risk rates from them. *Provocativeness*: 1. There is virtually nothing exciting or glamorous about the vigilance scenario, and it is unpopular to be reminded that we are imperfect at weighing and combining information [29]. *Likelihood based on available evidence*: 5. As we will see, studies with stronger designs tend to find lower rates of treatment-emergent mania. Additional arguments in favor of this possibility are: first, the inaccuracy of many clinical diagnoses of bipolar disorder; second, the inadequacy of many clinical evaluations in terms of ascertaining family history or prior history of hypomania [cf. 30,31]; and third, the failure of most clinicians to consider bipolar disorder as a possibility in youths until recently, and the widely uneven implementation of consistent, evidence-based practices around the country, even at present. *Informative way to evaluate*: research study conducting same intensity of follow-up for those exposed to antidepressants versus other compounds, or systematically varying the intensity of follow-up for the same antidepressant medication. Presenting clinicians with case vignettes where the context in which symptoms are presented is varied could also be informative. Ideally, use random assignment and a large trial to equate groups on characteristics besides compound.

Medication as irrelevant hypothesis

What we are witnessing is the natural course of the bipolar illness, not a response to the treatment. The 'natural course' confound is widely recognized as a rival hypothesis in methodology circles that potentially affects any design except for a randomized trial [32,33]. In the case of bipolar disorder, the possibility that changes in mood are due to the natural course of the illness is not a vague academic premise; it is a well-documented clinical phenomenon. *Potential pitfall*: blaming a treatment for an event that was completely unrelated. *Remedy*: find and rely on well-designed research about risks to avoid heuristics and clinical illusions about clinical phenomena. *Provocativeness*: 1. There is no element of intrigue, no blame to be assigned to the compound or the practitioner, except perhaps failing to recognize the 'great masquerade' of mental illness in its first guises. *Likelihood based on available evidence*: 6. *Informative way to evaluate*: combine studies looking at antidepressant-coincident mania (ACM) in cases with bipolar disorder randomized to either antidepressant or placebo (realistically, both as adjunct to another mood stabilizing compound) – this would help rule out a causal role of the compound. Good epidemiological and natural history studies are also needed to understand rates of hypomania (sorely lacking in epidemiological studies) and rates of recurrence [cf. 34].

False alarms hypothesis

Mislabeling juvenile behavior as pathological when it still falls within normal limits; mistaking aggressive behavior due to other causes as pediatric mania [35]; or alternatively, mistaking the return of energy and positive emotions as depression lifts for hypomania. *Potential pitfall*: attributing behavior to a disease that is not present. *Remedy*: use assessment tools that extend beyond the routine clinical interview, especially tools that rely on age norms or direct comparisons to other clinical samples. Adopt 'probability of diagnosis' approach from Evidence-Based Medicine to acknowledge when cases are ambiguous instead of clear-cut [28]. *Provocativeness*: 6, if you are skeptical about the diagnosis of pediatric bipolar disorder; 2 if clinically active in the area. The False alarm hypothesis appeals to those ready to jump on the 'pathologizing childhood' bandwagon [36], as well as playing upon concerns about the overdiagnosis of bipolar disorder [36]. Those who work in clinical settings or conduct research with these youths encounter severe enough impairment to make the 'just being a kid'

explanation implausible in most cases. *Likelihood based on available evidence*: 2. *Informative way to evaluate*: much work has been done validating the construct of pediatric bipolar disorder [37–39]. Based on the validity data, it is clear that at least some cases of mania reflect an underlying bipolar illness. Conversely, there are definitely cases that are labeled and treated as 'bipolar' when it is a completely different process leading to the symptoms. Careful individual assessment is the best way forward.

Bipolar depression hypothesis

Early onset depression is a risk factor for bipolar disorder [40–42], and many people with bipolar disorder first seek treatment during a depressed episode [43,44]. These findings suggest that when treating youths for depression, we are often dealing with the depressed phase of what will prove to be a bipolar illness. *Potential pitfall*: blaming treatment for the natural course of the illness; failing to recognize bipolar depression. *Remedy*: assessment, again – carefully evaluate family history of bipolar disorder, assess for prior hypomanias or manias; assess for mixed states. *Provocativeness*: 5. The appeal would come from the stealth factor, that the illness has been avoiding detection previously (contradicting current concerns about overdiagnosis of bipolar disorder). *Likelihood based on available evidence*: 6. *Informative way to evaluate*: at the research level, studies are needed that carefully follow children and teenagers with depression prospectively, to find how many of them develop hypomania or mania. The next generation of research needs to incorporate strategies to accurately detect hypomania, which has been the Achilles heel of prior research, leading to the ambiguities for bipolar II and cyclothymic disorder. A similar degree of sophistication about hypomania also needs to be deployed in clinical trials of antidepressants, especially placebo-controlled studies.

Guidelines for evaluating studies of harm

There has been a move within the field of Evidence-Based Medicine to develop a set of guidelines or criteria for evaluating studies quickly, gauging their design and appraising their validity and relevance for individual patients. These include the Consolidated Standards of Reporting Trials (CONSORT) criteria [32] for clinical trials, as well as a series of brief articles that appeared as a series in *JAMA* before being anthologized and expanded [45]. Perhaps the most accessible discussion of these guidelines and their application to individual cases is offered in the book, 'Evidence-Based Medicine' [28]. If antidepressants do in fact increase the risk of mania, it would be an example of treatment causing harm. Box 1 provides a set of criteria for evaluating whether the evidence about antidepressants causing harm – in other words, inducing mania – is valid (adapted [28]). We will refer to these criteria when evaluating the published studies.

Review of the evidence for antidepressants potentially inducing mania

Antidepressant-induced mania in adults

Antidepressant-induced mania is a well-known clinical phenomenon in adults [14,15]. Meta-analysis suggests that approximately 3.7% of individuals with unipolar depression may experience a switch to mania following exposure to a SSRI [46], while 24–44% of individuals with bipolar disorder may experience an affective switch while taking an SSRI [17,47]. Importantly, adults (and children) with bipolar disorder typically spend a larger percentage of time depressed than manic/hypomanic [48,49], suggesting that treatment of depression may be the most important aspect of psychopharmacological management of bipolar disorder [11, 50,51].

Mania coincident with SSRI usage in youths

The next portion of the review concentrates on the literature pertaining to mania and SSRIs in youths. We focused on SSRIs because the relatively benign side effect profile has made them almost universally preferred to the cyclic antidepressants and monoamine oxidase inhibitors in pediatric samples [2,52]. Medline and PsycInfo were searched using the terms 'children or adolescents or youth', 'mania', 'SSRI', 'induced mania' and 'antidepressant-induced mania'. Additional references were gathered from the reference list of identified articles. This search strategy identified 36 articles for the review.

Case studies of pediatric mania coincident with SSRI usage

There are many case studies describing antidepressant-induced mania in children and adolescents treated with SSRIs, including citalopram (five cases) [53,54]; fluoxetine (11 cases) [55–59]; paroxetine (seven cases) [60–63]; sertraline (five cases) [64–67]; and venlafaxine (a serotonin–norepinephrine reuptake inhibitor; one case) [69]. These reports describe a young person treated for anxiety or depression (and in one case, epilepsy) [53], who developed symptoms of mania or hypomania after treatment with an SSRI for periods of time that were typically short (8 weeks or fewer) [54,56–62,64–66], but were sometimes long (from 5 months to a year) [53,57,58,63]. The median time to onset of mania was 21 days, with a range from 2 to 365 days. These individuals varied in terms of family history. A total of 21% had a first-degree or other relative with diagnosed bipolar disorder; 45% did not have a family history of mood disorders.

Box 1

Criteria for evaluating whether evidence about antidepressant-induced mania is valid

Criterion	Evaluation of the literature
1. Were there clearly defined patient groups that were similar in all ways other than exposure to an antidepressant?	No comparison group in case studies. Comparison groups differ across other studies.
2. Were treatments and manic symptoms measured the same way in both groups? Was the assessment of mania objective or blinded to antidepressant exposure status?	Open-label trials and case studies not blinded.
3a. Was the follow-up period sufficiently long for mania to occur?	Variable, but often sufficient (extending out to a year or more).
3b. Was retention adequate? How were missing data treated?	Straus et al. [28] offer a rule of thumb of ignoring any study with more than 20% lost to follow-up, because this will likely introduce bias. Missing data are often not discussed in published reports on antidepressants and mania.
4. Do the results satisfy some of the diagnostic tests for antidepressants causing mania?	
4a. Is it clear that antidepressant exposure preceded the onset of the outcome?	If assessment of mania is not rigorous at baseline, then prior hypomania can escape detection.
4b. Is there a dose–response gradient?	Dose–response has not been demonstrated for antidepressant induction of mania yet.
4c. Is there any positive evidence from a withdrawal–rechallenge study?	We have not found a rechallenge study in the literature. There is a blinded withdrawal study [98].
4d. Is the association between antidepressants and mania consistent from study to study?	No. Results run the full gamut from increased rates of mania, to no difference in rates, to significant decreases in rates of mania.
4e. Does the association between antidepressants and mania make biological sense?	Yes, clearly.

Adapted from [28].

The onset of mania/hypomania usually followed the commencement of the SSRI, but in some cases it was the result of an increase in dose after the patient-tolerated lower doses. Cessation of antidepressant treatment led to a resolution of the manic/hypomanic symptoms in 59% of cases, while a mood stabilizer was used in 38% of the cases in order to mitigate symptoms [53–55,57,59,62,65,67,68]. Nearly all case studies reported that following the cessation of the

manic symptoms, the patient then remained ‘stable’, typically off of the antidepressant or sometimes at a lower dose; the patient may have continued on a mood stabilizer if one had been added. However, the period of time for which they were followed varied – a median of 20 weeks with a range from 2 to 52 weeks.

Taken as a whole, these case studies would seem to suggest that caution is warranted when treating children and adolescents with SSRIs, as there are documented cases of this treatment coinciding with mania or hypomania. However, it is also important to keep in mind that mood disorders show natural fluctuations (with the ‘Medication as irrelevant’ hypothesis representing the extreme view that what appears to be treatment-emergent mania is actually just a bipolar illness following its own natural course, independent of the presence or absence of antidepressant medication), and therefore causal links to the development of manic symptoms by the addition of an SSRI, or resolution of manic symptoms by removal of the SSRI, cannot be established by case studies. The pharmacokinetics of antidepressant medications make the use of A–B–A–B designs, which can be helpful tools for establishing causality or efficacy at the individual level, difficult owing to the long half-lives and resulting length of time needed to titrate or wash out medication. Additionally, case studies are probably a biased source of information, as they are written about patients who stand out in the clinician's mind. Reports of youths treated with SSRIs who do not develop mania do not appear in the research literature as case studies. The same heuristic may also operate at the level of the individual clinician: it is much more memorable when a case shows an adverse event such as mania versus a case that does not; and humans as decision-makers are prone to giving much greater weight to negative events as an evolved heuristic for avoiding risks [69].

Chart review studies of SSRI-induced mania

Several chart or case reviews have attempted to examine the relationship between SSRI treatment and mania in more systematic ways. Some studies' findings suggest that antidepressants might increase the rate of mania. Faedda, Baldessarini, Glovinsky and Austin reported a rate of 48.7% of children with bipolar disorder developing mania following treatment with a SSRI (n = 19 of 39 exposed) [70]. The antidepressant-induced manic episode was the episode that initiated the bipolar diagnosis in only 17% of those cases. The median latency to mania was 12.5 days (across all classes of antidepressants and stimulants). Another chart review of youths with bipolar disorder revealed that those receiving SSRI treatment were three-times more likely to report manic symptoms at their next follow-up visit than youths who did not take a SSRI [71]. Wilens and colleagues, when reviewing 82 consecutive admissions to a pediatric psychopharmacology unit who were prescribed an SSRI, found that five of the youth (6%) had developed manic symptoms while taking the SSRI [72]. A review of 79 consecutive hospital admissions showed that youths who had ever received an antidepressant had an earlier age of onset of bipolar disorder than youths who had not [73]. However, the latter study did not look at the effect of treatment with a SSRI separately from other classes of antidepressants. The pattern of findings in these studies could be explained by the Ignition or Scar hypotheses, but it also is consistent with the Bipolar depression hypothesis: youths with bipolar disorder might often have earlier ages of onset for their depression, leading to earlier antidepressant prescription. Another chart review study examined ‘drug-induced behavioral disinhibition’, and found that rates increased significantly with SSRI usage [74]. A strength of this study was that it included objective behavioral indicators, such as number of seclusions; but it is not clear how much overlap there is between ‘behavioral disinhibition’ and mania.

A pharmacoepidemiologic study of age effects [18] examined conversion to mania in children, adolescents, and young adults with anxiety or nonbipolar mood disorders. The authors analyzed mental health outpatient and pharmacy claims of 87,920 individuals, aged 5–29 years, over a median of 41 weeks. The study showed an overall prevalence of manic conversion of 5.4%. A

total of 49% of the converters had been exposed to a SSRI. SSRI treatment was associated with a hazard ratio of 2.1, roughly a twofold increase in the risk of conversion to mania. This effect size is concerning, yet also small enough that Evidence-Based Medicine authorities point out that it could be entirely attributable to extraneous factors besides an iatrogenic effect [28]. The authors reported that among those treated with SSRIs, youth younger than 15 years of age were at an increased risk for mania. Again, this design cannot distinguish between the Bipolar depression hypothesis versus the three iatrogenic possibilities.

In one of a few studies specifically examining antidepressant-induced mania in youths with bipolar disorder, Baumer *et al.* found that among 52 children and adolescents with or at risk for bipolar disorder (operationalized by having a parent with bipolar disorder), 50% experienced either a new manic episode or a worsening of an existing episode after being treated with varied antidepressants, approximately 80% of which were SSRIs, for an average of 1.4 years [11]. In a chart review study that followed youths for 12 months after first hospital admission for either a manic or a mixed episode, antidepressant use was associated with a recurrence of a mood episode [75]. The reporting of this study did not differentiate between manic versus depressed recurrence, though, and other aspects of the findings indicate that treatment refractoriness of depression might be influencing results.

Other studies have found no effect of antidepressants on the age of onset of bipolar or the manic symptoms observed in youths with bipolar disorder, including retrospective interview report about age of onset and current interview-based mood ratings in an outpatient setting [76]. Similarly, Soutullo and colleagues found that among hospitalized adolescents with bipolar disorder, a history of exposure to antidepressant treatment was not associated with a more severe course of hospitalization as measured by length of stay in the hospital, number of ‘as needed’ medications given, or seclusion and restraint orders [77]. At the other extreme, a study of youths with psychotic depression found that antidepressant use was associated with a fourfold decrease in risk of developing mania over the follow-up period, with cases followed for as long as 2 years [78].

A longitudinal study looking at the development of mania in a cohort of youths originally identified as having attention-deficit/hyperactivity disorder but no comorbid mood disorder is also relevant [79]. The youths were originally ascertained as a comparison group for a longitudinal study of pediatric bipolar disorder, with 6-year follow-up data providing the basis for analysis. Based on blinded interviews, 29% developed bipolar I with elation or grandiosity. Antidepressant use was not significantly associated with developing mania. These findings could be consistent with the Bipolar depression hypothesis: systematically excluding cases with pediatric depression may have eliminated cases initially identified as depressed who would later have cycled into mania. Excluding these might have eliminated the artifact that is interpreted as showing a ‘switch’ to mania in other studies.

In short, the chart review studies (including those with follow-up) have found inconsistent results, and the designs have not been strong for examining the issue of antidepressant usage precipitating mania. The studies with a follow-up component, high retention and the most structured assessments of mania have tended to produce the smallest effects. Overall, these findings appear most consistent with the Vigilance and Bipolar depression hypotheses. The Medication as irrelevant hypothesis appears at least as plausible as any of the Iatrogenic hypotheses based on the data.

Clinical trials

Several research groups have reported mania as an adverse event during both open-label and RCTs examining SSRIs as treatment for children and adolescents.

Citalopram—Among 174 youths treated for depression with citalopram or placebo in a RCT, none developed mania, although adverse events were reported spontaneously and mania was not formally assessed [80]. In an open-label trial of citalopram treatment for early onset major depressive disorder (MDD), Shirazi and Alaghband-Rad found that over the 6-week study period, 16.7% of children and adolescents experienced an unexpected switch to mania [81]. Since the design was an open trial, it is particularly vulnerable to the Vigilance issue; and because there is no comparison group, the findings do not provide information regarding increase of risk [28].

Escitalopram—Of 264 children and adolescents treated with escitalopram or placebo for depression, one developed mania; however, this occurred in the placebo condition [82]. Adverse event reporting was spontaneous or observational.

Fluoxetine—Perhaps the best-known study of fluoxetine for adolescent depression is the Treatment of Adolescent Depression (TADS) trial [30]. The TADS trial specifically assessed for the development of manic symptoms. Fluoxetine was given either alone or in combination with cognitive behavioral therapy. Four subjects (3.67%) on fluoxetine alone and one (0.93%) in the combination arm developed symptoms on the mania spectrum during treatment, versus one on placebo and none in the cognitive behavioral therapy only arm. However, three of the five who developed mania began the trial with high baseline mania symptom scores as assessed by the Adolescent Depression Scale, developed specifically for the TADS trial. A total of 38 patients overall began fluoxetine treatment with high baseline mania scores; therefore, most (92%) of patients actually tolerated fluoxetine well with respect to the development of mania or hypomania.

In another double-blind, randomized, placebo-controlled trial of fluoxetine for depressed children and adolescents, 6.25% (n = 3) of youths receiving fluoxetine experienced a manic episode during treatment versus a rate of 2% (n = 1) on placebo [83]. In a second randomized, placebo-controlled trial of fluoxetine for youths with depression, one participant out of 109 developed a manic reaction while no participants in the placebo group (n = 110) did. This difference was not statistically significant [3]. In the relapse prevention phase of this trial, there were no reports of mania among 20 patients remaining on fluoxetine, although whether it was specifically assessed for was not stated [84]. Go, Malley and Birmaher reported that during open-label clinical treatment, 30% of 40 youths with obsessive–compulsive disorder (OCD) and mood disorders developed manic or hypomanic symptoms when treated with fluoxetine or sertraline [59]. Because the study was open label, the Vigilance hypothesis is a major concern. Owing to the comorbid mood disorders, the Bipolar depression hypothesis is also viable.

Fluvoxamine—An 8-week RCT of fluvoxamine treatment for anxiety disorders, as well as a 6-month open-label follow-up trial of 128 participants from the 8 week trial, failed to identify any youths experiencing mania [85,86]. Neither publication specifically states that there was no occurrence of mania, nor is it clear what assessment strategy, if any, was used to assess for hypomania or mania.

Paroxetine—In a RCT of paroxetine treatment for 206 children and adolescents with MDD, adverse events were ‘gathered by spontaneous report’, and no incidents of mania were reported [7]. The development of mania was not specifically assessed.

Sertraline—McConville and colleagues found that one out of eight hospitalized adolescents with MDD developed mania during open-label sertraline treatment [87]. Wagner and colleagues conducted two large trials of sertraline treatment for MDD in children and adolescents; however, these trials failed to specifically assess for mania, and none was reported

[4]. When sertraline was used to treat OCD in 137 children and adolescents, both during a 12-week randomized placebo-controlled trial [88] and during a 52-week open-label extension study [89], none of the participants experienced manic or hypomanic symptoms. These findings are consistent with the Bipolar depression hypothesis – the 'switch' to mania appears when people have depression, but not when they are treated with antidepressants for other conditions (e.g., attention-deficit hyperactivity disorder) [79]. The pattern suggests that it is the depression, not the antidepressant, that appears more linked to the mania, as was also the case in the TADS trial (see above).

Venlafaxine—In the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial, one participant out of 83 randomized to receive venlafaxine developed hypomania [31], assessed using a mania screen and the Mania Rating Scale. In the same trial, no participants developed mania among 168 randomized to receive fluoxetine, paroxetine or citalopram and 83 randomized to receive venlafaxine in combination with cognitive behavioral therapy.

The rates reported here for mania as an adverse event during clinical trials may actually underestimate the true risk, as participants with a family history of bipolar disorder were excluded from most of these studies. Had these trials included youths with a higher risk of experiencing mania even in the absence of exposure to antidepressant treatment, rates of mania during SSRI treatment might have been higher. Ironically, there also appears to be a confound, where the studies with stronger designs (randomized, blinded and placebo-controlled trials) may have had less thorough or systematic assessment of manic symptoms, whereas open trials may have been more vigilant to the possibility of manic symptoms. It is again unclear whether SSRI treatment caused the manic/hypomanic symptoms, or whether these may have emerged naturally in the course of an existing mood disorder, but the weight of the evidence appears to favor the Bipolar depression hpothesis more than any of the Iatrogenic hypotheses (ignition, scar or side effect).

Risk versus benefit analysis

The Evidence-Based Medicine framework [28] also provides ways of quantifying the strength of association between antidepressants and mania. These include the relative risk (RR; the ratio of the rates of mania in the antidepressant exposed group, divided by the rate in the nonantidepressant comparison group), the odds ratio (odds of mania in the antidepressant group divided by odds of mania in the comparison group) and the number needed to harm (NNH). The NNH is the reciprocal of the difference in the rates of mania in the antidepressant exposed versus comparison group. Conceptually, the NNH is the number of patients that would need to be exposed to antidepressants before one more on average would develop mania. The NNH has a corresponding measure of the magnitude of beneficial treatment effects, the number needed to treat (NNT) in order for one more patient to have a good outcome. The NNT and NNH can be combined to create a likelihood of help versus harm (LHH; the reciprocals of the NNT divided by the reciprocal of the NNH, so that larger numbers indicate greater probability of benefit).

What would these metrics suggest about the relationship between antidepressants and mania? We focus on fluoxetine as an example, because: first, fluoxetine has the best evidence of efficacy for pediatric depression [6]; second, fluoxetine appears to be associated with somewhat higher rates of mania than other SSRIs [90]; and third, fluoxetine has multiple published RCTs where the rates of mania can be compared with rates in a randomly assigned placebo arm, providing some of the best evidence available on the issue [3,59,83]. Pooling the results of the three RCTs, the rate of mania on fluoxetine was 2.8%, versus a rate of 1.0% on placebo. The RR of mania is 2.8, approaching the range where we should be concerned (RR < 4 is ambiguous if the designs are weak; but for an RCT RR of > 3 would be 'convincing')

[28]. The NNH is 56, meaning that for every 56 youths exposed to fluoxetine, on average one more would develop mania. The NNH estimated separately for each RCT ranged from 24 to 145. On the other hand, fluoxetine appeared efficacious across all three studies, with NNT estimates ranging from 3.8 to 6.5, and a pooled estimate of 4.7. The LHH is 11.8 when all three studies are combined, and ranged from 6 to 22 for the studies separately. Thus, when focusing on the compound with the most evidence for efficacy and also the greatest concern about mania as an adverse event, patients appear roughly 12-times more likely to benefit than to experience mania; and even the worst case scenario is that patients would still be six-times more likely to benefit. Estimating the LHH separately for several studies is one way of conducting a 'sensitivity analysis', or examining the extent to which the LHH estimate changes depending on the starting values. Sensitivity analyses can also include 'what if' scenarios, where the LHH is recalculated using more liberal or conservative estimates of risk, so that the decision-makers can understand the effects of changing assumptions on the final estimates [28].

It is possible to further customize the LHH, adding additional information about individual factors affecting the probability of risk or benefit, as well as incorporating patient preferences. Straus *et al.* provide detailed examples of adding these factors into the equation (see page 139–143 [28]). On average, including patient preferences will typically shift the balance even further in favor of benefit instead of harm. Two major reasons for this are the evidence that depression creates more burden than mania, and has a worse effect on quality of life [91]; and also because depression is the more lethal phase of the illness (including being a major component of mixed states) [44]. It also may be possible to shift the balance further by providing psychoeducation to the family, using careful monitoring to detect mania, and establishing a plan for managing manic symptoms should they emerge. By increasing the knowledge and the external supports available, the risks associated with mania may be more contained. With close monitoring, it is more likely that treatment could be changed during hypomania rather than waiting until full blown mania manifests. At the same time, the irritable mood and aggression frequently associated with pediatric mania are often a chief concern of families and a major treatment target [92], so interventions that increase the risk of disinhibited, aggressive behavior may require more caution.

Limitations

There are several important limitations to keep in mind, both about the state of the literature, and also about this particular review. Decisive studies about the relationship between antidepressants and mania have not been conducted, so it is impossible for a review to draw decisive conclusions. Some limitations of the literature include:

- Most published articles do not satisfy most of the criteria for providing a valid source of information about risk of harm [28]. Case reports are not adequate, unless perhaps they used rechallenge, A–B–A–B designs, but these are clinically not conducted. See Box 1 for a list of the guidelines and other comments on the state of the literature;
- There are large differences in the rates of mania identified across studies and inconsistencies in the size of the findings, making it plausible that methodological issues (such as the Vigilance or False Alarm hypotheses) or the natural course of bipolar disorder (consistent with the Medication as Irrelevant or the Bipolar Depression Hypotheses) explain the findings, instead of one of the proposed iatrogenic mechanisms;
- There are major differences in the operational definition of mania across studies, and equally large differences in how mania is assessed; These make it much more difficult to interpret findings;

- There may be local and historical changes in patterns of diagnosis. The steep increases in the rate of bipolar diagnoses shows that there have been dramatic changes in practice that are independent of changes in actual rate of incidence. Clinicians may become hyper-vigilant to the possibility of mania. Cognitive heuristics and publication bias both will lead to over emphasizing the degree of risk;
- Many chart reviews and clinical trials excluded bipolar youth. We do not know rates of switching for these youth (versus youth with anxiety or MDD that has not yet shown itself to be bipolar) [cf. 76], although the adult literature suggests it could be higher than what we are seeing here. Conversely, studies with youths exposed to antidepressants who did not have a history of depression have consistently found low rates of mania [93–95]. The two competing explanations for this pattern of findings are that assessment of mania in these studies is not sufficiently systematic to be sensitive to instances that actually are occurring (a variant of the Vigilance hypothesis), or that it is previously undiagnosed bipolar disorder that was being treated for depression, and then subsequently manifested its associated manic symptoms (the Bipolar depression hypothesis). The insufficient sensitivity argument is less of a concern given that one of the studies finding no increase in risk was a secondary analysis of longitudinal data from one of the leading investigations of pediatric bipolar disorder [79].

An additional limitation of this review is that it does not attempt to meta-analyze the existing studies, relying instead on qualitative ways of appraising and describing the findings. The literature does not yet seem large enough to support a meaningful meta-analysis, particularly with so few studies reporting adequate information to estimate relative risks.

Conclusions

There has been widespread concern that antidepressants might be associated with mania, both at the level of individual cases and now at the public health level. Medication exposure is one of the potential factors under discussion for the rising rates of pediatric mania in the USA [24]. Practitioners want clear guidance about the risks so that they can avoid the potential harm of triggering manias in patients with depression. It is also unclear whether antidepressants should be in the armamentarium of treatment options for managing pediatric mood disturbance and, if so, for which patients. The available literature is complex and inconsistent, making it difficult to form an educated opinion quickly.

This review attempts to move beyond a ‘box score’ approach of tallying the number of studies finding evidence for antidepressants inducing mania or not. We started by laying out seven different models of how antidepressants could appear to be associated with mania. Three were variations of iatrogenic models, where antidepressants might ignite a pre-existing diathesis for mania, create a new and lingering risk for mania or create manic symptoms as a temporary side effect of the compound. Two of the models pertain to the natural course of the illness: one argues that mania occurs independent of the medication, that antidepressants are irrelevant (or perhaps even slightly protective). The second builds on the Natural course Hypothesis by pointing out that clinicians are most likely to encounter bipolar illness during the depressed phase, that the first phase requiring treatment is also often depression and that earlier age of onset for depression appears to be associated with bipolar disorder. In short, a constellation of factors may be resulting in a substantial portion of pediatric depression actually being on the bipolar spectrum. Ironically, a conservative stance about pediatric bipolar disorder could result in an underestimation of the risk factors and warning signs, leading to an initial underdiagnosis of bipolar disorder that then appears to ‘switch’ to mania as the practitioner follows the patient. The final two models are methodological artifacts that are often called ‘confounds’. Skeptics often raise the possibility that pediatric behavior ‘within the normal limits’ is mistakenly

pathologized. The Vigilance model holds that apparent changes in rates of mania are driven by shifts in the sensitivity of clinical diagnoses.

What becomes clear over the course of the review is that the iatrogenic models are the most provocative and the methodological artifacts are the least likely to command attention. However, the weight of the evidence appears to suggest that some of the least stirring or discussed models may actually have the most support. Conversely, the iatrogenic models have not accumulated strong evidence despite the high level of concern they invite; and the evidence is weakest in the RCTs that have the strongest designs.

On the basis of this review, the conclusion is to proceed with caution. Based on the LHH framework from Evidence-Based Medicine, antidepressants appear to offer a clear net benefit for the average patient. The Evidence-Based Medicine approach also offers practitioners a way of customizing and personalizing clinical decisions, taking into account individual risk factors and preferences. The scales will tip further in favor of antidepressant usage in cases where the depression is severe or refractory, and where the risks of mania can be contained by providing good psychoeducation to the family and deploying careful assessment tools that will be sensitive to the emergence of mania or side effects. In cases where there is a family history of bipolar disorder, or cases with a history of impulsive aggressive behavior, then the balance would shift away from SSRI usage (although the evidence of harm is not much more well-founded for these cases than for mania in general).

Executive summary

Background

- The decisive study to establish the risk of an antidepressant has not been conducted. This would require a double-blinded, placebo-controlled trial with excellent assessment of manic symptoms, including a lifetime history prior to randomization, and a long enough follow-up to capture the majority of subsequent manic events.
- Antidepressant-induced mania in adults is a generally accepted clinical phenomenon, even in the absence of such a decisive study.
- The existing literature regarding pediatric antidepressant usage and mania is almost entirely based on designs prone to bias.

Models of the relationship between antidepressants & mania (& seven potential pitfalls & remedies for practitioners)

- Ignition hypothesis – uncovering a latent diathesis, turning on genes that were already present. Although of great concern, there is little supporting evidence for this from studies with stronger research designs.
- Scar hypothesis – creating a new diathesis in the absence of prior biological risk. This is perhaps the most worrisome hypothesis, and also one of the most speculative, with no direct supporting evidence yet in the literature.
- Side effect hypothesis – temporary deleterious effect of drug, but not a true manifestation of a bipolar illness. This hypothesis appears to be plausible, but the effects appear to be rare in studies with strong designs.
- Vigilance hypothesis – increased monitoring for the illness, but no actual change in risk. This hypothesis is likely to contribute to the high rates of mania observed in open trials, which ironically often have used better monitoring of manic symptoms than many of the blinded, randomized, controlled trials.

- Medication as irrelevant hypothesis – what we are witnessing is the natural course of the bipolar illness, not a response to the treatment. This hypothesis appears consistent with longitudinal data about course of illness and epidemiological data; it can also account for much of the apparently high rate of manic symptoms emerging during the course of treatment for mood disorders.
- False alarms hypothesis – mislabeling juvenile behavior as pathological when it still falls within normal limits; mistaking irritability due to other causes as an indicator of pediatric mania; or alternately, mistaking the return of energy and positive emotions as depression lifts for hypomania. This is also a plausible hypothesis, especially given emerging evidence of large differences in diagnostic formulations for similar symptom presentations across practitioners, clinics and even countries.
- Bipolar depression hypothesis – when treating youths for depression, we are often dealing with the depressed phase of what will prove to be a bipolar illness. This appears to be a likely contributor to the rates of mania noted during treatment of mood, and actually could explain seemingly higher rates in youths than adults because of the possibility that bipolar depression will be the first phase of illness to drive treatment seeking.

Review of the evidence for antidepressants potentially inducing mania

- Case studies of selective serotonin-reuptake inhibitor (SSRI)-induced mania in youths are common, but add little evidence about how patients should be treated. Case studies are biased – ‘youth on antidepressants fails to become manic’ is unlikely to be published.
- Published chart review studies of SSRI-coincident mania generally fail to meet guidelines for demonstrating clear evidence of harm.
- Clinical trials exist for most of the antidepressants used with youths; however, the assessment and reporting of manic symptoms was not rigorous in older studies. This could lead to underestimating absolute rates of mania, but should not bias estimates of relative risk for antidepressants versus placebo.

Risk versus benefit analysis

- Depression is worse than mania in terms of burden on the individual and risk of suicide. The greater risk and burden may tip the scale in favor of continuing to use antidepressants to manage the depression, with close monitoring for mania.
- Fluoxetine has the best current data about treatment efficacy, and also some of the greatest concerns about potential associated mania. Based on three randomized trials, the likelihood of help versus harm (mania) on fluoxetine is more than 11, favoring antidepressant use, before considering patient characteristics or preferences.

Limitations

- Decisive studies have not been carried out. The literature does not support a clear ‘final answer’ about the relationship between antidepressants and mania.

Conclusions

- Proceed with caution. Despite the great concern about the possibility of antidepressants increasing the risk of mania, the studies with the strongest research designs find the smallest evidence of risk.

- Patients on fluoxetine are more than ten-times more likely to benefit than experience mania. Taking patient preferences into account will often tip scales further towards antidepressant usage to manage mood.
- Education about medication and side effects and careful monitoring for mania will further contain risks.

Future perspective

- Personalized approaches to medicine, including genetic and metabolic testing as well as technological improvements in assessment of mood and energy, will soon provide powerful tools to help gauge risk and response to antidepressants as well as other treatment regimens.

Future perspective

There are many ways that the situation will improve over the next 5 to 10 years. The clinical concern that antidepressants might induce mania has raised awareness to the point that future studies using antidepressants may do the systematic assessment of manic symptoms – both lifetime history prior to enrollment, as well as looking for emergence during treatment – needed to decisively address the issue. Improved assessed tools are already available (see [96] for review and discussion about implementation), and if they are adopted more in research and clinical practice there will be immediate improvements in the management of pediatric mood disorder. In the near future, there will be contributions from the personalized medicine vantage too, with improved assessment in terms of genotyping (including identification of individual differences in response to medication) [97], metabolic measures of physiological response to medication, and the use of noninvasive technologies (such as actimetry or cell-phone based life charting) to provide more rapid and objective measures of mood change. Although the issue of antidepressants and mania has been complex and contentious in the past, research is beginning to make contributions to evidence-based treatment, and the pace will accelerate rapidly.

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