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BIPOLAR DISORDERS (R HIRSCHFELD, SECTION EDITOR)

A Review of Antidepressant-Associated Hypomania in Those Diagnosed with Unipolar Depression—Risk Factors, Conceptual Models, and Management

Nav Gill[1] · Adam Bayes[2,3] · Gordon Parker[1,2,3]

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Abstract

Purpose of Review The nosology and management of antidepressant-associated hypomania (AAH) in the treatment of unipolar depression requires clarification. We sought to review recent studies examining AAH, focusing on risk factors, differing explanatory models, and management strategies.

Recent Findings AAH occurs more frequently in those of female gender, younger age, and with a bipolar disorder (BP) family history. Depressive features (e.g., suicidal ideation, psychotic symptoms) in those with AAH were similar to those with established BPs. Explanatory models for AAH describe it as (i) a transient iatrogenic event, (ii) a specific "bipolar III" disorder, (iii) indicative of "conversion" to BP, (iv) acceleration of BP, and (v) coincidental and unrelated to antidepressant medication. Management recommendations include antidepressant cessation, atypical antipsychotic medications, or switching to a mood stabilizer.

Summary Determinants and management of AAH in the treatment of unipolar depression requires considerable clarification, likely to be achieved by close clinical review and refined research studies.

Keywords Antidepressant · Hypomania · Bipolar disorder · Nosology · Management · Risk factors

Introduction

Antidepressants (ADs), like other psychoactive substances (e.g., stimulants, steroids), have the propensity to destabilize mood, precipitating both hypomanic and manic episodes. First described in the 1950s with the introduction of tricyclic antidepressants (TCAs) [1], and subsequently with newer classes of antidepressants, the phenomenon has been described in those experiencing unipolar [2, 3, 4••, 5, 6, 7••, 8–11] or bipolar (BP) depression [11, 12•, 13•] as well as in non-affective conditions, such as anxiety disorders [14–22].

More specifically, the emergence of hypomanic symptoms meeting diagnostic criteria for hypomania (e.g., DSM-5) shortly after initiation or a dose increase of an antidepressant medication has been termed antidepressant-associated hypomania (AAH) [3, 4••, 23]. AAH has been described as (i) an iatrogenic, reversible effect of ADs which abates on cessation of the drug [7••, 24]; (ii) a discrete form of BP disorder in which hypomania (or mania) only occurs with AD treatment [24], labeled "bipolar III" disorder and positioned as one of six primary BP subtypes [25]; (iii) antidepressant conversion of a unipolar depressive disorder to a BP disorder [11]; (iv) acceleration in the natural course of an underlying but then emerging bipolar condition [26]; or (v) a coincidental phenomenon unrelated to antidepressant treatment, occurring in "pseudounipolar" individuals [27] as part of the natural history of a nascent bipolar I disorder (BP I) or bipolar II disorder (BP II) [5, 28].

Related clinical scenarios include antidepressant induction of an "activation syndrome" [29]—as distinct from hypomania—which may include anxiety, agitation, hostility, akathisia, panic attacks, insomnia, aggression, and impulsivity. The activation syndrome has been observed during the first

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✉ Adam Bayes
a.bayes@unsw.edu.au

[1] Prince of Wales Hospital, Randwick, NSW 2031, Australia

[2] School of Psychiatry, University of New South Wales (UNSW), Sydney 2052, Australia

[3] Black Dog Institute, Sydney, NSW 2031, Australia

3 months of AD treatment, including in patients with non-affective psychiatric conditions [29]. Transient mixed or agitated depressive states (i.e., depression with excitatory symptoms) have also been found in some instances to be induced by ADs [30, 31]. DSM-5 has added a mixed-features specifier of major depressive disorder (MDD), which consists of both major depressive episode and modified hypomanic criteria. The change creates greater heterogeneity in depressive presentations (inviting the inclusion of AD associated mood disturbance) within the DSM-5 and also suggests a shift from a categorical to a spectrum or dimensional view of unipolar and bipolar disorders [32, 33]. Such a model may be supported at a genetic level, with genome-wide association studies (GWAS) assessing common genetic polymorphisms finding moderate genetic correlation between bipolar disorder and major depressive disorder, suggesting shared biology [34].

Whereas DSM-IV classified AAH as a "substance-induced mood disorder," DSM-5 now only includes such a diagnosis if it is "attributable to the physiological effects of …. medications" [35]. However, a "fully syndromal …episode that arises during treatment that persists beyond the physiological effect of the inducing agent (i.e., after a medication is fully out of the individual's system)" is sufficient evidence to make a BP I or BP II disorder diagnosis [35]. The past nosological uncertainty of classifying AAH as either a unipolar or a bipolar condition has resulted in differing pharmacological approaches to its management.

Aim: to examine the phenomenon of AAH occurring in those diagnosed with unipolar depression—including risk factors for its development, differing explanatory models, and current management strategies.

Methods

We reviewed the relevant literature on AAH occurring during treatment of those with a unipolar depressive episode, focusing on recent studies. For the purposes of this review, we define AAH as hypomania occurring shortly after commencement or dose increase of AD medication in individuals being treated for a unipolar depressive disorder, without a previous diagnosis of bipolar disorder.

Search Strategy

A literature search of PubMed, MEDLINE, Embase, and PsycINFO (up until July 2019) was conducted to identify potential relevant articles. The search terms were [(antidepressant OR SSRI OR TCA OR MAOI OR SNRI) AND (hypomania OR hypomanic OR switch*) AND (depression OR depressive OR unipolar depression)]. In addition, we searched online resources of America Psychiatric Association (APA), Royal College of Psychiatrists, European Psychiatric Association (EPA), World Psychiatric Association (WPA), Royal Australian and New Zealand College of Psychiatrists (RANZCP), World Health Organization (WHO), and National Institute for Health and Clinical Excellence (NICE) for relevant clinical practice guidelines.

Study Selection

Relevant studies (judged on title and abstract information) were evaluated in further detail. Studies were included if they examined AAH specifically or non-specifically. In addition, we searched the reference lists of obtained articles to identify additional studies that met inclusion criteria. We did not consider studies describing AAH occurring in those with an established BP disorder or other non-affective disorders. The retrieved studies were evaluated by first and second authors independently.

Study Evaluation

Studies were assessed and summarized qualitatively.

Results

Incidence

There is no clear estimate of the incidence of AAH in the treatment of unipolar depression, with studies reporting a wide variation in incidence ranging from 0.3 to 22.4% [3, 6, 7••, 23, 36-40]. This wide range of reported incidence in these studies could be accounted for by differences in study sample characteristics (inpatient vs outpatient populations), antidepressant class (studies with tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) monotherapy reported higher rates), diagnostic criteria (DSM vs Research Diagnostic Criteria), and study duration (studies with longer follow-up reported higher rates).

Onset

Studies differed in terms of clarifying the timing of AD exposure and subsequent mood disturbance when making an AAH diagnosis. The upper range of timeframes ranged from 4 to 12 weeks following commencement or a dose increase of the AD [4••, 41, 42]. Thus, there is no consistent timeframe established with respect to the onset of hypomania in relation to AD initiation or dose adjustment.

Age and Gender

Being female and having a younger age of onset of depression are risk factors for developing AAH in those with unipolar

depression [3, 7••, 11, 23, 24, 41, 43–46]. However, the higher rate of AAH in young people might be an artifact and represent the impact of an incipient BP disorder, as the peak age of onset of BP disorder is between 15 and 19 years of age [47].

Family History

Most studies have highlighted the presence of a positive family history of BP disorder in those exhibiting AAH [3, 6, 23, 24, 48]. Akiskal et al. [3] reported similar family history rates of BP disorder within both its AAH subgroup and its hypomania (unrelated to antidepressant therapy) subgroup (11.8% and 14.1% respectively). A study by Barbuti et al. [4••] also found similar rates in the antidepressant-associated hypomania or mania group and in the bipolar group (25.1% vs 25.3 respectively), which were higher compared to a unipolar depression cohort (10.2%). Therefore, family history studies suggest that in some cases, AAH may be more affiliated with the BP disorders and that the AD precipitates a switch in those genetically predisposed to develop a bipolar disorder.

Antidepressant Class

SSRIs appear to have the lowest incidence of observed AAH, with Peet [9] evaluating paroxetine, sertraline, fluvoxamine, and fluoxetine, and quantifying an incidence of hypomania or mania of 0.72%, with Barak et al. [49] reporting a rate of 0.15% in those treated with citalopram compared to 1.29% for those receiving a TCA. Few studies described risk rates for the serotonin noradrenaline reuptake inhibitors (SNRIs), with Dunner et al. [38] suggesting duloxetine to be of especially low risk in precipitating mood elevation, whereas venlafaxine is associated with comparatively high rates, especially at higher doses [11, 12•]. The propensity of venlafaxine to inhibit dopamine reuptake at high doses [50] may offer explanation of these particular findings. For the MAOIs, comparison studies quantified an 8.3% incidence of hypomania in those exposed to phenelzine, and a zero incidence with tranylcypromine [51]. There have also been case reports of omega-3 and St John's wort treatment for depression associated with hypomania [52, 53]. No specific incidence data for AAH was available on other newer classes of ADs with case reports only for bupropion [54] and vortioxetine [55].

A recent large meta-analytic review of 111 trials involving 56,212 participants reported TCAs to have a significantly increased risk of precipitating hypomania (and mania) compared to MAOIs, SSRIs, and SNRIs, which were found to be no different to one another in terms of risk [11]. The study was limited by a high degree of heterogeneity of analyzed studies. Overall, it appears antidepressants targeting multiple monoamine systems appear to have an increased propensity of inducing AAH compared with more selective agents (e.g., SSRIs) affording a lower risk [11, 12•, 36, 56].

Neurobiology

The neurobiological mechanism of AAH implicates the inadvertent activation of dopaminergic pathways [57], with prescription of certain psychostimulants (e.g., dexamfetamine)—which are known to act on these pathways—carrying a risk of inducing hypomanic or manic states. In addition to stimulation of serotonergic and noradrenergic receptor systems, certain ADs such as TCAs, MAOIs, SNRIs, and some SSRIs (such as paroxetine and sertraline at higher doses) may lose specificity and increase inhibition of dopamine reuptake (and noradrenaline in the case of SNRIs), thus inducing elevated mood states [57–59]. This is consistent with the notion of AAH being a dose-dependent phenomenon [56, 57, 60] and argues for dose reduction or slow dose increase as possible management strategies.

Thus, all AD classes, or any compound with antidepressant properties, have the potential to induce hypomanic states, with some suggestion that broader-acting ADs (i.e., those acting on a greater number of neurotransmitter systems) afford an increased risk.

Antidepressant Discontinuation/Dose Reduction

The reverse phenomenon-hypomania (or mania) following AD discontinuation or dose reduction has been reported infrequently in relation to SSRIs, TCAs, SNRIs, and MAOIs [61–64]. It has been proposed that those vulnerable to this form of mood switching may have frontolimbic brain abnormalities (i.e., volume loss, amyloid accumulation), as can occur in the elderly [65]. Withdrawal-induced cholinergic overdrive and post-cessation noradrenergic hyperactivity have been proposed as possible explanatory models for this clinical entity [66].

Depressive Features

Studies examining the quality of depressive episodes in those who have experienced AAH comparing to those with unipolar depression report elevated rates of suicidality, psychotic features, and depressive symptom severity in the former group [3, 7••, 43, 67]. Similar rates of melancholic [4••, 12•] and psychotic features as well as of depression severity [12•] have been found across AAH and BP disorder groups. However, one study found AAH depressive features to be more severe than in those with a BP II disorder, with the former exhibiting greater severity of depression, elevated depressive temperament scores, increased rates of psychotic features, hospitalization for suicidal behaviors and of completed suicide (13.7% vs 3.5%) [11]. In comparing AAH and BP with unipolar depression (without AAH), increased rates of past suicide attempts were found in the former two groups when compared to the latter [4••]. Additionally, both AAH and BP groups displayed

comparable rates of psychotic features, mixed features, early age of onset of depression, and frequency of depressive episodes—and which were increased compared to the individuals in the unipolar depression group without AAH [4••]. Dumlu et al. [12•] in a cluster analysis of four groups (i.e., those with bipolar I disorder (BP I), bipolar II disorder (BP II), unipolar depression with AAH, and recurrent unipolar depression), identified two clusters (i.e., unipolar depression in one cluster and AAH with BP I and BP II in a second cluster) and with the second cluster associated with greater depression severity, more suicide attempts, melancholic features, and greater chance of hospitalization. Thus, many of the depressive features in those experiencing AAH appear more closely linked to the presence of a nascent or extant bipolar disorder than to unipolar depression.

Clinical Course

The clinical course of individuals following an episode of AAH has revealed mixed results, either emerging as a time-limited phenomenon and without further episodes or else being a marker for development of bipolar disorder. A prospective study of 403 unipolar depressed participants treated with an AD found 12 developed AAH [7••]—and when the AD was either dose-reduced or withdrawn, no further episodes of hypomania had occurred during the 3-year follow-up period.

Other studies have found that an episode of AAH precedes eventual "conversion" to BP disorder [4••, 5, 12•, 23, 41, 43, 68, 69, 70•]. A prospective study of 206 outpatients with unipolar depression reported 100% predictive strength for an eventual BP disorder diagnosis over the course of a 1 to 9-year follow-up period for those who experienced an episode of AAH [48]. Lower but significant rates of observed bipolar conversion have been reported by Wada et al. [70•] in a study of AAH in those with unipolar depression, with a BP II conversion rate of 17.6% at 1-year follow-up. Akiskal et al. [26] concluded that AAH is most likely an acceleration in the natural course of an underlying but then emerging bipolar condition. Overall, it appears that rather than having a distinct and predictable course, AAH may reflect several differing models, with some expressions transient and self-limited and others indicative of development of a BP disorder.

Diagnostic Accuracy

It has been argued that the reported incidence of AAH in those with unipolar depression may be accounted for by the failure to initially identify a true underlying BP disorder [5, 12•]. Misdiagnosis of a true BP disorder as unipolar depression may arise due to (i) clinicians failing to enquire about symptoms of "highs," (ii) individuals not reporting highs as they fail to recognize them as being pathological or are not associated with impaired functioning, or (iii) difficulty establishing a BP II diagnosis owing to elevated mood states generally being less severe and by definition non-psychotic—as compared to BP I disorder. Additionally, in 35–60% of bipolar individuals, their first mood episode is in the depressed phase [71, 72] and it is estimated that, on average, 8.6% of individuals will go on to "convert" to a BP II disorder and 3.9% to a BP I disorder [2]. A meta-analysis of 27 studies found a delay of almost 6 years between onset of BP disorder and initial management [73], highlighting the need for clinicians to carefully exclude the presence of an underlying BP disorder in those presenting with AAH.

Treatment Pathways

Clinical practice guidelines for mood disorders are variable in addressing AAH. The Royal Australian and New Zealand College of Psychiatrists guidelines [74] do not consider the phenomenon in unipolar depression (only in those with a diagnosed BP disorder), while the current American Psychiatric Association (APA) guidelines (based on the DSM-5) and British Association of Psychopharmacology guidelines [75] state that hypomania/mania induced by ADs should permit the diagnosis of a BP disorder.

Use of ADs in those with a BP disorder has been associated with induction of rapid-cycling episodes and poorer long-term illness outcome [5], and with a mood stabilizer viewed as the optimal treatment. Conversely, prescription of an atypical antipsychotic (AAP) or a mood stabilizer for a truly unipolar individual with AAH risks exposure to unnecessary treatments with a greater side-effect burden. Management of AAH includes carefully re-evaluating the initial diagnosis to exclude a pre-existing BP I or II disorder. Secondly, there should be pre-emptive identification and management of mood-destabilizing factors (e.g., substance use, sleep disturbance, and psychosocial stressors) to reduce the risk of AAH [56]. Thirdly, psychoeducation should address the potential ambiguity of the diagnosis—viewing AAH as a transient adverse effect of medication differs markedly to it being a form of BP disorder [22].

Pharmacological treatment of AAH broadly includes (i) antidepressant dose reduction, (ii) AD discontinuation, (iii) mood stabilizer treatment, and/or (iv) initiation of an atypical antipsychotic (AAP). A dose-dependent relationship has been found between antidepressants and the emergence and remission of hypomania [43, 56, 57]. Several studies recommend AD dose reduction or discontinuation, with careful observation for emergence of further depression or mood elevation [39, 70•, 76], with a gradual dose reduction advised, even in the presence of ongoing hypomania, to prevent withdrawal effects that may exacerbate the elevated state [56]. Re-challenge with the same antidepressant is generally not advised [56]. Use of mood stabilizers to manage AAH was undertaken in a study by Wada et al. [70•] who suggested

continuing such treatment until there was an absence of spontaneous hypomania for a period of 3 to 5 years. This recommendation was based on findings from an 11-year prospective follow-up study of individuals with unipolar depression and which reported the majority of BP II conversions took place within the first five of years following a diagnosis of MDD [2].

Akiskal et al. [3] argue that AAH is a more depressive and unstable form of BP II disorder (with increased suicide risk), suggesting similar or more extensive use of mood stabilizers compared to those with a BP II disorder. Furthermore, Chun and Dunner [5] suggested that risk factors for polarity conversion (i.e., BP family history, psychotic features, earlier age of onset) should be considered when determining treatment duration and advising mood stabilizer coverage prior to future AD trials to reduce the risk of further AAH. Time-limited prescription of an AAP to target hypomania in the first instance, with mood stabilizer introduction only in those with more severe mood disturbance has also been suggested [56].

Navarro et al. [7••] recommended against use of mood stabilizers for AAH and instead favored adjustment of AD dosage as well as use of AAPs based on hypomania severity as measured by the Young Mania Rating Scale (YMRS); thus, (i) a 50% reduction in AD dose for a YMRS of < 12, (ii) AD withdrawal for a YMRS score of 13–16, or (iii) AD withdrawal and commencement of an AAP for a YMRS score of > 17. If remission is achieved by AD dose reduction or cessation, a second recommendation was to replace the original AD with an alternative in the same class at the lowest dose, at least 2 weeks following remission of hypomanic symptoms. If remission is achieved by AD withdrawal and AAP initiation, they then recommended reducing the antipsychotic dose by 50% after 2 weeks of remission, ceasing it 1 week later and replacing the original AD with an alternative from the same class at the lowest dose. This study reported no further instances of AAH following reintroduction of ADs, despite the absence of a formal mood stabilizer being introduced.

Discussion

We have reviewed the literature on antidepressant-associated hypomania in those with an initial diagnosis of unipolar depression. Limitations of the reviewed studies include, firstly, the majority of MDD randomized controlled trials have failed to include operationalized criteria by which hypomanic episodes were diagnosed with some studies also not distinguishing hypomanic as against manic states, disallowing delineation of each condition and consideration of differing AAH models for each presentation. Secondly, use of differing timeframes in defining AAH meant a lack of consistency in comparing studies. Thirdly, there were few long-term follow-up studies, thus risking not capturing individuals who went on to develop spontaneous hypomania. Fourthly, reviewed studies may have misdiagnosed participants as having unipolar depression when in fact they had a bipolar disorder. Lastly, the incidence rate of AAH is likely to be underestimated as studies typically did not capture this data prospectively but instead relied on spontaneous reporting of such episodes or were only detected if the hypomanic episode was more severe.

Study findings suggest that the literature describing AAH allows a number of differing conceptual models, as previously highlighted [5, 11]. Thus, it may be a transient and unique iatrogenic drug reaction (as observed in individuals with non-affective disorders) in individuals with unipolar depression. Alternatively, it may be a manifestation of a bipolar condition—either as a specific and unique form of BP disorder (BP III) where hypomania only occurs with AD exposure, antidepressant conversion of a unipolar depressive disorder to a BP disorder, acceleration of the natural course of an underlying bipolar disorder, or a coincidental phenomenon unrelated to antidepressant treatment, occurring as part of the natural history of a nascent bipolar disorder. A further model arises with consideration of a dimensional rather than a binary view of MDD and bipolar disorders. This is suggested by the introduction of mixed depression in DSM-5—which allows for the presence of hypomanic features—pointing to a subgroup of patients who may exhibit a degree of bipolarity, with a greater propensity towards induction of hypomania when exposed to antidepressants.

Our review argues that given the limited volume of evidence on AAH, lack of study homogeneity, and sparse follow up data available, a number of the described models may be operative. A small number of studies have described AAH occurring in individuals with depression where there is an absence of a family history of BP disorder, the elevated mood state is brief or of mild severity and which abates with AD dose reduction or cessation, i.e., it is an iatrogenic reaction. However, the majority of studies support the concept that AAH more closely resembles an intrinsic BP disorder—with an AD present to induce hypomania, or alternatively precipitating future hypomania—with family histories of bipolar disorder and depressive features resembling BP depression as evidenced by similar rates of melancholic and psychotic features, depression severity, an earlier age of onset of depression and increased frequency of episodes.

Conclusions

Increased rates of AAH are associated with female gender, younger age of mood disorder onset, a positive BP family history, and treatment with broader acting antidepressants (ADs). Similarities in depressive features and clinical course in those with AAH compared to those with established BP disorders have also been consistently reported, suggesting that

in the majority of cases, AAH is likely a form of bipolar disorder. Improvements in the nosological clarity of AAH should assist clinical decision-making. Dose reduction or cessation of ADs and short-term use of AAPs have been considered for acute management of AAH, with ongoing treatment potentially involving a switch to an alternative antidepressant or use of mood stabilizers. Further clarification of treatment approaches is required for this not uncommon clinical phenomenon.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Ball JR, Kiloh LG. A controlled trial of imipramine in treatment of depressive states. Br Med J. 1959;2:1052–5.
2. Akiskal HS, Maser JD, Zeller P, Endicott J, Coryell W, Keller M, et al. Switching from unipolar to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry. 1995;52:114–23.
3. Akiskal HS, Hantouche EG, Allilaire JF, Sechter D, Bourgeois ML, Azorin JM, et al. Validating antidepressant hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). J Affect Disord. 2003;73:65–74.
4.•• Barbuti M, Pacchiarotti I, Vieta E, Azorin JM, Angst J, Bowden CL, et al. Antidepressant-induced hypomania/mania in patients with major depression: evidence from the BRIDGE-II-MIX study. J Affect Disord. 2017;219:187–92 **This large study elegantly compared AAH or antidepressant-associated mania, with BP and MDD groups, concluding AAH may represent a subpopulation, sensitive to ADs.**
5. Chun B, Dunner DL. A review of antidepressant-induced hypomania in major depression: suggestions for DSM-V. Bipolar Disord. 2004;6:32–42.
6. Kupfer DJ, Carpenter LL, Frank E. Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. Am J Psychiatry. 1988;145:804–8.
7.•• Navarro V, Gastó C, Guarch J, Penadés R, Pintor L. Treatment and outcome of antidepressant treatment associated hypomania in unipolar major depression: a 3-year follow-up study. J Affect Disord. 2013;155:59–64 **This study provides a clinically useful treatment algorithm for managing AAH.**
8. Patel R, Reiss P, Shetty H, Broadbent M, Stewart R, McGuire P, et al. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ Open. 2015;5:e008341.
9. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry. 1994;164:549–50.
10. Rouillon F, Montgomery SA. Unwanted effects of long-term treatment. In: Montgomery SA, Rouillon F, editors. Long-term treatment of depression. Hoboken: Wiley; 1992. p. 84–8.
11. Tondo L, Vazquez G, Baldessarini R. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121:404–14.
12.• Dumlu K, Orhon Z, Özerdem A, Tural U, Ulaş H, Tunca Z. Treatment-induced manic switch in the course of unipolar depression can predict bipolarity: Cluster analysis based evidence. J Affect Disord. 2011;134:91–101. **This study used cluster analysis which supported inclusion of AAH on the bipolar spectrum.**
13. Truman CJ, Goldberg JF, Ghaemi SN, Baldassano CF, Wisniewski SR, Dennehy EB, et al. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the systematic treatment enhancement program for bipolar disorder (STEP-BD). J Clin Psychiatry. 2007;68:1472–9.
14. Berk M, Koopowitz LF, Szabo CP. Antidepressant induced mania in obsessive compulsive disorder. Eur Neuropsychopharmacol. 1996;6:9–11.
15. Diler RS, Avei A. SSRI-induced mania in obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 1999;38:6–7.
16. Himmelhoch JM. Social anxiety, hypomania and the bipolar spectrum: Data, theory and clinical issues. J Affect Disord. 1998;50:203–13.
17. Levy D, Kimhi R, Barak Y, Aviv A, Elizur A. Antidepressant-associated mania: a study of anxiety disorder patients. Psychopharmacology. 1998;136:243–6.
18. Mendhekar DN, Gupta D, Girotra V. Sertraline-induced hypomania: a genuine side-effect. Acta Psychiatr Scand. 2003;108:70–4.
19. Philip J, Janaki R. Antidepressant-induced mania in obsessive compulsive disorder. Indian J Psychiatry. 2012;54:194–5.
20. Ramasubbu R. Antidepressant treatment-associated behavioural expression of hypomania: a case series. Prog Neuro-Psychopharmacol Biol Psychiatry. 2004;28:1201–1207.
21. Vieta E, Bernardo M. Antidepressant-induced mania in obsessive-compulsive disorder (letter). Am J Psychiatry. 1992;149:1282–3.
22. Williams L. A family therapist's guide to bipolar III: antidepressant-induced mania or hypomania. Am J Fam Ther. 2007;34:4.
23. Benazzi F. Antidepressant-associated hypomania in outpatient depression: A 203-case study in private practice. J Affect Disord. 1997;46:73–7.
24. Baldissarini RJ, Faedda GL, Offidani E, Vázquez GH, Marangoni C, Serra G, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: A review. J Affect Disord. 2012;148:129–35.
25. Klerman GL. The spectrum of mania. Compr Psychiatry. 1981;22:11–20.
26. Akiskal HS, Bourgeois M, Angst J, Post R, Möller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of Bipolar Disorders. J Affect Disord. 2000;59:5–30.
27. Steele TE, Taylor CI. Hypomania and tricyclic antidepressant choice. Am J Psychiatry. 1980;137:1457–8.
28. Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? A hypothesis. J Affect Disord. 2004;78:81–4.
29. Harada T, Sakamoto K, Ishigooka J. Incidence and predictors of activation syndrome induced by antidepressants. Depress Anxiety. 2008;25:1014–9.
30. Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression. Acta Psychiatr Scand. 2007;433:50–7.

31. Sani G, Vöhringer PA, Napoletano F, Holtzman NS, Dalley S, Girardi P, et al. Koukopoulos diagnostic criteria for mixed depression: a validation study. J Affect Disord. 2014;164:14–8.
32. Park YM. The Mixed-Features Specifier of Major Depressive Disorder in DSM-5: Is It Practical? Psychiatry Investig. 2018;15:1009–10.
33. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand. 2014;129:4–16.
34. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013;45:984.
35. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders: diagnostic and statistical manual of mental disorders. Fifth ed. Arlington: APA; 2013. p. 129.
36. Bahk WM, Woo YS, Chae JH, Choi JH, Jun T, Kim K, et al. The incidence of antidepressant-associated mania and hypomania in major depression. Eur Neuropsychopharmacol. 2006;16:S317.
37. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized, controlled trial. JAMA. 2008;299:901–13.
38. Dunner DL, D'Souza DN, Kajdasz DK, Detkeb MJ, Russell JM. Is treatment-associated hypomania rare with duloxetine: secondary analysis of controlled trials in non-bipolar depression. J Affect Disord. 2005;87:115–9.
39. Menchon JM, Gasto C, Vallejo J, Catalan R, Otero A, Vieta E. Rate and significance of hypomanic switches in unipolar melancholic depression. Eur Psychiatry. 1993;8:125–9.
40. Zubieta JK, Pande AC, Demitrack MA. Two-year follow-up of atypical depression. J Psychiatr Res. 1999;33:23–9.
41. Saatcioglu O, Erim R, Tomruk N, Nihat A. Antidepressant-associated mania or hypomania: A comparison with personality and bipolarity features of bipolar I disorder. J Affect Disord. 2011;134:85–90.
42. Tomruk N, Saatcioglu O, Erim BR, Nihat A. A comparison of clinical characteristics in bipolar I disorder and antidepressant-associated mania/hypomania. Dusunen Adam. 2010;23:85–9.
43. Akiskal HS. The bipolar spectrum: New concepts in classification and diagnosis. Psychiatry update. Am J Psychiatry. 1983;2:271–92.
44. Bader CD, Dunner DL. Antidepressant-induced hypomania in treatment-resistant depression. J Psychiatr Pract. 2006;13:233–7.
45. Benvenuti A, Rucci P, Miniati M, Papasogli A, Fagiolini A, Cassano GB, et al. Treatment-emergent mania/hypomania in unipolar patients. Bipolar Disord. 2008;10:726–32.
46. Zivanovic O, Borisev L. How accurate can we predict antidepressant-induced hypomania? Eur Neuropsychopharmacol. 2003;13:233.
47. National Institute for Health and Care Excellence (NICE). Bipolar disorder: assessment and management: NICE Guideline [CG185]. London, NICE; 2016. https://www.nice.org.uk/guidance/cg185. Accessed 15 July 2019
48. Akiskal HS, Walker PW, Puzantian VR, King D, Rosenthal TL, Dranon M. Bipolar outcome in the course of depressive illness: Phenomenologic, familial, and pharmacologic predictors. J Affect Disord. 1983;5:115–28.
49. Barak Y, Kimhi R, Weizman R. Is selectivity for serotonin reuptake associated with a reduced emergence of manic episodes in depressed patients? Int Clin Psychopharmacol. 2000;5:53–6.
50. Stahl SM. Essential psychopharmacology: neuroscientific basis and practical applications. 2nd ed. Cambridge: Cambridge University Press; 2000.
51. Rabkin JG, Quitkin FM, McGrath P, Harrison W, Tricamo E. Adverse reactions to monoamine oxidase inhibitors. Part II. Treatment correlates and clinical management. J Clin Psychopharmacol. 1985;5:2–9.
52. Kinrys G. Hypomania associated with ω3 fatty acids. Arch Gen Psychiatry. 2000;57:715–6.
53. Nierenberg AA, Burt T, Matthews J, Weiss AP. Mania associated with St. John's wort. Biol Psychiatry. 1999;46:1707–8.
54. Budakli AA, Tutuncu R, Oner I, Ates MA, Algul A, Basoglu C. Bupropion induced hypomania: a case report. Bulletin of clinical psychopharmacology. Conference: 5th International Congress on Psychopharmacology and International Symposium on Child and Adolescent Psychopharmacology. Conference Publication 2013;23:194–5.
55. Pirdogan Aydin E, Dalkiran M, Ozer OA, Karamustafalioglu KO. Hypomanic switch during vortioxetine switch. Psychiatry Clin Psychopharmacol. 2019;29:114–6.
56. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord. 2003;5:407–20.
57. Ramasubbu R. Dose–response relationship of selective serotonin reuptake inhibitors treatment- emergent hypomania in depressive disorders. Acta Psychiatr Scand. 2001; 104:236–9.
58. Goodwick PJ, Goldstein BJ. Selective serotonin reuptake inhibitors in affective disorders. Basic Pharmacology. J Psychopharmacol. 1998;12:5–20.
59. Redrobe JP, Bourin M, Colombel MC, Baker GB. Psychopharmacological profile of selective serotonin reuptake inhibitor, paroxetine: implication of noradrenergic and serotonergic mechanisms. J Psychopharmacol. 1998;12:348–55.
60. Yamaguchi Y, Kimoto S, Nagahama T, Kishimoto T. Dosage-related nature of escitalopram treatment emergent mania/hypomania: a case series. Neuropsychiatr Dis Treat. 2018;14:2099–104.
61. Inanli I, Yildirim S, Goktas D, Eren I. Mania induced by reducing the dose of venlafaxine. Klinik Psikofarmakoloji Bulteni. Conference: 6th International Congress on Psychopharmacology. Antalya Turkey. Conference Publication. 2014;24:320.
62. Kora K, Kaplan P. Hypomania/mania induced by cessation of antidepressant drugs. Turk Psikiyatri Derg. 2008;19:329–333.
63. Kwok C, Chan HN, Lim L. Antidepressant-discontinuation mania in two patients with depression. Eur Psychiatry. 2015;30:1591.
64. Narayan V, Haddad PM. Antidepressant discontinuation manic states: a critical review of the literature and suggested diagnostic criteria. J Psychopharmacol. 2011;25:306–13.
65. Singh A, Alexopoulos GS. Mania during antidepressant withdrawal in late-onset depression. Int J Geriatr Psychiatry. 2013;28:654–9.
66. Saraiva S, Costa R, Mota T. Hypomanic episode upon venlafaxine discontinuation. European Psychiatry. Conference: 23rd European Congress of Psychiatry, EPA 2015. Vienna Austria. Conference Publication. 2015;30:1151.
67. Wada K, Sasaki T, Jitsuiki H, Yoshimura Y, Erabi H, Hada Y, et al. Manic/hypomanic switch during acute antidepressant treatment for unipolar depression. J Clin Psychopharmacol. 2006;26:512–5.
68. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry. 1995;152:1130–8.
69. Tay LK, Dunner DL. A report on three patients with "rapid cycling" unipolar depression. Compr Psychiatry. 1992;33:253–5.
70.• Wada K, Sasaki T, Jitsuiki H, Takaishi Y. One-year outcomes of unipolar depression patients with manic or hypomanic switch during acute antidepressant treatment. Int J Psychiatry Clin Pract. 2013;17:219–22. **This study examined use of mood stabilizers as maintenance therapy following AAH.**
71. Coryell W, Endicott J, Maser JD, Keller MB, Leon AC, Akiskal HS. Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry. 1995;152:385–90.
72. Howland RH. Induction of mania with serotonin re uptake inhibitors. J Clin Psychopharmacol. 1996;16:425–7.

73. Dagani J, Signorini G, Nielssen O, Bani M, Pastore A, Girolamo G, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. Can J Psychiatr. 2017;62:247–58.
74. Mahli G, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49:1–185.
75. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes TRH, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30:495–553.
76. Findling RL, Reed MD, Myers C, O'Riordan MA, Fiala S, Branicky L, et al. Paroxetine pharmacokinetics in depressed children and adolescents. J Am Acad Child Adolesc Psychiatry. 1999;38:952–9.