

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study.
<b>AUTHORS</b>	Patel, Rashmi; Reiss, Peter; Shetty, Hitesh; Broadbent, Matthew; Stewart, Robert; McGuire, Philip; Taylor, Matthew

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Philip J Cowen Dept of Psychiatry, University of Oxford
<b>REVIEW RETURNED</b>	15-May-2015

<b>GENERAL COMMENTS</b>	<p>I think the idea of using the CRIS database to look at the incidence of mania in depressed patients after antidepressant treatment is an excellent approach with the potential to yield important observational data. The authors are appropriately cautious about the issue of causation.</p> <p>The main problem I have is understanding the relationship between the timing of antidepressant treatment and the onset of mania. The authors emphasise that the history of antidepressant use preceded the formal diagnosis of depression by the Mental Health Services. However, presumably many of the patients with a diagnosis of depression would subsequently have received antidepressant treatment as part of their clinical management during the follow-up period. Also, presumably previous ongoing antidepressant treatment might have been changed by the specialist services? Because one usually thinks as mania being triggered by the presence of antidepressant treatment rather than its prior use, it seems important to know what patients were taking in terms of antidepressants when they actually were diagnosed with mania. Is it possible, for example, that patients might have no prior history of antidepressant use before the depression diagnosis (and therefore counted as 'non-exposed') but might still have had antidepressant treatment subsequently which triggered mania?</p> <p>Of course I might well be simply misunderstanding what the authors have done, but would welcome clarification of this issue.</p> <p>Some other points:</p> <p>After the diagnosis of depression were patients continually under the care of the specialist services or would some have been discharged back to the GP before becoming manic? Presumably CHRIS does not access GP records? If this is the case might some courses of subsequent antidepressant treatment have been missed?</p>
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	<p>Is the evidence that duloxetine (as opposed to venlafaxine) is associated with mania clear? The cited Tondo et al paper does not seem to show this. Related to that I wonder what the effect in the present analysis would be if duloxetine was combined with its fellow SNRI venlafaxine in the analysis. It also seems curious to include flupentixol as an antidepressant (whatever the BNF says) but perhaps very few people were taking it?</p> <p>Surprisingly, TCA treatment does seem to increase the risk of mania (Table 1) but this is the class of drugs most frequently implicated. Why might this be? Does it cast doubt on the validity of the approach?</p> <p>Are there data on other medication that patients may have been taking either at the time of their original antidepressant treatment or subsequently? For example, mood stabilisers and atypical antipsychotic drugs are often used to augment antidepressant medication and may, presumably, decrease the risk of antidepressant-induced mania.</p> <p>The authors say that they found a greater incidence of mania in patients aged 16-25 but I can't quite see this from the hazard ratios in table 1.</p>
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<b>REVIEWER</b>	Keming Gao Case Western Reserve University School of Medicine, USA
<b>REVIEW RETURNED</b>	29-May-2015

<b>GENERAL COMMENTS</b>	<p>In this large sample observational study of the association between antidepressant therapy and the late onset of mania/bipolar disorder, the authors found that among the patients with unipolar depression, antidepressant treatment was associated with an increased risk of subsequent mania/bipolar disorder. This study expanded previous studies in this area, but as the authors pointed out that due to the inherent weakness of such kind of a study, the cause-effect relationship could not be established. Meanwhile, as the authors described in the discussion, there are existing data support that some patients present with unipolar depression are vulnerable for developing first manic/hypomanic episode when they are treated with antidepressant(s). The question is who these people are and when the switching may occur. This study add little information on this important issue. It is true that this is a larger study and the results may be more generalable, but the findings will had a little impact on clinical practice.</p> <p>The authors need describe the dataset more thoroughly, which may help readers to understand how those data were collected. Who were mental health professionals, psychiatrist, psychologist, nurse practitioners, and/or social workers? Who entered the diagnosis of unipolar depression? Who entered the diagnosis of mania/bipolar disorder? Did a patient see the same provider all the time? What instrument the provider used for diagnosis, just clinical interview or a standard structured interview? What was the inter-provider reliability?</p> <p>On page 6, in "Ascertainment of prior antidepressant therapy" section, "Prior antidepressant therapy was defined as documentation of antidepressant treatment prior to date of diagnosis of depression"</p>
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	<p>appears confusing. Was the “date of diagnosis of depression” by a mental health professional or someone else? If by a mental health professional, antidepressant(s) should be started after the date of diagnosis.</p> <p>The followed sentence of “The definition was chosen to ensure that documented antidepressant use always occurred before any subsequent diagnosis of mania/bipolar disorder” is also unclear. Does this mean an antidepressant(s) was used all time or sometimes from the diagnosis of depression to the subsequent diagnosis of mania/bipolar disorder?</p> <p>If the use of antidepressant(s) was all the time from the diagnosis of depression to subsequent mania/bipolar disorder, in what time frame did the subsequent mania/bipolar disorder occur? Antidepressant-induced manic/hypomanic switching commonly occurs within the first 4-8 weeks after starting antidepressant(s) in bipolar disorder. The authors need take a look at if there is any association between the time of initiating antidepressant and diagnosis of bipolar disorder.</p> <p>The authors controlled age and gender for their regression analysis. The other important factor to control is the duration of antidepressant exposure, which may provide more clinical relevant information such as when clinicians should pay more attention to antidepressant-induced switching.</p> <p>It is possible that some patients were treated with multiple antidepressants before developing manic/hypomanic symptoms. How did the authors handle these cases?</p> <p>On page 9, second paragraph, “It is possible that the incidence rate of mania and hazard ratio associated with antidepressant therapy in our study was lower than previous studies because the same was drawn from patients presenting to secondary mental healthcare services. Patients presenting to mental healthcare services with unipolar depression may have already received antidepressant therapy from primary care services. Furthermore, patients may have developed symptoms of mania prior while being treated with antidepressants in primary care and would have presented to secondary care services already with an established diagnosis of bipolar disorder.” This is not a good argument. To support this, the authors should provide the rate of “established diagnosis of bipolar disorder” assessed by mental health professionals at the first visit and what the percentage of those with bipolar disorder were treated with antidepressant by their primary care physicians.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Reviewer Name Philip J Cowen  
 Institution and Country Dept of Psychiatry, University of Oxford

Please leave your comments for the authors below

I think the idea of using the CRIS database to look at the incidence of mania in depressed patients after antidepressant treatment is an excellent approach with the potential to yield important observational data. The authors are appropriately cautious about the issue of causation.

/\*Thank you for your supportive comments\*/

The main problem I have is understanding the relationship between the timing of antidepressant treatment and the onset of mania. The authors emphasise that the history of antidepressant use preceded the formal diagnosis of depression by the Mental Health Services. However, presumably many of the patients with a diagnosis of depression would subsequently have received antidepressant treatment as part of their clinical management during the follow-up period. Also, presumably previous ongoing antidepressant treatment might have been changed by the specialist services? Because one usually thinks of mania being triggered by the presence of antidepressant treatment rather than its prior use, it seems important to know what patients were taking in terms of antidepressants when they actually were diagnosed with mania. Is it possible, for example, that patients might have no prior history of antidepressant use before the depression diagnosis (and therefore counted as 'non-exposed') but might still have had antidepressant treatment subsequently which triggered mania?

Of course I might well be simply misunderstanding what the authors have done, but would welcome clarification of this issue.

/\*We agree that people who receive a formal diagnosis of depression in secondary mental healthcare services may also be started on, or changed to a different antidepressant. Our experience in another study investigating time to diagnosis and treatment to bipolar disorder in the same dataset (Patel et al. PLOS One, May 2015; 10(5): e0126530. doi: 10.1371/journal.pone.0126530.) suggests that the documentation of treatment for a mental health disorder occurs prior to the documentation of a formal diagnosis (the median difference in delay between documentation of treatment and diagnosis was around one month in this study on bipolar disorder). For this reason, it is likely that ascertaining documentation of antidepressant use prior to formal diagnosis of depression will elicit any new treatments which have commenced since being accepted to secondary mental healthcare services. In this way, patients with no prior antidepressant therapy who commence therapy soon after presenting to secondary care are likely to still be picked up by setting the date for measuring prior antidepressant use as prior to the date the depression diagnosis was recorded.

We agree that antidepressant use immediately preceding onset of mania may be most relevant in examining associations of different antidepressants with mania. However, it would not be valid to compare rates of prior antidepressant use in a group of patients with mania in the absence of a control group who are treated with antidepressants but do not develop mania. This is the reason why we chose to employ a retrospective cohort study design examining all patients with a diagnosis of unipolar depression presenting to SLaM NHS Trust mental health services, in order to reduce the likelihood of selection bias by only analysing the subgroup of patients who develop mania.

We have updated the methods and discussion section to clarify these points.\*

Some other points:

After the diagnosis of depression were patients continually under the care of the specialist services or would some have been discharged back to the GP before becoming manic? Presumably CHRIS does not access GP records? If this is the case might some courses of subsequent antidepressant treatment have been missed?

/\*We agree that the lack of primary care data is an important limitation in our study. This prevented us from comprehensively obtaining pharmacotherapy data prior to presentation to mental health services, and after discharge from them. This may have affected the association of certain antidepressants with subsequent mania if these were started outside secondary mental healthcare services and not recorded in the SLaM BRC Case Register analysed in our study. In order to address

this limitation, future studies would benefit from linking primary and secondary care datasets in order to obtain more comprehensive pharmacotherapy data. We have updated the discussion section to discuss this further.\*/

Is the evidence that duloxetine (as opposed to venlafaxine) is associated with mania clear? The cited Tondo et al paper does not seem to show this. Related to that I wonder what the effect in the present analysis would be if duloxetine was combined with its fellow SNRI venlafaxine in the analysis. It also seems curious to include flupentixol as an antidepressant (whatever the BNF says) but perhaps very few people were taking it?

/\*We agree that the categorisation of antidepressant therapy in the BNF may not reflect standard practice. It makes sense to consider duloxetine with venlafaxine as an SNRI although you rightly point out that Tondo et al suggest an increased association with venlafaxine but not duloxetine (we have amended the discussion accordingly). We also agree that despite being listed as an antidepressant in the BNF, flupentixol is not explicitly recommended for the treatment of depression in UK clinical guidelines and may have been more likely to be used to treat psychotic symptoms rather than depression.

Rather than combine duloxetine and venlafaxine into a single category, we have amended the groupings to remove duloxetine from the “other antidepressant” group and replaced it as a single predictor variable. We have also removed flupentixol from the “other antidepressant” group entirely. Interestingly, in the updated analysis, duloxetine is not associated with a statistically significant increased risk of mania (while venlafaxine is). However, there are only 248 patients who were exposed to duloxetine so it may be that the sample size is not sufficiently large to detect a small effect.

In light of these changes to our analysis, we have amended the methods, results and discussion section accordingly.\*/

Surprisingly, TCA treatment does seem to increase the risk of mania (Table 1) but this is the class of drugs most frequently implicated. Why might this be? Does it cast doubt on the validity of the approach?

/\*We agree that this is a curious finding. One possible explanation is the use of tricyclic antidepressants for other clinical indications such as neuropathic pain (often at lower doses than used to treat depression) which could have reduced their association with mania. Another possibility is confounding by indication, whereby a clinician’s perception of risk of mania with certain antidepressants could have influenced their decision of what to prescribe such that tricyclic antidepressants may have been deliberately avoided in patients thought to be at high risk of mania. We have expanded on this area further in the discussion section.\*/

Are there data on other medication that patients may have been taking either at the time of their original antidepressant treatment or subsequently? For example, mood stabilisers and atypical antipsychotic drugs are often used to augment antidepressant medication and may, presumably, decrease the risk of antidepressant-induced mania.

/\*We agree that it would be interesting to investigate the potential association of antipsychotic and mood stabiliser augmentation on subsequent mania. Unfortunately we are not able to reliably obtain data on antidepressant augmentation as the medication data in the SLaM BRC Case Register do not routinely include dose, timing or indication (for example, antipsychotics may have been prescribed to treat psychotic features of severe depression rather than to augment existing antidepressant therapy). For this reason, we were not able to include antidepressant augmentation in our analysis. However,

this is an important point and we have updated the discussion section to highlight this limitation and the need for studies which specifically address this question.\*/

The authors say that they found a greater incidence of mania in patients aged 16-25 but I can't quite see this from the hazard ratios in table 1.

/\*We apologise for this error – the text in the discussion should read 26-35 (in line with the abstract and results). We have amended the text accordingly.\*/

Reviewer: 2

Reviewer Name Keming Gao, MD, PhD, Associate Professor of Psychiatry  
Institution and Country Case Western Reserve University School of Medicine, USA

Please leave your comments for the authors below In this large sample observational study of the association between antidepressant therapy and the late onset of mania/bipolar disorder, the authors found that among the patients with unipolar depression, antidepressant treatment was associated with an increased risk of subsequent mania/bipolar disorder. This study expanded previous studies in this area, but as the authors pointed out that due to the inherent weakness of such kind of a study, the cause-effect relationship could not be established. Meanwhile, as the authors described in the discussion, there are existing data support that some patients present with unipolar depression are vulnerable for developing first manic/hypomanic episode when they are treated with antidepressant(s). The question is who these people are and when the switching may occur. This study add little information on this important issue. It is true that this is a larger study and the results may be more generable, but the findings will had a little impact on clinical practice.

/\*We acknowledge the inherent limitations of analysing observational data recorded in the clinical setting and agree that there is a need to better understand the underlying risk factors for people with depression (which is initially thought to be unipolar) who go on to develop mania. Nonetheless, we do feel that our analysis contributes to the literature by examining the association of antidepressant therapy with mania in the clinical setting and allows comparisons with existing meta-analyses which are based principally upon research cohorts rather than people receiving mental healthcare from standard clinical services.\*/

The authors need describe the dataset more thoroughly, which may help readers to understand how those data were collected. Who were mental health professionals, psychiatrist, psychologist, nurse practitioners, and/or social workers? Who entered the diagnosis of unipolar depression? Who entered the diagnosis of mania/bipolar disorder? Did a patient see the same provider all the time? What instrument the provider used for diagnosis, just clinical interview or a standard structured interview? What was the inter-provider reliability?

/\*The mental healthcare professionals who document data in clinical records include psychiatrists, psychologists, nursing staff, care co-ordinators and allied healthcare professionals. Diagnoses are generally recorded by psychiatrists and are based on clinical interview. There are no data on inter-rater reliability as the dataset is drawn from electronic health records of patients receiving standard clinical care. The SLAM BRC Case Register data were not specifically obtained for analysis in our study and are naturalistic. We have updated the methods section to clarify this.\*/

On page 6, in “Ascertainment of prior antidepressant therapy” section, “Prior antidepressant therapy was defined as documentation of antidepressant treatment prior to date of diagnosis of depression” appears confusing. Was the “date of diagnosis of depression” by a mental health professional or someone else? If by a mental health professional, antidepressant(s) should be started after the date

of diagnosis.

The followed sentence of “The definition was chosen to ensure that documented antidepressant use always occurred before any subsequent diagnosis of mania/bipolar disorder” is also unclear. Does this mean an antidepressant(s) was used all time or sometimes from the diagnosis of depression to the subsequent diagnosis of mania/bipolar disorder?

If the use of antidepressant(s) was all the time from the diagnosis of depression to subsequent mania/bipolar disorder, in what time frame did the subsequent mania/bipolar disorder occur? Antidepressant-induced manic/hypomanic switching commonly occurs within the first 4-8 weeks after starting antidepressant(s) in bipolar disorder. The authors need take a look at if there is any association between the time of initiating antidepressant and diagnosis of bipolar disorder.

/\*Please see our response to Professor Cowen which addresses these issues.\*/

The authors controlled age and gender for their regression analysis. The other important factor to control is the duration of antidepressant exposure, which may provide more clinical relevant information such as when clinicians should pay more attention to antidepressant-induced switching.

/\*We agree that duration and dose are important factors to consider. Unfortunately, it was not possible to obtain these data from the SLaM BRC Case Register. We have updated the discussion to highlight this limitation.\*/

It is possible that some patients were treated with multiple antidepressants before developing manic/hypomanic symptoms. How did the authors handle these cases?

/\*We employed a multivariable Cox regression analysis method which adjusted for treatment with more than one type of antidepressant\*/

On page 9, second paragraph, “It is possible that the incidence rate of mania and hazard ratio associated with antidepressant therapy in our study was lower than previous studies because the same was drawn from patients presenting to secondary mental healthcare services. Patients presenting to mental healthcare services with unipolar depression may have already received antidepressant therapy from primary care services. Furthermore, patients may have developed symptoms of mania prior while being treated with antidepressants in primary care and would have presented to secondary care services already with an established diagnosis of bipolar disorder.” This is not a good argument. To support this, the authors should provide the rate of “established diagnosis of bipolar disorder” assessed by mental health professionals at the first visit and what the percentage of those with bipolar disorder were treated with antidepressant by their primary care physicians.

/\*We acknowledge that in the absence of primary care data, we are unable to determine the extent to which antidepressant therapy in primary care was associated with symptoms of mania. A linkage between primary and secondary care datasets would be necessary to examine this possibility further. We have updated the discussion section to better explain this limitation. However, we do not feel that examining rates of exposure to different antidepressants among all people who present with symptoms of mania to healthcare services would be able to answer the question of whether there is an association of antidepressants with mania as such an analysis would lack a control group. We therefore maintain that, albeit with the limitations we have already discussed, our retrospective cohort study design including all patients presenting to mental health services with a diagnosis of depression (in the absence of a previous history of mania/bipolar disorder) is the most appropriate study design

to investigate any potential association of antidepressant therapy with subsequent mania using the data we had available in the SLAM BRC Case Register.\* /

### VERSION 2 - REVIEW

<b>REVIEWER</b>	Philip J Cowen Dept of Psychiatry, University of Oxford, UK
<b>REVIEW RETURNED</b>	18-Jun-2015

<b>GENERAL COMMENTS</b>	<p>I think the authors have responded to my comments well.</p> <p>If I have understood their methodology correctly it is not only an issue of being unsure about the 'data on timing or dose of antidepressant therapy' in relation to the onset of mania. It also appears that they can't be sure that the patients were taking the same medication at the time of the manic illness as was documented previously (for example, psychiatrists may switch from an ineffective SSRI to a TCA). If this is the case I think it should be noted as well.</p>
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### VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Philip J Cowen

Institution and Country Dept of Psychiatry, University of Oxford, UK

Please leave your comments for the authors below

I think the authors have responded to my comments well.

If I have understood their methodology correctly it is not only an issue of being unsure about the 'data on timing or dose of antidepressant therapy' in relation to the onset of mania. It also appears that they can't be sure that the patients were taking the same medication at the time of the manic illness as was documented previously (for example, psychiatrists may switch from an ineffective SSRI to a TCA). If this is the case I think it should be noted as well.

/\*Thank you for your suggestion. You are right to note that it is not possible to be certain that a patient was taking the same antidepressant at the time of onset of mania. In this regard, the data on antidepressant therapy obtained in our study can be considered as an exposure which occurs prior to developing mania but not necessarily occurring concurrently to onset of mania. As you state, a patient could have been switched from one antidepressant to another because of lack of efficacy and then subsequently developed mania. We have acknowledged this limitation in the updated Discussion section of the manuscript.\* /