Bipolar III

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Abstract

Bipolar III is an emerging diagnosis used to describe mania induced by antidepressant therapy prescribed for bipolar patients in a depressive episode. This article reviews the evidence and summarises the safest way to treat bipolar depression.

Key words: bipolar disorder, antidepressant agents, depressive disorder, manic episode

What is Bipolar III?

The term Bipolar III is controversial. It is not included in DSM-IV-TR or ICD-10 criteria. It is not recognised by NICE, the Royal College of Psychiatrists or any of the bipolar charities. However, the Akiskal Schema of bipolar subtypes (1) uses the definition: Hypomania induced by the use of antidepressant drugs.

The aetiology of Bipolar III

Bipolar III has an ambiguous aetiology. On one hand, it might be purely iatrogenic, that is, a hypomanic state induced in someone in whom the bipolar diagnosis been missed previously. On the other hand, the antidepressant might just have created a hypomanic state earlier than it would have presented naturally. Research indicates that 12% of unipolar patients go on to develop hypomanic/manic symptoms within 15 years (2). Does bipolar III represent a quicker development of this or is it, in fact, a separate diagnosis?

What is the evidence for Bipolar III?

It has not been possible to find literature on hypomania being induced in non-diagnosed bipolar patients by antidepressant use. This is not entirely surprising, since it is not possible to identify that a patient has a diagnosis of bipolar disorder before the first hypomanic/manic episode. The available publications have been case studies and papers describing the "switch" to hypomania/mania in patients with known bipolar disorder.

The table below shows information from a meta-analysis of the prevalence of mania induced by different antidepressant treatments when used in bipolar patients (3).

Antidepressant	**Patients reporting Trials**	**% Patients reporting trials with affective shift**
All SSRI Trials	706	22%
One or more SSRI	353	33%
Bupropion	209	18%
Venlafaxine	102	17%
Heterocyclics	83	23%
Nefazodone	67	7%
ECT	49	14%
MAOIs	48	15%
Mirtazepine	35	9%
Total Antidepressant Trials	**1250**	**19.5%**

After Truman (3).

This data shows that all types of treatment for depression are potentially dangerous when used in bipolar patients; on average, they cause a 'switch' in 1 out of every 5 patients treated. The table also highlights that the risk differs, depending on which treatment is used. However, it does not take into account the other adverse effects of the treatments. For example, the 'safest' treatment in terms of "switch", nefazodone, is not used widely due to the rare but severe risk of hepatotoxicity. It would be of interest to carry out further research comparing the use of the overall safest antidepressant, for the shortest duration (with regular clinic appointments to determine the end of the depression accurately), compared to other treatment options and placebo.

It is interesting to consider the stance that different countries have taken on the literature available. The American and Canadian guidelines changed in 2002 to discourage antidepressant use in bipolar patients; in contrast, the European guidelines allow the use of antidepressants for the depressive phase of bipolar disorders. The current NICE guidelines state that treatment should only be started in moderate/severe depressive episodes and can be either a SSRI antidepressant or quetiapine (4).

How can the risk of Bipolar III be reduced?

The risk of "switch" with antidepressant treatment can be reduced by 60% by adding a mood stabiliser as illustrated by the table below.

Antidepressant-associated hypomanic/manic switches in bipolar depression with and without Mood Stabilisers (MS) (5,6,7,8)

	Without MS	With MS
Number of patients	351	382
Hypomanic/manic "switch"	33 – 68 %	12 – 20 %

However, this research does not consider whether it would be just as effective to use a mood stabiliser without the antidepressant or in combination with a different drug, for example, an antipsychotic (as advised in the NICE guidelines). This combination has been proved to be effective and is the first-line of treatment for bipolar depression with psychotic features (9).
It could also be argued that the antidepressant itself has mood de-stabilising effects as antidepressants have been noted to push bipolar patients into a mixed state (10).
Before prescribing an antidepressant it is also important to consider the type of patient because the 'switch' is more likely to happen in certain patients, as follows (11).

- Specific subtypes of bipolar - mixed episodes, rapid cycling courses. Low risk in bipolar II.
- Specific patients - comorbidities, a recent history of mania/hypomania, early beginning, psychotic features, a positive genetic load.

Conclusion

Treatment is based on a balance of risks. The aetiology of Bipolar III is iatrogenic and so it contradicts the guiding principle: "First, do no harm". Antidepressants have not been proved to be superior to placebo or mood stabilisers combined with an antipsychotic for the treatment of bipolar depression. If a drug is ineffective and harmful to 1 in 5 patients then why use it? However, we cannot simply decide not to prescribe antidepressants, as in the correct context they have proven efficacy and cost-effectiveness. Clinicians need to gather as much information about the patient as possible to ensure that the risk of bipolar disorder is minimal. If there are traits suggestive of bipolar disorder, the risks and benefits of using an antidepressant must be weighed against those of other therapies. These are summarised in the following table.

Risks of antidepressant (12):	Risks of not using an antidepressant:
Mania	Chronicity of symptoms
Increased cycle acceleration	Suicide
Mixed state	Patient disengaging with services

After Salvi (12).

How to prescribe antidepressants safely

If antidepressants are used to treat bipolar depression, start with a low dose and titrate up as required. The patient needs to be reviewed regularly (ideally every 2 weeks) so that the antidepressant can be stopped when symptoms improve. The antidepressant needs to be stopped as per the guidelines – when significantly less severe symptoms have been present for 8 weeks, start slowly to reduce the dose over several weeks while maintaining anti-manic medication (Royal College of Psychiatrists guidelines). Particular care is needed with venlafaxine and paroxetine as they are associated with a higher risk of withdrawal symptoms (NICE guidelines).

When diagnosing unipolar depression it is essential to take a longitudinal history, asking specifically about a history of any possible hypomanic/manic episodes. The mood disorders questionnaire can be of value in helping to elicit these elements of the history. This practice should facilitate the early diagnosis of bipolar disorder which should, in turn, assist the clinician in deciding on the possible risks and benefits of prescribing antidepressant medication. Whether hypomania/mania precipitated by the prescription of an antidepressant should be categorised as "Bipolar III" remains open to debate but there is no doubt about the importance of clinicians recognising the risk that elevated mood states may result from prescribing antidepressants in bipolar disorder.

GP Comment

What have I learned from this paper?

"Bipolar III" has been defined as a hypomanic/manic state induced by prescribing an antidepressant in a patient with bipolar disorder.

Although the diagnostic category of "Bipolar III" is not universally accepted, it remains important to be aware of the risk of antidepressant-induced hypomania/mania when prescribing for patients with bipolar disorder.

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