Clinical overview

Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration

Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration.

Objective: To address whether switch of depression into hypomania or mania or cycle acceleration in patients with bipolar disorder is caused by antidepressants or whether this phenomenon is attributable to the natural history of bipolar disorder itself.

Method: A critical review of the literature, pointing at sources of bias that have been previously overlooked. For examining the causation in question, the Bradford–Hill criteria were applied, i.e. specificity of the potential causative agent, strength of effect, consistency in findings, dose–response relation, temporal relation with exposure to agent preceding effect and biological plausibility.

Results: There is a scarcity of randomized studies addressing the question, and the available studies all suffer from various forms of bias. However, there is some evidence suggesting that antidepressants given in addition to a mood stabilizer are not associated with an increased rate of switch when compared with the rate associated with the mood stabilizer alone.

Conclusion: When combined with a mood stabilizer, antidepressants given for acute bipolar depression seemingly do not induce a switch into hypomania or mania. Whether antidepressants may accelerate episode frequency and/or may cause other forms of destabilization in patients with bipolar disorder remain to be properly studied.

Clinical recommendations

- In bipolar disorder, switch from depression into hypomania or mania commonly occurs as a natural course of the illness.
- In terms of switch risk, antidepressants seem safe when combined with a mood stabilizer. However, antidepressants given as monotherapy cannot be recommended, at least not when treating patients with bipolar disorder type I.
- Many clinicians relate switches to antidepressant treatment most likely because antidepressants may often shorten the depressive episode, thereby bringing a switch into focus.
- When a patient develops mania or a mixed state in the aftermath of a depression while being on antidepressant, stopping the antidepressant (or reducing the dose) seems advisable in most cases, even though there is no guiding evidence on this issue.
- Acceleration of episode frequency is also a common feature of bipolar disorder, and any proof of causation by the use of antidepressants has not yet been provided.
Introduction

For decades, a debate has been ongoing about two potentially harmful effects of antidepressants in bipolar disorder, i.e. the induction of hypomania/mania and of rapid cycling. Warnings against the administration of antidepressants to patients with bipolar depression are reflected in current American treatment guidelines, e.g. the American Psychiatric Association guideline (1). On the other hand, European treatment guidelines, like the British Association for Psychopharmacology guideline, are less cautious in recommending antidepressants for bipolar disorder (2).

Based on one of the first comprehensive reviews of the literature on this issue, Wehr and Goodwin (3) suggested that some patients with bipolar disorder may become manic and a few experience rapid cycling when treated with antidepressants. However, at the same time, they emphasized the lack of controlled and unbiased studies evaluating this potential adverse effect. One of the later sources of the scepticism against the use of antidepressants in bipolar disorder is the influential and widely cited paper by Peet (4). On the basis of a pooled analysis of data from randomized clinical trials (RCTs) on patients with bipolar depression, provided by pharmaceutical companies, he found that in bipolar depressives, mania occurred statistically significantly more often with tricyclic antidepressants (TCAs) (in 11.2% of cases) than with selective serotonin re-uptake inhibitors (SSRIs) (in 3.7% of cases). However, the difference between the occurrence of mania with TCAs and with placebo (in 4.2% of cases) was not statistically significant. A later comprehensive review by Henry and Demotes-Mainard (5) was less sceptical, and so was the balanced critical summary of the development seen from a European point of view, published by Möller and Grunze (6). Most recently, the authors of a meta-analysis of randomized trials on antidepressants for bipolar depression concluded that the trial data did not suggest that hypomania/mania is a common early complication of treatment with antidepressants (7). This was also concluded in a systematic review by Visser and Van Der Mast (8).

Aims of the study

The essential question addressed in this review is whether switch of depression into hypomania/mania in patients with bipolar disorder is caused by antidepressants or whether this switch is a phenomenon attributable to the natural history of bipolar disorder itself. Furthermore, if this switch and the use of antidepressants are in some ways linked, what does it then mean? Whether antidepressants accelerate cycling independently of any potential mania-inducing action will be addressed more briefly, as valid data on this are scarce. A different but related and clinically important question that will not be addressed directly is whether treatment with antidepressants is related to development of hypomanic/manic symptoms in patients primarily diagnosed with (unipolar) major depressive disorders. Finally, the transition from a depressive episode into an episode with mixed hypomanic/manic and depressive symptoms, which may also be considered a switch, will not be discussed due to lack of data.

Material and methods

Our review is essentially a critical evaluation of published RCTs on antidepressants for bipolar disorder, where sources of bias that have been previously overlooked are pointed out. The published RCTs were identified through an electronic search of MEDLINE through PubMed. In addition, some major meta-analyses, reviews and observational studies were selected, based on an
Extensive electronic search and reference lists of retrieved articles. If not otherwise specified, the reviewed RCTs were conducted double-blindly. RCTs included in cited meta-analyses were not cited separately.

For examining the causation in question, we applied the Bradford–Hill criteria, i.e. specificity of the potential causative agent, strength of effect, consistency in findings, dose–response relation, temporal relation with exposure to agent preceding effect and biological plausibility (9).

Results

Efficacy of antidepressants in bipolar depression

Obviously, any discussion of treatment-related adverse effects has no real meaning if the treatment in question has no clinically relevant efficacy. Our starting point is that antidepressants are beneficial for the treatment of acute bipolar depression, even this has been severely understudied and therefore needs further evaluation in sound RCTs. As pointed out by a recent authoritative review by Möller et al. (10), taking the same starting point, the insufficiency of formal evidence relates to the history of the clinical development of antidepressants, as, for the early trials on TCAs, both unipolar and bipolar depressive patients were recruited, without any differentiation in outcome evaluations. Later on, when the unipolar–bipolar distinction had been adopted and newer antidepressants were tested, patients with bipolar disorder were excluded to avoid the emergence of hypomania or mania, no matter whether this was linked to the therapy or not. Additionally, the basic assumption that antidepressants cause switching has further limited the number of trials testing these drugs in bipolar depression. Accordingly, the recent meta-analysis by Gijsman et al. (7) demonstrated the scarcity of RCTs evaluating the efficacy of antidepressants against placebo in acute bipolar depression. However, based on four RCTs, they found that antidepressants were superior to placebo in terms of response, with a number needed to treat of 4.2 (95% CI 3.2–6.4), which is comparable with effect sizes in other areas of clinical psychopharmacology. A fifth RCT was identified but excluded from the pooled efficacy analysis as only remission rates were provided; this study was overall negative, but positive in a subgroup analysis. In interpreting the results of the meta-analysis, it should be noted that in the majority of the patients, the antidepressant or the placebo was combined with lithium or olanzapine. Indirectly supporting that antidepressants work in bipolar depression, two observational historical follow-up studies demonstrated comparable acute efficacy of antidepressants in unipolar and bipolar depressed patients (10).

In a recent, large placebo-controlled trial conducted as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (the STEP-BD), no benefits of adding an antidepressant (paroxetine or buproprion) in comparison with adding placebo to a mood stabilizer in bipolar depressed patients could be shown (11). However, as pointed out by the authors, the high rate of comorbid psychiatric conditions in the study sample and the fact that the enrolled subjects were already receiving clinical treatment at participating sites may have contributed to the negative findings. Additionally, at randomization, patients had already been treated within the framework of the STEP-BD for around half a year on average, and presumably a substantial number of patients may have shown non-response to other antidepressants before randomization. Moreover, additional treatment with antipsychotics, some of them known to be somewhat effective in treating bipolar depression, was allowed.

How to define switch?

Even though the term switch is often used, there is no clear consensus on its definition. Most would probably consider a switch as occurring when a change from depression into hypomania/mania takes place within the same day, and also when there is a depression on one day and a hypomania or mania on the next day. But what if there is a symptom-free interval of several days, a week, several weeks or even months? In reports addressing the switch phenomenon, this time aspect has not been discussed. In accordance with the current classification systems, which separate two mood episodes of the same polarity by a period of 2 months of remission, a working group of the International Society of Bipolar Disorder is currently discussing a suggestion to define a switch as a change from depression to hypomania or mania developing within 2 months after remission, as opposed to considering such a change a recurrent episode of hypomania or mania, if it occurs later than 2 months after remission (W. A. Nolen, personal observation). In addition, the term treatment-emergent hypomania/mania is often used without explanation or definition. Besides lacking preciseness, this wording may indicate a causal link between the switch into hypomania/mania and the treatment (e.g. with an antidepressant) in terms of induction or precipitation of mood elevation.
Therefore, we will avoid this term in the course of this paper.

Switch as a basic phenomenon of bipolar disorder

The direct transition of depression into hypomania/mania without a symptom-free interval was fundamental for the definition of the ‘folie à deux forme’ proposed by Baillarger (12) in 1854 in Paris; the switch was interpreted as a ‘reaction’ to the preceding depression, emphasizing that switching is part of the bipolar course of illness (13). Some years later, a variety of observed course patterns of bipolar disorder including switches was described (14, 15). On the basis of this literature, published at a time when no effective treatment of depression was yet available, we can conclude that switching is indeed a natural phenomenon inherent in the disorder. However, this observation obviously does not exclude the possibility that specific treatments may increase the likelihood of switching. It argues only against the criterion of specificity, as treatment is not the only factor that can be linked to switching.

To compare the frequency of switching before and after antidepressant treatments were available, a retrospective chart review of admissions for depression from 1900 to 1989 (patients with unipolar and bipolar disorders separated) was carried out (16, 17). As displayed in Table 1, switch rates in unipolar depressed patients were, respectively, 3.0% and 4.6%, before and after the introduction of antidepressants; in bipolar depressed patients, similar rates of around 29% were observed for the two periods. In addition, the rates did not differ across the three time periods after 1958. In this study, switches were defined as immediate changes from depression to hypomania/mania. When unipolar and bipolar depressed patients were analysed together, the total switch rate since 1958 was 9.2%.

The finding that rapid cycling seems to be a risk factor for switching (19), supports the notion that switch from depression to hypomania/mania in bipolar disorder is a phenomenon inherent in the illness. In addition, Akiskal et al. (20) observed that among patients primarily diagnosed with nonbipolar affective disorder, a subsequent development of hypomaniac/ manic symptoms associated with treatment with antidepressants was more or less specifically associated with a positive family history of bipolar disorder and a later development of what they called ‘spontaneous’ mania.

Switch during treatment with antidepressants: short-term trials

Antidepressants vs. placebo. There are many observational studies showing a temporal relationship between the use of antidepressant and switching, suggesting that antidepressants may induce or precipitate hypomania/mania in bipolar disorder [see review by Wehr and Goodwin (3)]. However, due to frequent spontaneous occurrences of switches as outlined above, all these studies suffer from selection bias and are therefore essentially inconclusive. The best way to overcome this source of bias is to conduct randomized parallel-group, placebo-controlled trials.

In the aforementioned meta-analysis by Gijsman et al. (7) evaluating the efficacy of antidepressants in bipolar depression, only five RCTs comparing an antidepressant with placebo (n = 725) could be identified. In these trials, 75% of the patients were concomitantly treated with a mood stabilizer (including olanzapine); only two smaller trials of the five trials were monotherapy trials. Operational criteria for switching into mania were predefined in only two of the five trial reports, while none of the reports were clear as to whether switching only comprised an immediate switch from depression or also the development of hypomaniac/manic symptoms after a symptom-free interval. Nevertheless, inferences on switch could be made from all of them, and the pooled total switch rates when on treatment with antidepressants and placebo were 3.8% and 4.7%, respectively, and not statistically

Table 1. Switch rates from depression to hypomania/mania among random samples of hospital admissions from 1900 to 1981

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<td>266</td>
<td>72</td>
<td>76</td>
<td>987</td>
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<td>12</td>
<td>4</td>
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<td>36</td>
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<td>Switches (%)</td>
<td>1900–1957: 3.0*</td>
<td>1958–1981: 4.6*</td>
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<td>Bipolar disorder (numbers)</td>
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<td>3</td>
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<td>28</td>
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<td>119</td>
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<td>Switches (numbers)</td>
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<td>–</td>
<td>3</td>
<td>3</td>
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<td>Switches (%)</td>
<td>1920–1957: 29.2</td>
<td>1958–1981: 29.5</td>
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*P = 0.4. Data from 1920 to 1981 are published in Angst (16); data from 1900 to 1919 are in part published in Angst et al. (17).
significantly different. However, as the majority of the patients received a mood stabilizer, interpretations of the potential risk of antidepressants given in monotherapy are not possible.

A thorough analysis of the switch data from the largest of the RCTs included in the meta-analysis revealed that there was absolutely no increased rate of hypomanic or manic symptoms in patients treated with a combination of fluoxetine and olanzapine ($n = 86$) when compared with patients treated with olanzapine alone ($n = 370$) or placebo ($n = 377$) (21), despite a superior antidepressant efficacy of the combined treatment. Additionally, the recent, placebo-controlled RCT from the STEP-BD cited previously showed that predefined switch into hypomania or mania occurred in 10.1% of bipolar depressed patients randomized to a combination of a mood stabilizer and an antidepressant (paroxetine or bupropion) ($n = 179$) and in 10.7% in patients randomized to a mood stabilizer alone ($n = 187$) (11).

One antidepressant vs. another antidepressant. Based on a subset of six RCTs comparing TCAs with other antidepressants ($n = 370$), Gijsman et al. (7) found switch rates of 10% and 3.2%, respectively, a difference that reached statistical significance, but again, only three of these six trials had operational, predefined criteria for mania, and none of the reports provided information on the duration of the symptom-free interval. Despite the fact that additional mood stabilizers were frequently used in this subset of trials as well, the different switch rates observed between classes of antidepressants may suggest causality through an underlying biological mechanism. However, comparisons of switch rates like this, computed as the number of switches divided by the total number of treated patients, may introduce a bias that has been previously overlooked. The point is that the likelihood of switching into hypomania/mania is dependent on the course of depressive symptoms: a patient who has remitted from depression seems to be at a higher risk of switching than a patient with persistent depressive symptoms (22). Therefore, the higher switch rates observed with TCAs might be simply a methodological artefact explained by a higher efficacy of TCAs. On the other hand, this point may be seemingly contradicted by another finding from the cited meta-analysis, namely that TCAs in comparison with other antidepressants were not associated with higher efficacy. However, this finding was based on only 296 of the 370 patients used for the analysis of switch rates, and more importantly, only one of the trials ($n = 74$) reported remission rates (7). In addition, it should be noted that none of the reports which provided numbers of patients with response or remission were clear as to whether patients who switched were also counted as responders/remitters or not. Evidence that remission rates in patients on TCAs may be higher than those seen in patients on other antidepressants comes from the Danish University Antidepressant Group comparing clomipramine with three newer antidepressants in mixed populations of unipolar and bipolar acutely depressed in-patients (23).

A recent study from the Stanley Foundation Bipolar Network also addressed whether various antidepressants as adjuncts to mood stabilizers may differ in their potential risk of inducing switch (24). When bipolar depressed patients on a mood stabilizer ($n = 184$) were randomly assigned to a 10-week trial with bupropion, sertraline or venlafaxine, a switch into mania (operational defined) occurred in 10% and 9% of the patient treated with bupropion and sertraline, respectively, and in 29% of the patients treated with venlafaxine; based on survival analysis, the time to switch were reported to be statistically significantly shorter in the latter group when compared with that in the two other groups (24). As the remission rates in the three groups were comparable, the potential source of bias mentioned above could seemingly not explain this difference in switch rates. However, the authors found that the increased switch rate on venlafaxine was largely accounted for by an increased risk of switch in the subgroup of rapid cyclers, and for this subgroup no specific information regarding remission rates were reported. In addition, the shortening of time to switch may simply reflect the shortening of depression, i.e. the efficacy of the particular antidepressant.

In another comparative RCT not included in the meta-analysis reviewed above because it was not double blind, venlafaxine and paroxetine were compared as an add-on treatment for patients with bipolar depression (25). Four bipolar depressed patients treated with venlafaxine plus a mood stabilizer ($n = 30$) developed predefined hypomania or mania during the 6 weeks trial as compared to one patient treated with paroxetine ($n = 30$). The switch rates were not statistically significantly different, but the authors suggested that there was a slightly higher risk of switch with venlafaxine. Interestingly, there was also a numerically slightly but not statistically significantly higher remission rate associated with venlafaxine.

In the comparison of switch rates associated with different classes of antidepressants by Peet (4) cited above, the rates were also computed using the total number of treated patients as the denominator,
i.e. not taking any differences in remission rates into consideration.

Switch during treatment with antidepressants: long-term trials

As outlined above, there are limited controlled data on the relationship between treatment with an antidepressant and immediate switching. However, controlled data on the relationship between treatment with an antidepressant and the development of hypomanic/manic symptoms in patients with bipolar disorder after a symptom-free interval are even more limited. In an early trial by Prien et al. (26), patients with bipolar disorder on imipramine had a higher rate of mania than those receiving placebo. However, numbers were very low and the difference was not statistically significantly different. In a subsequent trial, Prien et al. (27) treated patients with bipolar disorder, who were euthymic at the beginning of the study with imipramine, lithium or their combination over a follow-up period of up to 2 years. In this study, they found lower (and similar) rates of mania in the groups receiving lithium monotherapy or lithium plus imipramine when compared with the rate in the group receiving imipramine monotherapy. However, whether this suggests that lithium does protect against mania induced by imipramine or whether lithium simply prevents the natural occurrence of mania is uncertain. Finally, in a comparable trial by Quitkin et al. (28) comparing only lithium monotherapy and lithium plus imipramine, there were numerically (but not statistically significantly) more patients treated with a combination of imipramine and lithium than patients treated with lithium alone who developed a manic episode over a follow-up period of up to 2.5 years.

Switch in bipolar disorder type 1 vs. switch in bipolar disorder type 2

A post hoc analysis of the data set from the Stanley Foundation Bipolar Network mentioned above indicated that depressed patients with bipolar disorder type 2 given an antidepressant and a mood stabilizer might have a lower switch rate than patients with bipolar disorder type 1 receiving the same treatment modalities (29). However, the potential differences in remission rates between the two types of bipolar disorder were not taken into account. There are also other studies suggesting a low risk of switch in bipolar disorder type 2 even when treated with antidepressant monotherapy (30, 31).

Switch and dosing of antidepressants

With regard to a dose–response effect for antidepressants, i.e. higher doses producing higher switch rates, which would argue towards causality, there is some anecdotal information but no evidence in terms of RCTs. On the contrary, there are data suggesting that some antidepressants are well tolerated in high doses: fluoxetine in a dose of up to 60 mg/day (32) and sertraline in a dose of up to 200 mg/day (24).

ECT and the risk of switch

It is interesting that the debate on switch focuses strongly on antidepressants and often neglects electroconvulsive therapy (ECT), which is still the most powerful antidepressant treatment. The literature on ECT and switches is rather limited (33, 34), and very high switch rates of up to 50% during ECT are reported; this high rate may be linked to the high antidepressant efficacy of ECT.

Antidepressants and cycling

Another controversial issue closely linked to the issue of switching is whether the use of antidepressants may accelerate episode frequency in patients with bipolar disorder, eventually leading to rapid cycling (35). In an observational study (n = 16), Ghaemi et al. (36) found that the use of antidepressants was associated with a more than twofold increase in the number of episodes per year compared with the year before start of the antidepressant. However, as pointed out by Coryell et al. (37), the temporal association between treatment with antidepressants and rapid cycling reported in observational studies could most likely be explained by the fact that the included patients sought treatment for depression, which independently has been found to be a predictor of rapid cycling. In addition, based on their own long-term follow-up of 345 patients with bipolar disorder over a mean of 13.7 years, the authors could not find any evidence that treatment with TCAs (or by inference other antidepressants as well) was even associated with rapid cycling (38). The two randomized studies cited above comparing patients with bipolar disorder on imipramine plus lithium with those on lithium alone also did not demonstrate an association between rapid cycling and treatment with imipramine (27, 28). In a recent review by Kupka et al. (39) of predictors of rapid cycling in bipolar disorder, it was concluded that systematic data on any causal role of antidepressants in the development of rapid cycling are lacking.
A potential link between rapid cycling and the use of antidepressants has also been addressed in prospective studies with daily assessments of mood. In a recent naturalistic three-centre study in the USA and Canada, mood changes of 80 patients with bipolar disorder (33 receiving no antidepressants and 47 receiving antidepressants) were self-assessed through daily recordings of their mood over 3 months. As expected, patients on antidepressants spent a greater number of days in depression compared with patients not on antidepressants. The same was true for patients with bipolar disorder type 2 compared with patients with bipolar disorder type 1. However, switching and rapid cycling did not differ between the two diagnostic subgroups and between the two treatment groups (40). These conclusions were recently confirmed by an extension of the sample (by the inclusion of more centres) to 182 patients (41).

**Discussion**

How can our knowledge of antidepressant-associated switch be improved?

Despite the fact that the switch phenomenon can be examined through various types of RCTs, e.g. comparisons of antidepressant and placebo on top of a mood stabilizer, the only way to study the risk of antidepressants *per se*, i.e. when they are given alone, is obviously by conducting placebo-controlled monotherapy trials. However, as antidepressants (despite a possible absence of any switch inducing potential) apparently do not protect against the emergence of manic symptoms, the relevance of such trials could be questioned, at least for patients with bipolar disorder type 1. Even in conducting RCTs, one needs to be aware that the sample sizes required to produce a sufficient statistical power for not overlooking a clinically relevant difference in switch rates should be relatively large, as switching is a rare event after all. On the other hand, RCTs are generally not powered for adverse events, and numerical differences should be looked at regardless of any absence of statistically significant differences.

Besides the importance of the overall study design, attention should be paid to the fact that the analyses may introduce errors in between-group comparisons of risks of switching. As switching into hypomania or mania may more likely develop through or after a clinically observable phase of remission than directly from depression, in addition to an intention-to-treat analysis including all the subjects in the denominator whether they remit or not from their depression, a subanalysis using the number of remitters as the denominator for the risk calculations should always be provided (42). However, when selecting a subsample of remitted patients from a randomized trial for further analyses, one needs to be aware that the treatment groups then may not be balanced any more in terms of baseline clinical variables such as number of previous episodes or previous rapid cycling. Additionally, the statistical power will be reduced.

In more recent reports, time to switch as opposed to switch rates is used as an outcome measure and analysed through survival analysis. This can be misleading, because a seemingly favourable outcome, longer ‘survival’ until switch, may essentially reflect an unfavourable outcome: longer time being in non-remitting depression. One way to use survival analysis for the study of the switch phenomenon would be to consider the point of remission as the starting point (time zero). In this way, it would be possible to address any differential time course in the development of switches.

Another methodological point is that trials are restricted to a certain observation period and therefore cannot give information about the total rates of switches; non-responders may switch after completion of the acute study, i.e. after a late drug-induced or spontaneous remission from the episode. Actually this was the case during the follow-up after the 10-week acute treatment period of the aforementioned study by the Stanley Foundation Bipolar Network (24). To be able to include all cases of remission, longer periods of observation, e.g. up to 1 year, are needed.

When studying the potential negative impact of antidepressants or any other treatment in bipolar depression in terms of switch into hypomania/mania, the overall course of illness (including a patient’s perspective) also needs to be taken into account. Even if antidepressants could be found to induce switches to a larger extent than other treatments, then it might be that the total burden of illness due to shortening of total duration of depression would be diminished. One way to address these aspects is to measure total morbidity, i.e. total duration (and severity) of depression, mania and hypomania, across the time of observation and to compare this across treatment groups. Assessments with the life chart method (43, 44) or with the chrono method (40) will actually make it possible to obtain this information on overall morbidity. Unfortunately, with these methods, mixed symptomatology cannot be sufficiently assessed, making it impossible to capture the phenomenon that a patient may develop hypomaniac or manic symptoms while still

**Antidepressants and switching into hypomania/mania**
being depressed. This clinically important aspect of the switch phenomenon has not been addressed in controlled studies hitherto. Linked to this issue is the fact that the available studies operating with predefined criteria for switch into mania allow the presence of a few manic symptoms without recording them, see, e.g. Sachs et al. (11).

When evaluating whether antidepressants (or any treatment) may accelerate cycling, it is crucial not only to measure the total number of episodes (which is possible with both methods mentioned above), but also total morbidity, as a patient with multiple brief episodes can spend less total time in them than a patient with a few long episodes.

Summarizing – towards a consensus?

We know for certain that switches from depression into hypomania/mania and/or acceleration of cycling are in many cases attributable to the natural history of bipolar disorders. On the basis of the available studies, and taking the methodological limitations into account, we could not find any conclusive unbiased evidence supporting the notion that antidepressants can induce switching or accelerate cycling. However, it should be noted that stating that there is no evidence for such a risk is obviously not the same as stating that there is evidence for no such risk. Nevertheless, there is some evidence suggesting that antidepressants given in addition to a mood stabilizer are not associated with an increased rate of switch when compared with the rate associated with the mood stabilizer alone, despite the fact that the efficacy of the combined treatment in some studies has been found to be larger than that of the mood stabilizing treatment alone. On the other hand, some studies have shown that particular antidepressants (TCAs and venlafaxine) seem to be more associated with switching than others, even when combined with a mood stabilizer, which suggests a causal link. However, this needs to be re-evaluated in properly designed randomized studies addressing the methodological points discussed in detail above. Moreover, the potential risk that antidepressants may induce mixed states needs to be addressed in future studies. Likewise, there are no systematic data guiding whether to continue or discontinue an antidepressant when hypomaniac or manic symptoms develop in a patient treated with an antidepressant. Finally, future sound RCTs on antidepressants for the treatment of bipolar depression are needed for further evaluation of the potential benefits of these drugs.

How can we understand that many clinicians, despite the lack of evidence, relate switches to treatment? Besides the potential explanation that even valid clinical experience may not always be captured in strict evidence, what happens most likely is that antidepressants often change the course of the illness, bringing a switch into focus: compared with placebo, effective antidepressant treatments create more remitters, and as a consequence of the remission and the nature of the illness a further, sometimes rather quick, switch into hypomania or even mania may follow. Likewise, the probability of observing switches within the first few weeks of treatment will increase with higher antidepressant efficacy of a given treatment, explaining the impression that the probability will be higher with ECT than with some antidepressants such as the SSRIs. And finally, of course, we have to be aware that the assumption that antidepressants induce switching is also influenced by experts, guidelines and by the industrial marketing of alternative pharmaceutical products.

Taken together, the belief that antidepressants (even in combination with mood stabilizers) induce switches and/or rapid cycling is not sufficiently justified by evidence. This belief may create unnecessary anxiety not only among clinicians but also among patients and their relatives. With the current level of evidence, no strong clinical recommendations can be made. However, to be on the safe side, antidepressants given as monotherapy cannot be recommended, at least not when treating patients with bipolar disorder type 1. Likewise, when a patient develops mania or a mixed state in the aftermath of depression (or later) while on an antidepressant, stopping the antidepressant (or reducing the dose) is clinically advisable in most cases.

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Declaration of interest

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Antidepressants and switching into hypomania/mania


