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Antidepressants and Psychostimulants in Pediatric Populations:

Is there an Association with Mania?

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Abstract

This article reviews the literature that examines whether exposure to psychostimulants or antidepressants precipitates or exacerbates manic symptoms, or decreases the age at onset of mania in pediatric populations. A PubMed search using relevant key words identified studies targeting five distinct clinical groups: (i) youth without a diagnosis of bipolar disorder (BD) at the time of exposure to psychostimulants; (ii) youth with a diagnosis of BD at the time of exposure to psychostimulants; (iii) youth without a diagnosis of BD at the time of exposure to antidepressants; (iv) youth with a diagnosis of BD at the time of exposure to antidepressants; and (v) youth who develop BD after exposure to these medications.

In patients with attention-deficit hyperactivity disorder (ADHD), the risk for mania was found to be relatively low with the use of psychostimulants. For patients with BD and ADHD, effective mood stabilization is important prior to adding a stimulant. For children with depression and/or anxiety, the risk of antidepressant-induced mania (AIM) was generally low (<2%), but the risk of general 'activation' secondary to a selective serotonin reuptake inhibitor (SSRI) may be greater (2–10%). However, rates of AIM in specialty clinics appear to be much higher. SSRIs may be particularly problematic in specific populations, such as those with some symptoms of mania or a family history of BD, but the precise risk is unknown. There is no clear evidence that stimulants or SSRIs accelerate the natural course of BD development in overall samples, but in individual cases prescribers should proceed cautiously when using these agents in youth already at risk for developing BD, such as those with ADHD and mood dysregulation, a history of prior AIM, a history of psychosis, or a family history of BD.

1. Introduction

The use of psychotropic medications in children and adolescents has risen steadily over the past decade.[1] Psychostimulants have long been used in children with attention-deficit hyperactivity disorder (ADHD)[2–4] and, more recently, antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), have been approved by the US FDA for the treatment of pediatric anxiety disorders and depression.[5,6] However, the advent of effective pharmacotherapy has incited concern that these agents may also precipitate mania in children.

Currently, medication-induced manic episodes do not qualify as a diagnosis of bipolar disorder (BD) by *Diagnostic and Statistical Manual of Mental Disorders (4th edition)*

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[DSM-IV] criteria.[7] Therefore, if a child has a *de novo* manic episode that is clearly associated with the addition or dose increase of a psychostimulant or AD, for example, the child does not meet the criteria for BD. However, if later on the child develops a spontaneous manic episode, then he or she would meet the criteria for BD. Whether this second manic episode would never have occurred without the medication, or whether it would have occurred later without medical intervention, is also the subject of concern. That is, do these agents accelerate the onset to the first manic episode in some children?

The difficulty in answering this question resides in the dilemma that agents that are simultaneously effective for alleviating symptoms of ADHD, depression, and anxiety may also be poorly tolerated with regard to mood stabilization. As such, we are bound to weigh the risks and benefits of these agents. However, the risks of precipitating manic episodes pharmacologically are not clearly known. Here, we attempt to synthesize a rational approach to this dilemma by exploring the relevant studies that have been published on this topic.

This article reviews the literature that examines whether exposure to psychostimulants or antidepressants precipitates or exacerbates manic symptoms, or decreases the age at onset of mania in pediatric populations. Five clinical groups distinguish themselves and warrant individual review: (i) pediatric patients without a diagnosis of BD at the time of exposure to psychostimulants (table I); (ii) pediatric patients with a diagnosis of BD at the time of exposure to psychostimulants (table II); (iii) pediatric patients without a diagnosis of BD at the time of exposure to antidepressants (table III); (iv) pediatric patients with a diagnosis of BD at the time of exposure to antidepressants (table IV); and (v) pediatric patients who develop BD after exposure to these medications (and the issue of decreasing the age at onset of BD) [table V]. We have divided the existing relevant literature into these groups to address two separate questions: (i) how should clinicians pharmacologically treat children with a primary diagnosis other than BD who present with risk factors for BD, such as family history, or symptoms that are subthreshold for BD; and (ii) how should clinicians pharmacologically treat children with a primary diagnosis of BD when they demonstrate co-occurring illness including ADHD, or unremitted depressive symptoms in the context of BD and may benefit from adjunctive treatment with psychostimulants or antidepressants?

To investigate these issues, we performed a PubMed search for all extant articles in English using the terms ‘children’, ‘psychostimulant,’ and ‘mania’; ‘children’, ‘antidepressant,’ and ‘mania’; ‘children’, ‘medication induced,’ and ‘mania’; and ‘children’, ‘bipolar disorder,’ and ‘age at onset’. We then selected the most relevant studies to this topic, and augmented with any studies of which we were aware but that did not appear in our search results. Many of the studies offered mixed results, raising further questions, and therefore offer opportunities for future research. This review maps the development of the current research and examines its strengths and limitations, discusses clinical implications based on these findings, and suggests the next steps in the research agenda.

2. Psychostimulants in Pediatric Patients Without a Diagnosis of Bipolar Disorder (BD)

Some contend that the combination of hyperactivity, impulsivity, distractibility, and emotional lability describes either a subtype of ADHD, ADHD with co-occurring juvenile mania, or a presentation of juvenile mania itself.[9] Nonetheless, in youth who do not meet criteria for BD but clearly at least meet ADHD criteria, a trial of psychostimulants is often the first course of pharmacologic action.

However, a common concern is that psychostimulant treatment may induce mania (stimulant-induced mania [SIM]) in these children. Case reports have described SIM and

psychosis in children with ADHD.[32,33] while these reports contribute to the field by raising clinical questions for further exploration, when making clinical treatment decisions, over-reliance on such vivid clinical vignettes can be problematic. As a result of publication bias, case reports usually describe relatively uncommon significant adverse events, rather than typical outcomes without such events. Coupled with the availability heuristic, which describes a clinician's tendency to estimate the likelihood of something occurring as directly related to how easy it is to imagine,[34,35] concern for SIM may be over-weighted based on these reports.

Fortunately, there are several studies that shed a more empirically-based light on this issue. Four studies have examined the effects of psychostimulants on children with ADHD and some manic symptoms (table I). Two studies specifically examined the potential for a switch from ADHD to BD with exposure to psychostimulants.[9,14] ADHD youth with symptoms of mania in these studies had a more severe illness profile and a greater number of co-morbidities than the subjects without manic symptoms.[8,9,14] In these studies, children with a more severe clinical profile (i.e. ADHD plus mania symptoms) treated with psychostimulants had no differences in adverse effects from children with uncomplicated ADHD, including rebound[8] or worsening of mania.[8–10] In fact, treatment with methylphenidate was associated with reduced symptoms of ADHD and no worsening of mania[8–10] In addition, treatment with psychostimulants over several years, regardless of baseline illness severity, was not a risk factor for the development of BD through the age of 25 years.[9] The second study suggested that treatment with a psychostimulant was protective against the development of BD.[14] Collectively, these findings suggest that psychostimulant exposure is not instrumental in the development of BD. Moreover, symptom severity at the time of presentation may be the primary predictor of psychostimulant treatment, which also does not predict a greater chance of BD outcome.[9]

In the context of co-occurring ADHD and BD, the onset of ADHD may precede the onset of mania in individuals with a prepubertal and early adolescent bipolar I disorder phenotype (PEA-BP-I).[36] This phenomenologic study coupled with the findings from Carlson and Kelly,[8] Carlson et al.,[9] and Galanter et al.[10] suggest the existence of a variant of ADHD that may be a precursor to, or a nascent form of juvenile BD.[37] Psychostimulants appear to be *not* associated with SIM or with the development of BD even in this at-risk population. However, it should be noted that some of these data may have been confounded by clinician hesitancy to prescribe stimulants to children who appeared to be developing manic symptoms.

Furthermore, since treatment with psychostimulants is so common in children, studies of pediatric patients with ADHD and some manic symptoms often suffer from range restriction.[38,39] When the majority of children in a study are treated with psychostimulants, the insufficient variability in the sample limits the magnitude of the observed relationship between psychostimulant use and mania or BD. Remarkably, despite this limitation, the finding from the Tillman and Geller[14] study that psychostimulant exposure is associated with less switching to BD is all the more powerful, as only 6% of the subjects studied had not been exposed to psychostimulants. Therefore, although psychostimulants in individual cases may induce mania or mood dysregulation (such as dysphoria or irritability), they do not commonly result in mania and, in most cases, are helpful in the treatment of ADHD. Further research on subgroups of children who respond in this manner is needed to aid clinicians in deciding in whom to avoid psychostimulant treatment.

3. Psychostimulants in Pediatric Patients with BD

ADHD is highly co-morbid among youth with BD, with rates up to 85% depending on the age of the child.[37] According to expert consensus guidelines, bipolar symptotms should be stabilized first, and if residual symptoms of ADHD exist and impact functioning then an additional medication to treat ADHD should be added.[40] Although considered first-line pharmacotherapy for the treatment of ADHD,[4] psychostimulants are often approached with caution for fear of destabilizing mood and worsening illness prognosis in children with BD.[24,33,41] To address this concern, there have been three prospective trials examining the effects of psychostimulants when added to mood stabilizers in euthymic youth with BD for the treatment of co-morbid ADHD, and one prospective study of atomoxetine (table II).[16,19,21,23]

Three of the four studies demonstrated that the addition of psychostimulants/atomoxetine improved symptoms of ADHD in children with BD.[6,19,21] In all four studies psychostimulants/atomoxetine were added once patients were stabilized on a mood stabilizer for at least 3 weeks. Upon the coadministration of a psychostimulant, 2.5–10% of all patients had an adverse mood or behavioural effect (e.g. mania, hypomania or suicidality), which resolved when the psychostimulant was discontinued. Thus, greater than 90% of subjects remained euthymic, and while there was significant concern for acute mood destabilization, when treatment with the causative agent was withdrawn in those who were affected, mood instability resolved fairly quickly. While significant benefit was seen in the target symptoms of ADHD overall, in one study ADHD symptoms did not significantly change, but depression ratings did improve.[23] In all four studies, the severity of manic symptoms was comparable between subjects treated and not treated with psychostimulants. Additionally, in a retrospective chart review of 59 subjects with BD and ADHD, the addition of psychostimulants to their medication regimen was not found to increase mood destabilization.[27]

Therefore, while, in individual cases, mania, hypomania, and mixed mood states are possible with exposure to psychostimulants in children with BD taking mood stabilizers, the addition of a psychostimulant to treat co-morbid ADHD appears generally beneficial. However, it is clear that despite the presence of a mood stablizer, youth with BD and ADHD may still react to psychostimulants with an increase in manic symptoms, or even mania. Thus, based on the limited number of studies available, our current recommendation would be to stabilize the mood as fully as possible, then to carefully add a psychostimulant in patients with residual ADHD symptoms, while vigilantly monitoring for the emergence of mania or suicidality. The relatively short half-life of psychostimulants aid in the rapid cessation of deleterious effects to the brain. The prompt resolution of symptoms thought to be secondary to psychostimulant treatment in the above four studies would support this approach.

4. Antidepressants in Pediatric Patients Presenting with Depression and/or Anxiety (i.e. Without a Diagnosis of BD)

Antidepressants, especially SSRIs, are used widely to treat depression, dysthymia, and anxiety disorders among children. However, at least 29 published case reports describe pediatric patients with treatment emergent mania (TEM) or hypomania when exposed to SSRIs,[42] also known as antidepressant-induced mania (AIM).[43,44] Pooled together, these studies report hypomanic or manic symptoms that appear any time between 2 weeks and 1 year after initial SSRI exposure.[42] In 21% of such patients represented in these studies, there was a family history of BD. These case reports have raised several questions: (i) what is the link between SSRIs and mania; (ii) does an adverse reaction to SSRIs represent a predisposition to BD; and (iii), if so, who is vulnerable?

It is difficult to interpret the significance of these case reports, given their limited information. For example, manic symptoms following the administration of an antidepressant may represent the natural course of BD after an initial depressive episode. Alternatively, the DSM-IV classifies such mood changes in response to a medication as a substance-induced mood disorder,[7] and is consistent with the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters of TEM.[45] There is also the possibility of a causal relationship between exposure to SSRIs and those with a propensity for BD. However, there are no placebo-controlled trials that explore this potential link in children. The greatest concern for clinicians is the possible scenario where a patient with latent BD develops emerging manic symptoms following treatment with an antidepressant.

Among adults with unipolar and bipolar depression, AIM is an established occurrence with rates cited at 1% and 20–40%, respectively, and there is a greater risk of AIM with exposure to tricyclic antidepressants (TCAs) than with SSRIs.[43,46] No pediatric prospective controlled trials exist to determine if subjects with a history of AIM are at greater risk for spontaneous manic episodes, accelerated episodes of cycling, or earlier age at onset of their first manic episode.

In children without a diagnosis of BD, rates of AIM are best estimated from numerous randomized controlled trials (RCTs) of SSRIs. However, the definition of physical, psychiatric, and behavioural adverse events varies widely across these studies. Furthermore hostility, aggression, and behavioural activation often represent a separate category from TEM. In 2004, in the wake of concern for possible increased risk of suicidal behaviour related to exposure to antidepressants, the FDA reported on ‘treatment emergent hostility or agitation’ following administration of all antidepressants with a combined relative risk of 1.79 (95% CI 1.16, 2.76).[47] The incidence rates of mania were not specifically investigated by the FDA. However, Cheung et al.[48] pooled data from RCTs and case reports, and found that the mean rate of mania was 2% across the seven clinical trials reviewed, with the highest incidence of mania occurring with fluoxetine (6%); for placebo, the incidence was 0–2%. Resolution of symptoms occurred in the majority of cases when the antidepressant dosage was reduced or treatment was discontinued. Similarly, Carlson and Mick[49] reviewed reports of mania and manic-like symptoms from 11 RCTs for anxiety and depression, and found that rates ranged from <5% to 20% but on average were lower with placebo data removed. Of note, none of the RCTs were specifically designed to screen for the development of mania during exposure to an SSRI. Only the Treatment of Adolescents Depression Study (TADS)[50] used a unique measure, the Adolescent Depression Scale Mania Sub-Scale (ADSMS-S), to rate mania-related symptoms at baseline and during treatment.[51] However, as the authors noted, the ADSMS-S is not a validated measure, it lacks inter-rater reliability, and it may have reflected symptoms not attributable to mania, such as inattention associated with depression or ADHD. In spite of this limitation, all four treatment arms of TADS demonstrated a decrease in the ADSMS-S score over 12 weeks, suggesting that in youth with unipolar depression, the risk for AIM is relatively low.

This conclusion is in stark contrast with several other retrospective studies that found much higher rates of AIM in children. Wilens et al.[52] reviewed the charts of 82 children and adolescents receiving SSRIs for either depressive disorders or obsessive-compulsive disorder (OCD), and found that 22% had a psychiatric adverse event, with 6% experiencing manic symptoms, after the administration of SSRIs, with a median time to onset of the psychiatric adverse event of 91 days. The authors did not describe how manic symptoms were defined and, in a table of adverse events elicited, elation, grandiosity, decreased need for sleep, or pressured speech were not listed. There was no significant association between the psychiatric adverse events and any specific psychiatric diagnoses, including BD, age, sex, concurrent medication, dose of SSRI, or specific SSRI used. Specifically regarding

conversion to mania in OCD patients, two retrospective chart reviews, one of OCD patients aged 12–17 years[53] and one of youth with OCD and BD,[54] both reported a 30% switch rate upon exposure to serotonergic agents.

In 2004, Martin et al.[30] analyzed psychiatric and pharmacy data from 87 920 individuals aged 5–29 years seeking mental health services, for rates of manic conversion with and without administration of antidepressants. A new diagnosis of BD was presumed to represent a manic conversion and was found at a rate of 5.4% of patients over a median of 41 weeks of follow-up. Forty-nine percent of youth had been exposed to an SSRI, with a hazard ratio for manic conversion of 2.1; this ratio was 3.7 for other antidepressants, and 3.9 for TCAs. The age group at highest risk for this conversion was 10–14 years, suggesting a developmental factor in the risk for AIM. The relationship between age and manic conversion in this study is discussed further in section 6 (table V). While this study suggested that exposure to antidepressants is a significant risk factor for manic conversion it is unclear if these events represent a true manic switch as no clinical data were reviewed.[26,55]

Finally, Baumer et al.[26] studied a cohort of children with mood symptoms, but not full mania, and at least one parent with BD. The investigators used direct patient interviews regarding retrospective events, supported by medical records, and carefully recorded the presence of manic symptoms within 1 month of antidepressant initiation. Fifty-five percent (12/22) of this high-risk constituency experienced a negative psychiatric reaction to an antidepressant trial, and 36% (8/22) experienced AIM, defined as at least 1 day of mania. As these rates are much higher than those from RCTs previously mentioned in this section, it is possible that this group, at genetic risk for BD, is at higher risk for AIM than the general population of depressed youth. Also, as some patients had other antidepressant exposures without AIM, it would make sense that the rates of AIM were higher than might be expected for a single prospective trial.

Thus, given the higher rates of AIM in retrospective studies of youth in regular clinical care and youth genetically loaded for BD, it is possible that these youth differ substantially from those in the large-scale RCTs of SSRIs. Some of the large RCTs of SSRIs in youth did, in fact, exclude subjects on the basis of a family history of BD.[56,57] This exclusion, taken with the lack of screening for the development of AIM, may explain why rates of AIM were so low in large RCTs of SSRIs in youth. This discrepancy may be another example of how outcomes from large-scale RCTs of psychotropic agents commonly do not reflect outcomes in the general community because of significant differences in the respective populations.

Therefore, how should depressed youth at high risk for BD be treated? In the only study that attempted to prospectively investigate SSRI treatment of this group (table III), Findling and colleagues[25] randomized nine children with major depressive disorder (MDD), with at least one parent with BD, to either open paroxetine monotherapy or paroxetine and divalproex sodium (valproate semisodium) combination therapy. Fifty percent of subjects developed manic symptoms, regardless of adjunctive divalproex treatment. Although small, this study supports the great risk for AIM in this population. Of note, none of the patients pre-emptively started divalproex before the administration of paroxetine, and divalproex serum levels may not have been high enough, as subjects were titrated to a target dose of 50–100 μg/mL. In addition, two children were also treated with the addition of methylphenidate, and developed mania and psychosis, respectively.

There have been a few studies of alternative treatments to target depression in youth with a family history of BD.[25,58,59] In an open-label study of divalproex monotherapy in children with a parent with BD, six of seven subjects with either MDD or dysthymia were considered

responders with no instances of TEM.[60] While quetiapine was found similarly helpful in at-risk populations,[61] lithium was no better than placebo for treating such depressed youth.[58] Further studies with larger sample sizes and multiple treatment arms, including placebo, a mood stabilizer alone, an SSRI alone, and a mood stabilizer plus an SSRI, would help delineate the optimal treatment algorithm for this challenging patient population. Furthermore, as anxiety has been proposed to be an initial presenting condition in a subset of youth who later develop BD,[62–64] more stringent pharmacotherapy studies need to be conducted in that population as well.

In summary, RCTs of SSRIs for unipolar depressed and anxious youth have reported relatively low rates of AIM, although family history data for these cohorts were not included for most of these studies and offspring of BD parents were excluded in some cases.[56,57] Moreover, the low incidence of AIM in RCTs of SSRIs may be due to limited screening for AIM and absence of extensive co-morbidities in the study population. Retrospective case studies collectively report much higher rates of poor outcomes from antidepressant exposure, ranging from 5.4% to 55% for TEM,[24] psychiatric adverse events[52] and AIM.[30,53] Therefore, there appears to be a significant risk of AIM in certain populations, particularly those with familial loading for mood disorders. The search for other markers of AIM have led to investigations that, as detailed in a review, suggest that the serotonin transporter (5-HTT)-linked polymorphic region polymorphism is moderately associated with AIM in patients with BD,[65] although the one pediatric study included in the review did not identify the polymorphism as a risk factor for developing AIM (possibly because of small sample size).[26] Further work in this area may reveal a connection as other genetic markers are identified. Meanwhile, taking a careful history for prior AIM, psychosis, age of onset of depressive symptoms, and family history for mood disorders coupled with close monitoring of ‘red flags’ in response to SSRI treatment, such as changes in sleep, irritability, and psychosis, will help clinicians identify those at risk for AIM.[66,67]

5. Antidepressants in Pediatric Patients with BD

In the adult literature it has been fairly well established that a switch in polarity can occur in 24–44% of BD patients treated with antidepressants.[68,69] In addition to mania induction, antidepressants have been associated with mood destabilization and a 4-fold increase in rapid cycling in adults exposed to TCAs.[70,71] Therefore, the Expert Consensus Guidelines for adults with bipolar depression recommend, first, optimization of the mood stabilizer regimen, followed by the addition of either a second mood stabilizer or, when necessary, treatment with an antidepressant for a limited time because of the risk for mood destabilization.[72]

In children, the AACAP practice parameters regard SSRIs as useful for treating bipolar depression when co-administered with at least one mood stabilizer.[45] However, caution is advised as antidepressants may destabilize mood or precipitate a manic episode. Manic symptoms associated with an SSRI may represent a substance-induced mood disorder, the unmasking of a bipolar spectrum disorder, or disinhibition secondary to the agent. This caveat about secondary mania underscores the clinical dilemma faced in treating bipolar depression and the questions that remain unanswered about the pathophysiology of AIM compared with incidents of spontaneous mania.[46]

Our limited understanding of the neurobiologic complexity of switches in mood polarity breeds genuine uncertainty about how to treat the depressive phase of BD.[73] The following notable studies have investigated the effect of antidepressants on children with existing diagnoses of BD (table IV).

In 2000, Biederman et al.[27] completed a chart review of 792 consecutive patients who were treated in their outpatient psychopharmacology clinic, and identified 59 subjects with BD at the time of presentation for treatment. Among this group of patients with BD, a Clinical Global Impression (CGI) rating scale[17] was applied retrospectively to each clinic note from each visit to gauge illness severity and symptom profile at baseline. Types and numbers of medications were also inventoried to track the change in symptoms as a result of treatment intervention. Findings showed that depressive symptoms were 6.7 times as likely to improve with serotonin-specific antidepressants compared with TCAs, psychostimulants, mood stabilizers, and typical antipyschotics that were not significantly associated with an improvement in depressive symptoms. However, manic symptoms were 3-fold more likely to develop in those who received a serotonin-specific antidepressant than in those subjects who had not. In general, mood stabilizers improved manic symptoms but had no effect on the symptoms of depression. Conversely, serotonin-specific antidepressants did not interfere with the antimanic effects of mood stabilizers.

Several limitations of this informative study warrant mention. First, few children in this group were treated with mood stabilizers, thereby limiting information about the potential protective effect of mood stabilizers when co-administered with antidepressants. Second, if there had been random assignment for treatment with a particular class of drug, then we could more confidently infer that drug class was directly related to outcome, i.e. change in mood symptoms. Because the participants were not randomly assigned, the apparent relationship between the treatment and the outcome may reflect an unmeasured confounding variable such as characteristics of individuals including co-morbidities, severity of illness, family history of mood disorder, or possible history of AIM. Finally, Biederman et al.[27] recognized that second-generation antipsychotics were rarely prescribed at the time by treating physicians, therefore these important data are absent.

A later study by Faedda[24] indicated a higher rate of TEM among youth with BD and a risk of harm, with 4–9% of children demonstrating suicidal, homicidal, or psychotic behaviour. Of 82 subjects with DSM-IV criteria for BD of modified duration, 57 patients were exposed to a mood-elevating agent and 33 (58%) of these patients experienced TEM. Forty-four percent had been exposed to antidepressants and 18% to psychostimulants, with a median latency for all TEM of 14 days. The risk of TEM by drug class for antidepressants and psychostimulants was 76% and 24%, respectively.

These high rates raise concern about how to address depression, or other illnesses commonly treated with SSRIs, such as OCD, in the setting of co-morbid BD. The patients in the Faedda study[24] (table III) were selected from a mood disorder clinic and may represent children with unusually severe illness and who are, therefore, prone to rapid mood cycling.[74] The authors stated that the “increased cycling rates among the drug-exposed patients was confounded by high prevalence of rapid-cycling, and short exposures to mood-elevating agents”.[24] One could infer that the addition of a mood-elevating agent originally occurred because the patient was mood unstable, i.e. experiencing depression, and that the observed ‘response’ was the result of the natural course of the illness cycling from a depressed to manic state and not TEM. In addition, when the offending medication was discontinued, symptoms usually resolved within 2 weeks. However, this change upon discontinuation only potentially represents a causal relationship to the drug. Discontinuation of medication and return to baseline clinical state could suggest a predilection for a substance-induced mood disorder or a natural progression of the illness, or even a regression to the mean.[75] Finally, as for the study by Biederman et al.,[27] it is unclear how many children were taking mood stabilizers when mood-elevating agents were added.

In another similar study that examined only the addition of antidepressants and not psychostimulants, no specific investigation was made as to whether manic switch rates were lower among those on concurrent mood stabilizer treatment.[54] Among a group of pediatric patients with BD and OCD requiring treatment with high doses of SSRIs or TCAs for remission of OCD symptoms, 30% of the patients "had manic symptoms soon after antidepressant treatment," and no mood stabilizer was found to have an anti-OCD effect.

Baumer et al.[26] investigated the frequency and risk factors for AIM among bipolar youth with at least one parent with BD, distinguishing between a general negative psychiatric reaction to an SSRI and AIM. Importantly, mood states prior to exposure to an SSRI were assessed retrospectively so that spontaneous mood changes/cycling could be differentiated from changes related to medication administration. Of the 52 children studied, 50% experienced AIM; 69% of these children had BD I or II, and 31 % had subsyndromal illness (bipolar disorder, not otherwise specified). Among this unique cohort familially loaded for BD, risk factors associated with AIM included the presence of co-morbidities and a diagnosis of BD I.

In contrast to these studies, in a prospective follow-up of 89 children with BD, Geller et al.[76] reported that neither antidepressants used in 29% of subjects nor psychostimulants used in 60% of subjects predicted recovery from or relapse to mania. For relapse or recovery from mania, a patient needed to be symptom-free for 2 weeks. This long duration may have excluded patients who developed mania but, on the other hand, excluded those with transient TEM.

SSRIs have not been studied systematically for bipolar depression in youth. As they may cause AIM or confer a risk for worsening of illness course in such youth, an effort has been made to find alternative treatments. In the only placebo-controlled study of a psychotropic agent for the treatment of pediatric bipolar depression, 32 adolescents with depression associated with BD I were randomized to 8 weeks of double-blind treatment with either quetiapine or placebo.[59] The investigators found no significant difference in response rates between treatment groups (both >60%). In open studies, both lamotrigine and lithium have been found efficacious in treating adolescents with bipolar depression.[77,78]

We might speculate from the studies reviewed in this section that children with BD who are not receiving mood stabilizing agents may be at a higher risk for AIM[24,26,27] than those with concurrent mood stabilizer treatment, but to date there are no prospective studies that specifically compare the effects of antidepressants and placebo when added to an existing mood stabilizer in bipolar depressed youth. We could also speculate that antidepressants with shorter half-lives may be 'safer' to use in youth with or at risk for BD, in that the central effects could be stopped sooner and patients could return to baseline quicker, but again there are no data to support this supposition. Therefore, it is clear that additional studies are needed on how best to treat this subset of patients who require treatment with serotonergic agents for depression or anxiety disorders, and who are simultaneously vulnerable to mood destabilization.

6. Medication Exposure and the Age at Onset of BD

Other than directly causing mania, there is growing concern that psychostimulants and antidepressants may accelerate or cause an earlier onset of BD, leading to mania at an earlier age than otherwise would have occurred, if at all. Some postulate that the high rate of pediatric BD in the US is related to the frequent use of antidepressants and stimulants in youth.[79] Others propose that the offspring of parents with an earlier age at onset of psychiatric symptoms have been shown to have more severe illness, suggesting some type of genetic anticipation.[80] Other studies have established that a significant number of

prepubertal children with early onset unipolar depression later develop BD.[81,82] Thereby, several theories have been proposed regarding factors that may influence the age at onset of BD, but there is little empirical evidence to predict the age at onset of BD for each specific individual. The following research focuses on the relationship between the age at onset of BD and prior medication exposure through retrospective studies based on patient and family recollection (table V).

The presence of ADHD may be associated with the subsequent development of BD independent of stimulant exposure, raising the question of whether stimulants are a precipitant of BD independently of co-morbid ADHD.[9,14] Adults with BD and a history of ADHD diagnosed in childhood reported an earlier age at onset of their bipolar symptoms (11.3 years) than those without ADHD (15.6 years).[80] In these cases, stimulants may have been administered to patients with yet undiagnosed BD that presented as ADHD with concurrent mood symptoms; namely, the drug may not have accelerated the age at onset of BD as the illness may have already been present. As mentioned in section 2, Tillman and Geller[14] followed 81 youths with ADHD for up to 6 years, of whom 28.5% developed BD. When comparing those who were treated with and without stimulants, stimulant exposure was not a factor for the development of BD. Indeed, treatment with a stimulant was associated with *not* developing BD, whereas significant predictors of manic switching included a more severe baseline score on the Children's Global Assessment Scale (CGAS),[15] paternal recurrent MDD, and *less* stimulant use. Bipolar I disorder in first-degree relatives and exposure to antidepressants were not predictive of manic switch (table I).

By contrast, DelBello et al.[83] found that prior exposure to stimulants in 34 adolescents hospitalized for mania lowered the age at onset of BD, based on the theory that exposure to increased dopaminergic activity may prime the neuropathophysiology of mania. Moreover, independent of a diagnosis of ADHD, they proposed a causal relationship between stimulant exposure and an earlier age at onset of BD by way of direct precipitation of affective episodes. This relatively small study based on parent and child recollection did not measure illness severity or capture information about family history, which may have further delineated the study group as a subpopulation of patients particularly vulnerable to developing BD. The conclusion that stimulants accelerate the illness course by decreasing the age at onset and precipitating mania are contrary to those of several other studies, which determined that stimulants either do not cause harm or in fact improve symptoms of mania,[8–10,27] or were protective against developing BD.[14]

Many children of parents with BD who already have ADHD with mood symptoms and/or MDD may present with a prodrome, which then progresses towards full BD.[76,80] These children, discussed in section 2 as having a potentially higher risk for AIM, might also be considered more vulnerable to an earlier age at onset of BD when exposed to mood-elevating agents.[25,26,31] To address this possibility, Chang et al.[31] examined the effect of psychotropic medication exposure on the age at onset of BD in 106 children with either BD I or II (n = 63) or subsyndromal symptoms of BD (n = 43) and one bipolar parent. Unlike other studies,[24,30] this study marked the onset of BD by the first manic or hypomanic episode that was clearly not linked to TEM, thereby eliminating confusion with SIM or AIM. Antidepressant and stimulant exposure before the onset of spontaneous mania were not correlated with an earlier age at onset of BD, whereas mood stabilizer exposure was associated with a *later* age at onset of BD. The authors concluded that the prophylactic administration of a mood stabilizer prior to the first manic episode in at-risk youth may have protective effects and warrants further verification. Conversely, SSRIs and stimulants do not appear to have significant effects on age at onset of BD.

Finally, in a review of 79 consecutive hospital admissions, antidepressant exposure (but not stimulant exposure) was associated with an earlier age at onset of BD.[84] The age at onset of BD was discernable in only 24 charts, no structured interview was used for diagnostic purposes, and the definition of BD onset was not clearly stated. The authors mention the lack of family history included in the charts reviewed, so speculation about high-risk subgroups was, therefore, impossible. The authors furthermore suggested that because the average duration of treatment before the bipolar diagnosis for antidepressants (6.7 ± 8.22 months) and stimulants (55.5 + 20.42 months) differed so significantly, antidepressants are associated with an earlier age at onset of mania than stimulants. As they point out, this finding is open to several interpretations, including that either stimulants are protective of BD onset, BD more often presents with depression rather than symptoms of ADHD, or antidepressants are indeed a risk factor of earlier age at onset of BD while stimulants are of lesser concern for developing BD at an earlier age compared with no medication exposure. Finally, children treated with a mood stabilizer and antidepressants had a later age at onset of BD, suggesting that mood stabilizers had a protective effect.

Several other studies have demonstrated that antidepressants do not necessarily accelerate BD onset in youth with mood disorders.[76,83,85] In a high-risk group of youth with MDD with psychosis (MDD-P), 13% of patients developed mania or hypomania within 2 years.[83] MDD-P patients who were treated with antidepressants were 4-fold less likely to develop mania (BD I) or hypomania (BD II) than those who were not treated with antidepressants, after controlling for site differences. Additionally, Pagano et al.[85] examined antidepressant and psychostimulant use pre- and post-BD diagnosis to look for patterns related to the age at onset and clinical presentation at the time of illness. In this retrospective case series of 267 BD I youth, there was no association found between initial psychostimulant and antidepressant use, and the onset of BD I or related symptoms. Notably, children treated with antidepressants prior to BD diagnosis had lower Young Mania Rating Scale (YMRS) scores, although only 3% of those in the study fell into this category.[18]

According to the kindling hypothesis, any type of intervention, whether pharmacologic or psychosocial, that would acutely reduce mood symptoms and associated stress could then diminish the likelihood, or delay the onset, of fully expressed future episodes of a mood disorder.[86] Therefore, if antidepressants are helpful for acute symptoms they could be protective,[27,83] but if they are not,[24,26,27] then they could worsen the disease process. It may be that at some point in neurodevelopment, in the ‘right’ children, SSRIs and even stimulants may be beneficial in supporting normal neuronal development and decreasing symptoms of anxiety/depression/ADHD, which allows for normal and healthy psychosocial functioning, increased self esteem, and decreased negative Stressors. This would then lead to healthier brain development and less likelihood of BD development. However, at some point during brain development, and also in the ‘wrong’ child, these agents may actually be deleterious, paving the way for a manic episode that then leads the brain (via kindling) to be more susceptible to mood episodes and *de novo* mania in the future. Thus, the story might be more complex than simply that SSRIs and stimulants are either ‘good’ or ‘bad’.

7. Discussion and Conclusions

Psychostimulants have had a long track record of safety and efficacy in children with ADHD.[4] Thus, it appears that while individual children may react to stimulant treatment with mania and/or psychosis, the risks are small. Nonetheless, parents and patients should be educated about this risk so prompt action can be taken and the medication stopped. While it might appear that risk may be heightened in a subpopulation of children with ‘complex’ ADHD, punctuated by significant mood symptoms that represent a possible prodrome of BD, the data do not support this concern.[9,27,87] There is similar concern in children with

ADHD who have a strong family history of BD.[88] Even within these subgroups, individuals may respond well to stimulants, although caution and careful monitoring is recommended. Indeed, treatment with stimulants may even be somewhat protective against the development of BD.[9,14] Treating impulsivity, inattention, and hyperactivity may promote healthy psychosocial and academic development, thereby minimizing Stressors and supporting self esteem, and thus decreasing the likelihood of progression towards a full mood disorder. The use of stimulants not only as treatment for ADHD but also as prophylaxis for the development of mania in some children requires an experienced clinician who is vigilant of the potential for adverse outcomes. Understanding of the ethical issues regarding informed consent, assent, and refusal, as well as parental and patient psychoeducation are essential.[89,90]

In children with an established diagnosis of BD, psychostimulants are frequently used to treat co-morbid ADHD. Overall, there is still a small risk for mood destabilization, and mania, with adjunctive stimulant treatment. Thus, it appears that it is prudent to maximize mood stabilization and ensure euthymia before adding a stimulant to the medication regimen of such children. Again, careful monitoring is needed to identify any worsening of mood after stimulant treatment begins. In addition, atomoxetine may be a useful option if stimulants are ineffective or problematic,[21] and the effect size of the open-label study reviewed in this article was similar to the response in a larger RCT of subjects with ADHD.[91] There is still no data on the adjunctive use of other FDA-approved treatments for ADHD, such as guanfacine or clonidine, or non-FDA-approved pharmacotherapy, such as modafinil or bupropion.

For children presenting with symptoms of depression and/or anxiety, the risk of AIM is generally low (approximately 2% in one pooled study),[92] but the risk of general ‘activation’ secondary to an SSRI may be greater (2–10%).[93] SSRIs appear to be particularly problematic in specific populations, such as those with some symptoms of mania or a family history of BD, but the precise risk is unknown. However, it is known that approximately 20% of youth with MDD develop manic episodes by adulthood.[67,94–96] Consistently reported risk factors for developing BD among depressed youth have been rapid onset, psychomotor retardation, psychotic features, a family history of unipolar depression or BD, and a history of AIM.[45] Thus, although it is not clear that by triggering mania psychotropics can accelerate or cause the development of BD, caution should still be used when considering the use of SSRIs in youth who are already at high risk for developing BD.

For youth diagnosed with BD and experiencing depressive episodes, SSRIs may improve depression but can destabilize mood in the form of AIM.[26,27] There has been no investigation of whether SSRIs can induce rapid cycling in children, although this has been demonstrated in adults.[44] In addition to AIM, an increased risk of suicidal ideation and behaviour has been identified in as many as 25% of pediatric BD patients, which far exceeds the 4% cited with SSRIs in the general pediatric population.[24,26,47] Thus, the addition of an SSRI to target depression should likely be done only after a mood stabilizer has been administered. Alternative treatment options for BD depression in youth include lamotrigine and lithium, although placebo-controlled trials have not yet been performed for these agents.[97] Unfortunately, in the only placebo-controlled study of an agent for adolescent bipolar depression, quetiapine was not more effective than placebo.[59] As there were high rates of response (>60%) in both groups, psychosocial interventions should be considered as adolescents with bipolar depression may be particularly responsive to psychotherapy.[98]

The issue of stimulants or antidepressants accelerating the natural course or even causing BD is complex. Currently, there are no data that clearly address this question, and the data

that are available are somewhat contradictory. At this point it appears prudent to use these agents with caution in populations at high risk for mania. Prospective, controlled studies of these agents in at-risk populations are needed to shed light on this important, but difficult to study, question.

Investing time in a thorough assessment and reassessment over time can clarify diagnosis and prevent adverse events by screening for risk factors associated with TEM. Special attention should be applied to those youth with co-morbidities, a positive family history of BD, an early age of onset of illness, psychosis, or prior history of AIM/SIM. Clinicians should continually reassess their working diagnoses and treatment planning rationale, and invest in systematic monitoring of mood, anxiety, sleep changes, and thoughts or behaviours of self-harm using validated rating scales such as the Children's Depression Rating Scale (CDRS), YMRS, Multi-dimensional Anxiety Scale for Children (MASC),[99] and the Columbia-Suicide Severity Rating Scale (C-SSRS)[100] during the course of treatment (with or without medication).

Several special considerations with treatment include the stopping and starting of antidepressants in the setting of TEM. The abrupt discontinuation of an SSRI after established treatment, even with a concurrent mood stabilizer, may result in mania.[101] All antidepressant treatments should be judiciously tapered unless they are clearly causing dangerous behavioural symptoms, such as full mania. However, there is no evidence base on how to treat youth with TEM. Those meeting full criteria for mania with impairing symptoms should probably have the SSRI discontinued and a mood stabilizer started. For those with mild symptoms, whether to decrease the dose of the SSRI and titrate more slowly or stop the SSRI completely and monitor is not known. Lastly, if mania resolves, do we again challenge with another SSRI or do we need to use a mood stabilizer? There are many children with depression, with and without a family history of affective disorders, who develop TEM on the first SSRI and not on the second. Does that first trial increase the risk for developing BD? Prospective studies to address these management and risk assessment questions need to be conducted to identify who is at highest risk for AIM and SIM and what to do when it occurs.

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Table I

Pediatric studies examining the effect of psychostimulants in patients (pts) with attention-deficit hyperactivity disorder (ADHD) [i.e. without a diagnosis of bipolar disorder (BD)]

Study, y	Objective and population	Method	Results	Conclusions	Limitations
Carlson and Kelly,[8] 1998	Determine response to treatment of mania with a stimulant (drug and dose unspecified) Inpatients aged 5–12 y with ADHD and manic (n = 29) and non-manic (n = 19) symptoms not meeting criteria for BD	p, 1-wk trial with PL followed by a 2-wk trial with stimulant Blind ratings from teacher and nurse	Children with mania symptoms had more severe illness Improved teacher and nurse ratings with stimulant treatment No greater AEs among pts with manic symptoms when treated with stimulants vs PL No worse outcomes after medication wore off between manic and non-manic children Depression and anxiety ratings did not improve for either group	Symptoms of mania were markers of more severe illness regardless of diagnosis. Exposure to stimulants did not negatively impact children with symptoms of mania. Both groups improved from treatment with stimulants	A diagnosis of BD was not formally assessed by structured clinical interview
Carlson et al.,[9] 2000[a]	Examine long-term effects of MPH exposure in boys at risk for BD, and examine if these subjects are at greater risk for adult mania spectrum disorders as a result of exposure to MPH 75 boys aged 4–12 y followed up between ages 21 and 23 y to assess adult diagnosis	rt, longitudinal, all subjects treated with MPH, diagnoses made at the time using DSM-II were 'translated' into DSM-IV 'emulated' diagnoses using blind raters reviewing the medical record Subjects were placed into high (n = 17; MAX) and low (n = 58; MIN) illness-severity categories	Duration, dosing, side effects, and response to medication in the MAX and MIN group were similar 13 were diagnosed with a mania spectrum disorder as an adult; an equal percentage of these were from the MAX and MIN groups There was no variance between MAX and MIN groups in the degree or quality of response to MPH Both groups showed a significant positive improvement in ADHD symptoms	Stimulant use in children with ADHD was not a risk factor or predictor of adult BD. No differential response to stimulants in boys with or at risk for childhood mania vs those without childhood mania. Stimulant use in children with co-morbidities who have or may be developing BD did not precipitate or exacerbate mania	Structured clinical interviews were not used to determine diagnoses. Follow-up was rt
Galanter et al.,[10] 2003	Examine how children with ADHD and some manic symptoms not meeting BD criteria respond to treatment with MPH Subset of 270 subjects aged 7–9 y from the MTA study[11] receiving 1 mo MPH titration	rt, 1-mo duration Two 'mania proxies' were constructed to retrospectively measure manic symptoms using CBCL[12] and DISC[13]	11.9% were manic by CBCL, 10.7% were manic by DISC, 2.6% were manic by both All subjects from both groups responded similarly to MPH Higher doses of MPH were inversely proportional to ratings of crabbiness and worry	Subjects with ADHD and manic symptoms responded well to MPH with no increase in AEs compared with subjects with ADHD and no manic symptoms. MPH treatment was associated with fewer mania symptoms	Short duration. MPH titration schedule did not reflect real-world escalation of dose. The original MTA study was not designed to examine ADHD and mania symptoms Proxy measures used were not validated for pediatric ADHD and mania
Tillman and Geller,[14] 2006[a]	Examine rate, risk, and predictors of switch from ADHD to PEA-BP-I through a 6-y follow-up assessment Youths aged 7–16 y with ADHD (n = 81) with CGAS[15] score <60 vs controls (n = 94) Subjects with a history of	p, baseline, 2-, 4- and 6-y follow-up ratings. Raters were blinded to diagnosis	28.5% of ADHD subjects developed PEA-BP-I or -II, 9.9% of ADHD subjects developed PEA-BP-II, 2.1% of healthy controls developed PEA-BP-I. 83.3% of switchers to PEA-BP-I were treated with stimulants, 98.1% of non-switchers to PEA-BP-I were treated with stimulants. No specific baseline manic-like	PEA-BP-I is a validated diagnosis with unique symptoms not overlapping with other diagnoses. ADHD subjects on stimulants were less likely to switch to PEA-BP-I. Antidepressant exposure was not associated with	Skewed for Caucasian ethnicity and high social economic status. High rate of stimulant treatment among all subjects

Study, y	Objective and population	Method	Results	Conclusions	Limitations
	BD or MDD were excluded		symptoms among ADHD subjects were significant in predicting switch	developing BD. Three predictors of switch from ADHD to PEA-BP-I were lower baseline CGAS; father with recurrent MDD rather than a family history of BD; and treatment without a stimulant	

[a]This study is relevant to sections 2 and 6 of the main text.

AEs = adverse events; **CBCL** = Child Behavior Checklist; **CGAS** = Children's Global Assessment Scale; **DISC** = Diagnostic Interview Schedule for Children; **DSM-II** = Diagnostic and Statistical Manual of Mental Disorders, 2nd edition; **DSM-IV** = DSM, 4th edition; **MAX** = maximum; **MDD** = major depressive disorder; **MIN** = minimum; **MPH** = methylphenidate; **MTA** = Multimodal Treatment of Children with ADHD; **p** = prospective; **PEA-BP-I** = pre-pubertal and early adolescent bipolar I disorder; **PEA-BP-II** = PEA-BP II disorder; **PL** = placebo; **rt** = retrospective.

Table II

Pediatric studies examining the effect of psychostimulants (and atomoxetine) in patients (pts) with bipolar disorder (BD)

Study, y	Objective and population	Method	Results	Conclusions	Limitations
Scheffer et al.,[16] 2005	Examine, in a 3-phase study, if the addition of MAS was a safe and effective treatment of ADHD symptoms compared with PL in youth aged 6–17 y with BD I (n = 31) or II (n = 9)	In phase 1, youth were treated with 8 wk of DVPX for resolution of manic symptoms. In phase 2, DVPX responders (n = 32) were then treated in a p, r, db, pc, 4-wk, co design for 2 wk with MAS 5 mg bid or PL, then 2-wk, co to the other group. In phase 3, youth (n = 23) completed a 12–wk, open-label, follow-up with DVPX and MAS Clinical evaluations occurred monthly The CGI[17] rating scale was the main outcome measure for assessing change from baseline ADHD symptoms	80% treated with DVPX alone had 50% reduction in YMRS[18] scores YMRS ratings were no different for either group CGI was greater for those taking MAS than with PL No carryover effect from co sequence One subject experienced mania with coadministration of MAS and DVPX. Symptoms resolved with discontinuation of MAS 50% of pts in the 12-wk, open-label follow-up required increased doses of MAS to maintain ADHD symptom control	DVPX was effective in treating mania, although ineffective in treating co-morbid ADHD. Adding MAS to DVPX was safe, tolerable and effective for symptoms of ADHD in BD youth. Treatment with MAS did not improve or worsen mania symptoms	Stabilization with DVPX was open-label. MAS dosing was conservative at 5 mg bid. A higher dose of MAS may have further reduced ADHD symptoms or may have resulted in more manic symptoms. Long-term outcome beyond 12 wk of follow-up unknown
Findling et al.[19] 2007	Examine short-term efficacy of MPH in euthymic youth with ADHD and BD 24 youth aged 5–17 y 16 youth completed the study Subjects met criteria for both ADHD and BD I or II, or NOS	p, r, db, pc, 4-wk, co. Every pt underwent randomly assigned dosing sequences composed of 1 wk each of PL; MPH 5 mg bid; MPH 10 mg bid; MPH 15 mg bid The best dose wk was determined (after unblinding) using a parent ADHD rating scale and report of AEs Mood stabilizers utilized included DVPX + lithium (n = 12); DVPX alone (n = 3); and lithium alone (n = 1)	Significant difference between PL and 'best dose' on ADHD scales. No significant difference between PL and 'best dose' on CDRS-R;[20] and YMRS No difference between dosing strengths	MPH may be a safe and effective treatment for co-morbid ADHD in youth treated with DVPX, lithium or DVPX + lithium. Adjunctive MPH treatment did not affect mood stability. MPH was superior to PL on the total score for parent completed ADHD-RS-IV rating scales. Higher doses of MPH were not more efficacious	Small sample size, short duration. MPH was immediate release with bid dosing; therefore, no information about effects of long-acting MPH is available. Clonidine in some pts may have confounded results
Chang et al.,[21] 2009	Examine if atomoxetine is effective for treating co-morbid ADHD in euthymic youth with BD I or II Youth aged 6–17 y (n = 12 enrolled; n = 10 completed) Euthymia was defined by 3 consecutive wk of no hypomania, mania, mixed or depressive episodes	8-wk open-label ITT analysis Atomoxetine mean final dose of 59.2 mg/d Evaluations were performed weekly Response = 25% reduction in ADHD-RS-IV,[22] remission = 40% reduction in ADHD-RS-IV symptoms Mood stabilizers utilized included typicals (n = 8), anticonvulsants (n = 9), and lithium (n = 2)	67% responders, 50% remitters, 92% with reduction in ADHD-RS-IV. No change in YMRS or CDRS. No subjects became manic or mixed, one discontinued in wk 4 because of hypomania, one discontinued in wk 2 because of persistent suicidal ideation	Atomoxetine is effective in treating ADHD in youth with BD receiving a mood stabilizer. Moderate effect size of 0.73	Open-label study, small sample size Unclear if symptomatic worsening (n = 2) coincided or correlated with administration of atomoxetine
Zeni et al.,[23] 2009	Examine if adjunctive treatment with MPH was safe and effective for	4-wk co trial: 2 wk with MPH or PL, then switch to the other group for 2 wk	No significant difference in ADHD or mania symptoms when MPH was added. Significant decrease in	MPH did not improve ADHD symptoms but did improve self-report	Small sample size. Challenges comparing results as this study

Study, y	Objective and population	Method	Results	Conclusions	Limitations
	treatment of ADHD symptoms compared with PL in euthymic youth with BD I or II treated with ARI Youth aged 8–17 y (n = 16 enrolled; n = 14 completed)	ARI dose range 5–20 mg/d, mean dose of 12.81 mg/d MPH was administered bid: first wk 15 mg total/d; second wk 35 mg total/d Weekly assessments using rating scales to measure changes in symptoms of ADHD and mood as well as overall clinical improvement	depressive symptoms was noted according to secondary self-report. One subject discontinued because of onset of mixed mood state with manic features	of depressive symptoms. MPH added to a mood stabilizer may be helpful in treating depressive symptoms in BD	used a mixed-effects model analysis unlike similar studies. Short duration

ADHD = attention-deficit hyperactivity disorder; **ADHD-RS-IV** = ADHD-rating scale-IV; **AEs** = adverse events; **ARI** = aripiprazole; **bid** = twice daily; **CDRS** = Children's Depression Rating Scale; **CDRS-R** = CDRS-Revised; **CGI** = Clinical Global Improvement; **co** = crossover; **db** = double-blind; **DVPX** = divalproex semisodium; **ITT** = intent to treat; **MAS** = mixed amphetamine salts; **MPH** = methylphenidate; **NOS** = not otherwise specified; **p** = prospective; **pc** = placebo-controlled; **PL** = placebo; **r** = randomized; **YMRS** = Young Mania Rating Scale.

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Table III

Pediatric studies examining the effect of antidepressants (ADs) in patients (pts) with depression and/or anxiety (i.e. without a diagnosis of bipolar disorder [BD])

Study, y	Objective and population	Method	Results	Conclusions	Limitations
Faedda,[24] 2004[a,b]	Examine if children exposed to mood-elevating agents develop TEM and examine predictors of TEM 82 subjects (mean age 10.6 y) with DSM-IV criteria for BD, with modified duration, selected from chart review. 83% with BD prior to TEM. 17% given BD diagnosis following TEM	rt. Records were rated for completeness. TEM was diagnosed if all four criteria were met: mixed or manic episode after a mood-elevating agent; TEM within days of exposure to new agent or dose increase; >4 of 13 key symptoms being newly present or worsening; and discontinuation of the suspected agent and/or additional need for treatment with antimanic drugs	69% had received a mood-elevating agent; 58% of these met criteria for TEM TEM latency within median of 14 d TEM in 43.8% with ADs; 48.7% with SSRIs; and 18% with stimulants Risk by drug class associated with TEM: ADs 76%, and stimulants 24% 4–9% exposed to drug had suicidal, homicidal, or psychotic behaviour	TEM was associated with early-onset anxiety; exposure to mood-elevating agent; and female sex. TEM was not associated with family history, adoption, educational status, age at onset of manic symptoms, and current age. Resolution of TEM was associated with removal of the agent in most cases	Sample was from a specialty clinic with over-representation of more severe cases. Spontaneous rapid cycling in juvenile BD may confound findings that mood changes were related to drug-elevating agents. Reports of TEM and adverse response are based on an rt parental report made prior to referral to the specialty clinic
Findling et al.,[25] 2008	Examine response to treatment with AD vs AD with MS for children who present with MDD with at least one parent with BD Nine children (aged 7–16 y) with MDD CDRS >40	r, p. Subjects either received paroxetine monotherapy or paroxetine-DVPX. Paroxetine monotherapy started at 10 mg/d and could be titrated up as necessary. DVPX was adjusted to serum levels between 50 and 100 μg/mL. Pts with residual ADHD symptoms who were euthymic could be treated with a stimulant	Most subjects had only temporary relief of depressive symptoms. ≥50% had hypomania, mania or suicidality when treated with paroxetine. Two of five on combo therapy developed mania. Study was discontinued because of poor outcomes	Neither treatment was effective in treating depressive symptoms. Pts were followed for an average of 21 wk. Children deteriorated when paroxetine was lowered or missed, suggesting treatment should last >6 mo	Small sample size. No treatment arm with MS monotherapy. Study was open-label

[a] Examined youth with and without BD as well as exposure to ADs and psychostimulants.

[b] This study is relevant to sections 3, 4, and 5 of the main text.

ADHD = attention-deficit hyperactivity disorder; **CDRS** = Children's Depression Rating Scale; **combo** = combination; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **DVPX** = divalproex semisodium; **MDD** = major depressive disorder; **MS** = mood stabilizer; **p** = prospective; **r** = randomized; **rt** = retrospective; **SSRIs** = selective serotonin reuptake inhibitor; **TEM** = treatment-emergent mania.

Table IV

Pediatric studies examining the effect of antidepressants (ADs) in patients (pts) with a diagnosis of bipolar disorder (BD)

Study, y	Objective and population	Method and measures	Results	Conclusions	Limitations
Baumer et al.,[26] 2006	Investigate frequency of and risk factors for AIM in pediatric youth with or at risk for BD, and examine the relationship between allele and genotype frequencies of the 5-HTT polymorphism. Primary hypothesis was a younger age at AD exposure would be associated with AIM 52 subjects: 30 with BD, 22 with subthreshold mania. 47 subjects with SSRI exposure were genotyped for the 5-HTT polymorphism. Median age 15.1 y. All subjects had a parent with BD	rt. Parent interviews to evaluate for manic/depressive symptoms pre- and post-medication changes. YMRS was used to rate mood and behaviour pre- and post-change in AD status and during a negative reaction or at 1 mo. Suicidal ideation was assessed with CDRS-R. Subjects were classified into four groups: RXN+, RXN−, AIM+ (must be ≥1 d) or AIM−. If subjects were worse prior to change in AD status then they needed an increase of four on the YMRS to be considered AIM+. Allele and genotype frequencies at the 5-HTTLPR were compared between AIM+ and AIM− groups	64.4% = RXN− 50% = AIM+ (38.5% with a new manic episode, 11.5% with worsening of existing mania), 25.5% had new onset suicidal ideation within 3 mo of AD exposure AIM+ vs AIM− groups did not differ significantly in relation to allele or genotype frequencies of the 5-HTT polymorphism AIM+ subjects had more co-morbidities and BD I more often. Time to onset of AIM was not affected by the presence of the *s* allele. Concomitant use of an MS or atypical antipsychotic did not limit the incidence of AIM. Neither sex nor AAO of mania were associated with AIM	Youth with or at high-risk for BD may be particularly vulnerable to AIM. 5-HTT polymorphism was not a risk factor for AIM. Risk of AIM might be directly correlated with severity of BD, and greater number of co-morbid diagnoses. Higher frequency of AIM in younger pts was not supported. Care should be taken in treating suspected bipolar depression in at-risk youth as there is a high incidence of AIM in this population. Lamotrigine or lithium may be better first-line options. Treatment emergent suicidal ideation may be a higher risk in BD pts than MDD pts	rt with chance of recall bias. Small sample size. Study design was naturalistic and not case controlled. There was no control group of subjects exposed to only MSs without ADs to differentiate between AIM and natural course of the illness. YMRS is not validated to be used retrospectively. Ethnic makeup of the sample skewed the frequency of genetic types
Biederman et al.,[27] 2000	Evaluation of which treatments are most effective and destabilizing in the management of bipolar depression in 59 pts, all diagnosed with BD; mean age 10.8 y, and all followed up in the clinic at least twice after initial evaluation	rt chart review. CGI retrospectively applied to progress note of each visit rating the severity of symptoms at baseline and follow-up. The type and number of medications were inventoried: MSs, SSRIs, TCAs, stimulants, and typical antipsychotics	Depressive symptoms were 6.7-fold more likely to improve in visits when subjects received an SSRI than when they did not. TCAs, stimulants, MSs and typical antipsychotics were not associated with improvement in depressive symptoms. Manic symptoms were 3-fold more likely to develop in visits when subjects received an SSRI than when they did not. 32 of 59 subjects with BD did not have manic symptoms at baseline, and 53% of these had relapse of manic symptoms. MS improved manic symptoms but had no effect on depression	SSRIs improved BD depressive symptoms and worsened BD manic symptoms. MSs improved manic symptoms. SSRIs did not inhibit the improvement from MSs. SSRIs may be used safely to treat depression during mixed episodes of BD, with concomitant use of an MS. Stimulants were not manicogenic and were not particularly helpful in the treatment of depressive or manic symptoms	Sample may represent subjects with more severe illness Non-randomized Data were grouped by medication class to gain statistical power. Rater recording clinical data from the chart was not blind to the treatment status of the subject. True protective effect of MS against SSRI mood destabilization is unknown as too few subjects were treated with MS prior to onset of mania. Role of atypical antipsychotics is unknown. Relative risk between depressive symptoms and treatment with stimulants was not fully examined

5-HTT = serotonin transporter; **5-HTTLPR** = 5-HTT-linked polymorphic region; **AAO** = age at onset; **AIM** = antidepressant-induced mania; **CDRS-R** = Children's Depression Rating Scale-Revised; **CGI** = Clinical Global Improvement; **MDD** = major depressive disorder; **MS** = mood stabilizer; **rt** = retrospective; **RXN** = reaction; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **YMRS** = Young Mania Rating Scale; **+** = positive; **−** = negative.

Table V

Age at onset (AAO) of bipolar symptoms associated with psychotropic medication exposure

Study, y	Objective and population	Method and measures	Results	Conclusions	Limitations
DelBello et al.[28] 2001	Examine demographic and clinical characteristics of youth with BD, with and without a history of stimulant treatment, and examine if medication exposure was associated with AAO of BD 34 hospitalized youth aged 12–19 y, 22 with co-morbid ADHD. Diagnosed at admission with BD – manic or mixed state	rt. Primary assessment measures: WASH-U-K-SADS,[29] clinical interview, and medication history inventory	62% of subjects had exposure to a stimulant prior to BD onset. Those with stimulant exposure were more likely to have co-morbid ADHD AAO of BD was 10.7 y for those exposed to stimulants, 13.9 y for those not exposed to stimulants, 8.9 y vs 12.7 y for those treated with two or more stimulants (marginal significance; $p = 0.07$). No significant correlation between AAO of BD and duration of stimulant treatment. No difference in AAO of BD with and without co-morbid ADHD	Treatment with stimulants may be associated with younger AAO of BD independent of ADHD diagnosis. Behavioural sensitization via stimulant exposure may produce TEM	Small sample size, rt design with recall bias. Study lacked family history data that may have identified high-risk individuals
Martin etal.,[30]2004	Evaluate pharmacoepidemiologic data for risk of conversion to mania by AD class and pt age Subjects aged 5–29 y with primary diagnoses of depression or anxiety	rt. Data from insurance claims across 200 companies with related pharmacy claims between 1997 and 2001. Psychotropics were separated into six categories based on class. Conversion = a new diagnosis of BD as assessed by two or more insurance claims. Non-enduring (<28 d) symptoms of conversion were excluded. Conversion rates = outcome events/no, of person-y of observation Cox proportional hazards regression analysis adjusted for confounding factors. Time-dependent co-variates were created to account for the changing medications over time	4786 of 87 920 pts converted with a period prevalence of 5.4%. Conversion rate among those treated with AD was 3-fold more than among those unexposed. 15- to 19-y-old group had the highest number of converters when all types of ADs were combined. Rates of conversion with TCAs and other ADs were greater than those for SSRIs. Conversion rate for age × AD exposure was significantly higher in the 5- to 14-y-old group than the 15- to 29-y-old group	Age is an effect modifier on AD-associated manic conversion. There is an inverse relationship between age and relative hazards of conversion for those exposed to SSRIs and other ADs but not TCAs. Treating as few as ten children in the 10- to 14-y-old range with an SSRI would result in at least one conversion event. A careful benefit-risk analysis should be made when weighing treatment interventions to minimize potential harm	Manic conversion was used rather than manic switch as clinical information was not available; administrative information was the primary dataset. Pubertal status of pts and information on medication compliance was not available. Differentiation between natural progression of the illness, popular trends in prescribing and diagnosis, and true substance-induced mood disorder is difficult to tease out
Chang etal.,[31]2010	Examine psychotropic medication exposure among children at risk for BD and retrospectively determine the effect of medication on the AAO of BD 106 offspring of BD parent. 63 with BD I or II: 77.8% with BD I,22.2% with BD II, 88.3% with one or more co-morbid	rt. AAO was determined by mo of first manic or hypomanic episode that was clearly not linked to TEM. Prior exposure to psychotropic medication was determined by interview and chart review. Duration of medication exposure was rounded to the nearest mo	Medication exposure in BD youth prior to AAO: 25.4% unexposed, 46.7% stimulant, 51.7% SSRI, 39.7% atypical AD, 15% TCA, 10.2% atypical AP, 11.7% VPA, 11.9% lithium, 15.9% AD and MS, and 28.6% AD and stimulant Medication exposure in subsyndromal youth: 62.8% stimulants, 39.5% SSRI, 25.6%	Children with BD vs those with subsyndromal BD had been exposed to a greater number and type of psychotropics. AD and stimulant exposure was not correlated with an earlier AAO of BD. MS exposure was associated with a later AAO of BD. Exposure to lithium alone, but not VPA or CBZ alone, was	rt study. Information was collected from parents and charts to determine medication exposure and AAO. Some children had concurrent treatment with MS when treated with SSRIs and/or stimulants so there may have been a

Study, y	Objective and population	Method and measures	Results	Conclusions	Limitations
	diagnoses; mean AAO was 11.3 y. 43 with subsyndromal BD: ADHD plus MDD, dysthymia or cyclothymia OR YMRS >12 OR CDRS-R >28; 42% of subsyndromal BD youth had two or more co-morbid diagnoses		atypical AD, 7.0% TCA, 27.9% atypical AP, 43.3% VPA, and 7% lithium	associated with later AAO. Treatment with MS prophylactically prior to significant symptoms in at-risk youth may have protective effects and needs to be further studied	protective effect in combo treatment. AAO may be skewed by using the first manic episode not associated with TEM

AD = antidepressant; **ADHD** = attention-deficit hyperactivity disorder; **AP** = antipsychotic; **BD** = bipolar disorder; **CBZ** = carbamazepine; **CDRS-R** = Children's Depression Rating Scale-Revised; **combo** = combination; **MDD** = major depressive disorder; **MS** = mood stabilizer; **pt(s)** = patient(s); **rt** = retrospective; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **TEM** = treatment-emergent mania; **VPA** = valproate; **WASH-U-K-SADS** = Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia; **YMRS** = Young Mania Rating Scale.