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# Avoiding Drug-Induced Switching in Patients with Bipolar Depression

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## Abstract

Antidepressant-induced switching is a major risk during the treatment of bipolar depression. Despite several clinical studies, questions remain regarding both the definition of these mood switches and the most appropriate therapeutic strategy to avoid this adverse effect.

This review will first briefly consider the current guidelines for the acute treatment of bipolar depression. We will then review the mechanisms of action of antidepressant and mood stabilisers, and the switches induced by various types of antidepressant treatments, or triggered by antidepressant withdrawal, as well as by atypical antipsychotics. We then will address the risk of mood switch according to the type of mood stabiliser used. The propensity to mood switches in bipolar patients is subject to individual differences. Therefore we will describe both the clinical and biological characteristics of patients prone to mood switches under antidepressant treatment. However, the clinical characteristics of the depressive syndrome may also be a key determinant for mood switches. Various data help identify the most appropriate drug management strategies for avoiding mood

switches during the treatment of bipolar depression. Selective serotonin reuptake inhibitors appear to be the drugs of first-choice because of the low associated risk of mood switching. Antidepressants must be associated with a mood stabiliser and the most effective in the prevention of switches seems to be lithium. Whatever the mood stabiliser used, effective plasma levels must be ensured. The optimal duration of antidepressant treatment for bipolar depression is still an open issue – prolonged treatments after recovery may be unnecessary and may facilitate mood elation. Moreover, some mood episodes with mixed symptoms can be worsened by antidepressants pointing to the need for a better delineation of the categories of symptoms requiring antidepressant treatment. Finally, as a result of this review, we suggest some propositions to define drug-induced switches in bipolar patients, and to try to delineate which strategies should be recommended in clinical practice to reduce as far as possible the risk of mood switch during the treatment of bipolar depression.

There have been many studies addressing acute treatment of mania and prophylaxis for bipolar disorders. In contrast, few studies have been devoted specifically to treatment strategies for depression in patients with bipolar disorders, and the results of such studies have been limited or inconclusive.[1] Indeed, most of what is known about the treatment of depression is derived from clinical trials that systematically excluded depressed bipolar patients. The section of the National Institutes of Mental Health workshop report dealing with the treatment of depressed bipolar patients stresses the need for more research in this field.[2] A recent review on use of antidepressant for bipolar depression notices that available information on this field is not adequate to conclude.[3] However, depressive episodes in patients with bipolar disorder are associated with considerable morbidity and mortality. The mean duration of bipolar depressive episodes is far longer than that of manic episodes, and more than 20% of bipolar depressive episodes have a chronic course.[4] In addition, 19% of bipolar patients kill themselves.[5] However, concerns about the risks, such as manic episodes and rapid cycling, associated with antidepressant treatment, continue to hamper the establishment of an optimal treatment paradigm for bipolar depression.

The objective of this article is to review the literature focused on *the risk of switch* during treatment for bipolar depression. Thus, some studies about treatment of bipolar depression may not be considered because they do not report data about mood switches. Data sources included the MEDLINE database and relevant references from articles obtained in this search and in major reviews. This review will first briefly consider the current guidelines for the acute treatment of bipolar depression. We will then review the mechanisms of action of antidepressants and mood stabilisers, and the switches induced by various types of antidepressant treatments, or triggered by antidepressant withdrawal, as well as by atypical antipsychotics. We then will address the risk of mood switch according to the type of mood stabiliser used. The propensity to mood switches in bipolar patients is subject to individual differences. Therefore we will describe both the clinical and biological characteristics of patients prone to mood switches under antidepressant treatment. However, the clinical characteristics of the depressive syndrome may also be a key determinant for mood switches. Finally, as a result of this review, we suggest some propositions to define drug-induced switches in bipolar patients, and to try to delineate which strategies should be recommended in clinical practice to reduce as far as possible the risk of mood switch during the treatment of bipolar depression.

## 1. Guidelines for Treating Depressive Episodes in Bipolar Patients

There are very few specific data on the efficacy of antidepressants in bipolar depression. Generally, the results of studies of non-bipolar depression are extended to bipolar depression partly because regulatory agencies, including the US FDA, have not required separate studies of bipolar depression. Moreover, bipolar depressed patients are now frequently excluded from studies of antidepressants because patients with concomitant medication, for example mood stabilisers, cannot be included.

Various guidelines for therapeutic strategies for bipolar disorders have been defined by expert consensus. Guidelines for the acute treatment of bipolar depression suggest different treatments depending on the severity of the current depressive episode and the type of bipolarity.[6,7] In bipolar I patients with psychotic depression, the recommended treatments are either electroconvulsive therapy (ECT) or the combination of an antipsychotic, a mood stabiliser, and an antidepressant. For severe depression without psychotic features, the treatment of choice is the combination of a mood stabiliser and an antidepressant. For milder major depressive episodes, a mood stabiliser alone or a mood stabiliser and an antidepressant are recommended. There is a clear consensus against using an antidepressant without a mood stabiliser in bipolar I patients. More recently, the revised guidelines of the American Psychiatric Association suggest lithium or lamotrigine as first step for depressive episodes.[8] For bipolar II patients, antidepressants can be used alone if hypomanic episodes are mild and infrequent. Psychotherapy can be also useful for this group of depressed patients.

The first choice antidepressant for bipolar disorders is bupropion or a selective serotonin reuptake inhibitor (SSRI).[7] After recovery from a major depressive episode in bipolar disorder, the question is how long should antidepressants be continued. Currently, there is no consensus. For most of clinicians, the decision depends on an evaluation of history and response to medication. This review collects data pertinent to the management of bipolar depression and avoidance of mood switching.

## 2. Drugs and Mechanisms of Action

Despite genetic and neuroimaging studies in humans, and extensive studies in animal models of depression, little is known of the biological mechanisms underlying mood alterations, and most of our current knowledge is derived from pharmacological data. The most widely used treatments for manic episodes are antipsychotics (acting by blockade of dopamine and serotonin receptors subtypes with a wide range of pharmacological profiles) and mood stabilisers. Blockade of monoamine inactivation is the prominent mechanism of antidepressant treatment, leading to both an increased half-life of the neurotransmitter in the synaptic cleft and to an increased diffusion space around the synapse. These spatial and temporal changes in neurotransmitter function can be achieved through inhibition of chemical inactivation of the neurotransmitter by monoamine oxidase inhibitors (MAOIs) [MAO type A being more specific for serotonin neurotransmission, and MAO type B for dopamine neurotransmission]. However, the most widely used antidepressants block the reuptake inactivation of monoamines. Tricyclic antidepressants (TCAs) act mainly by inhibiting the reuptake of noradrenaline (norepinephrine), dopamine and serotonin. Other drugs are more specific for a given neurotransmitter system, and this may account for the differences between the action of SSRIs and those of atypical drugs such as bupropion (mostly noradrenergic and dopaminergic) and venlafaxine (mostly noradrenergic and serotoninergic). Dopamine reuptake blockers, such as amineptine, have been used as antidepressants in some countries, but their cocaine-like dopaminergic mechanism of action and their propensity to induce addiction have led to removal from the market.

Few data are currently available regarding the brain targets and the functional alterations resulting from the action of these drugs on the CNS. Serotonin activates a wide diversity of brain receptors, including the 5-$HT_2$ family of serotonin receptors

coupled to the phospholipase-C (PLC) pathway through members of the $G_q$-$G_{11}$ family of transduction proteins. Alterations in protein kinase C activity and in inositol phosphate metabolism, two effectors of PLC, have been described in depressive and manic patients.[9,10] Inositol has been proposed as a treatment for bipolar depression.[11] Inositol phosphate metabolism may be a second messenger pathway in the mechanism of mood alterations and stabilisation, since the main classes of mood stabilisers (lithium, carbamazepine and valproic acid) all act by inositol depletion[12] although other mechanisms have been postulated.[13,14] However, this basic knowledge does not allow prediction of which drug and which mechanism are involved in drug-induced mood switches.

## 3. Antidepressants and Mood Switches

### 3.1 Tricyclic Antidepressants

Bunney[15] reviewed 80 studies involving 3923 patients mostly treated with TCAs for depression and found that the incidence of mania or hypomania was 9.5%. The first more systematic studies of treatment with TCA were those by Prien et al.[16,17] and they considered mood elation under such treatment as established. The first study compared 2 years of lithium maintenance with imipramine maintenance in unipolar and bipolar I patients.[16] This study reported that 67% of bipolar patients receiving imipramine had manic episodes, and this was double the spontaneous rate in the placebo group. A subsequent large-scale multicentre study of bipolar I patients compared maintenance treatments using lithium, imipramine, or a combination of the two.[17] Fifty-three percent of the imipramine-treated patients had manic or mixed recurrence, compared with 26% of the patients treated with lithium and 28% receiving the combination treatment. However, these studies do not answer the question concerning switches induced by TCAs. They addressed the prevention of the occurrence of new episodes as a function of the maintenance treatment that could be due to the natural course of the illness rather than mood-switch.

Akiskal et al.[18] reported that 44% of patients with cyclothymia developed clear hypomania in the course of treatment with TCAs and that this represents a validating criterion for inclusion in the bipolar affective group. Wehr and Goodwin[19] conducted a longitudinal study in a group of 26 bipolar patients (type I and II) whose treatment included periods of TCA administration. Of 19 patients who responded to medication, 18 showed manic or hypomanic switches while on TCAs. The onset of manic episodes occurred, on average, 21 days after treatment began, whereas the average time of onset of hypomania in bipolar II patients was 35 days. This study is well known for its results concerning rapid cycling induced by TCAs in manic-depressive patients. Lewis and Winokur[20] reported some controversial data. In a retrospective case note survey they found that a switch to mania occurred during 23% of admissions when TCAs were used and in 34% when no treatment was given. They concluded that TCAs do not increase the risk of switching to mania. However, this conclusion must be viewed with caution because treatment allocation was not random, but was by the physician's choice, with the consequent risk of bias, and also because a switch was defined as a patient becoming manic within six months. This raises the issue of switch definition. Indeed, the natural course of the disease may contribute to the occurrence of switches while on antidepressants. Taking this problem into account Altshuler et al.[21] found in a longitudinal retrospective study that 35% of 51 patients had likely antidepressant-induced manic episodes (most treated with heterocyclic antidepressants) and 26% experienced cycle acceleration.

Other studies compared the incidence of switching between TCAs and other antidepressant medications. Pooled data from databases of pharmaceutical industries show that mood switches occur considerably more frequently with TCAs (11.2%) than with SSRIs (3.7%) or placebo (4.2%).[22] However, these apparently low rates of switching should be viewed with caution: information concerning the use of mood stabilisers, and the inclusion of unipolar and bipolar subjects is lacking, there is no strict diagnos-

tic criteria for mania and hypomania, the percentage of rapid cyclers included is not known and the duration between onset of treatment and mood elation was not defined.

One prospective study assessed the response to naturalistic treatment of 29 bipolar I patients who experienced a total of 79 depressive episodes.[23] The treatment given consisted principally of mood stabilisers used alone or in combination with antidepressants. They showed that switches occurred in 28% of their patients and were judged to be extremely disruptive in only 10%. In this study, manic or hypomanic episodes had to occur within 2 months of each depressive episode to be recorded as such. Surprisingly, antidepressant treatment combined with mood stabiliser therapy was not associated with a higher frequency of post-depressive mood elation than mood stabiliser therapy alone. Switch rates for TCAs and MAOIs were 32% and 35%, respectively, but TCAs were associated with more intense switches.

### 3.2 Selective Serotonin Reuptake Inhibitors

The safety and tolerability of SSRIs have made these drugs the standard first-line treatment for bipolar depression.[7] However, few reports have assessed the efficacy of SSRIs in bipolar depression and the risk of drug-induced mania with this type of antidepressant. Some studies of adverse events associated with SSRIs in bipolar patients are only descriptive[24,25] and there are few double-blind studies reporting the use of SSRIs in bipolar depression. The first was by Cohn et al.,[26] who compared fluoxetine with imipramine and placebo in double-blind treatment of bipolar I depression. Unfortunately, few of the patients in this study were receiving lithium (25%). This makes it difficult to interpret the risk of mania relative to that associated with the standard use of mood stabilisers together with antidepressants. The mania switch rate was low in all three groups in the 6-week double-blind phase, but in the open crossover phase, about 15% of those on fluoxetine switched to mania or hypomania. Thus, this study showed also that after 3 weeks of treatment the level of treatment response to fluoxetine (60%) was better than that to imipramine (40%), but not statistically significant, and that only 7% of fluoxetine-treated patients discontinued treatment due to adverse events, versus 30% of patients treated with imipramine.

The second study was by Young et al.[27] It was a large multicentre, industry-sponsored clinical trial comparing paroxetine, imipramine and placebo, as an add-on to lithium, in refractory bipolar I depression. No case of mania was reported with paroxetine whereas mania occurred in about 10% of patients treated with imipramine.

The third double-blind study compared the addition of paroxetine to a mood stabiliser (lithium carbonate or divalproex sodium [valproate semisodium]) with a second mood stabiliser for inpatients being treated with divalproex or lithium.[28] Significant improvements in depressive symptoms were recorded for both groups during the 6-week trial. However, the drop-out rate was significantly higher for the group treated with the two mood stabilisers than for the group treated with a mood stabiliser and paroxetine. The addition of paroxetine to the treatment of 11 patients did not lead to the onset of manic symptoms in the 6-week period.

The largest series of SSRI treatment of bipolar II patients and non bipolar patients with fluoxetine monotherapy reported a low mania switch rate in bipolar patients (3.8% during a treatment period of 12 weeks).[29]

We assessed[30] the response of 44 patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[31] criteria for bipolar disorder to naturalistic treatment given for at least 6 weeks. We found that switches to hypomania or mania occurred in 24% of patients treated with SSRIs. There was no difference in the incidence of switches for fluvoxamine (33%, 4 of 12), fluoxetine (25%, 2 of 8) and paroxetine (20%, 2 of 10) but the size of each subgroup was too small for definitive conclusion.

At this time, there is no one favourite SSRI for depression treatment in bipolar patients. Moreover, some clinicians disagree about the advantages or disadvantages of some of these drugs. For example,

fluoxetine seems to have advantages for patients with prominent anergia[32] but some practitioners consider that the long half-life of the metabolite is a disadvantage in cases of mood switch. Further studies are required to compare SSRIs with each other, may be associated with difference risks of switching.

### 3.3 Monoamine Oxidase Inhibitors

Himmelhoch et al.[33] reported the frequency of mood elation to be 21% with an irreversible and nonselective MAOIs and 25% with imipramine within 12 weeks of treatment. This controlled and double-blinded study was conducted in bipolar patients with anergic depression. It showed that 30 to 60 mg/day of tranylcypromine was significantly more effective than 100 to 300 mg/day of imipramine and was equally effective for bipolar I and II. Moclobemide, a reversible inhibitor of monoamine oxidase type A (eliminating the need for a restricted diet) also seems to be effective in bipolar depression[34] but no information is available concerning mood switch.

Stoll and colleagues[35] analysed data in a retrospective study comparing 49 consecutive inpatients with antidepressant-associated manic states with 49 matched inpatients with spontaneous mania. They found that antidepressant-associated mania tended to be milder and of shorter duration than spontaneous mania. They suggested that MAOIs and bupropion trigger manic states that are milder than those triggered by TCAs and fluoxetine. However, there was no difference in any variable assessed except for the Clinical Global Impression severity score on admission. Silverstone,[36] in a randomised, double-blind, multicentre study compared the efficacy, tolerability and risk of precipitating mania of moclobemide and imipramine in the treatment of bipolar depression during a 8 weeks period. There were no statistically significant differences between the two groups on any measures.

Thus, some authors suggest that even if MAOIs are not simple to prescribe, they offer the most credible alternative to ECT for bipolar patients who have not responded to SSRI or bupropion.[37] However, MAOIs cannot be used shortly following SSRI treatment because of the risk of serotonin syndrome,[38] and have to be prescribed cautiously to patients taking lithium for the same reason.

### 3.4 Bupropion, Other Newer Antidepressants and Electroconvulsive Therapy

Bupropion, a selective noradrenaline and dopamine reuptake inhibitor, has been suggested for the treatment of bipolar depression, not only because of its efficacy, its favourable adverse effect profile but also because of a probably lower risk of inducing switches to hypomania or mania.[39,40] The most recent double-blind trial was done by Sachs et al.[41] to assess efficacy and rate of treatment-emergent mood elation in depressed bipolar patients when bupropion or desipramine was added to an ongoing therapeutic regimen of lithium or an anticonvulsant. Mania or hypomania was observed in five of ten desipramine-treated patients, but only one of nine treated patients during the 1 year maintenance phase. However, Fogelson et al.[42] did not find that bupropion is less likely to induce mood elation than other antidepressants.

Other more recent studies are inconclusive.[43,44] One multicentre study by the Stanley Foundation research network is underway and another one by the Systematic Treatment Enhancement Program for Bipolar Disorder has recently been started to provide some answers to this issue.[45]

The efficacy and safety of venlafaxine were examined in 17 bipolar II patients versus 31 unipolar patients with major depression.[46] After a 1-week placebo lead-in, patients were randomly assigned to double-blind treatment with venlafaxine once versus twice daily starting at 37.5mg daily and increasing up to 225mg daily. The overall efficacy in bipolar and unipolar patients by 6 weeks of treatment was similar and no episodes of venlafaxine-induced 'manic switch' were observed in either patient group. The author concluded that these preliminary findings suggest that short-term, 6-week venlafaxine treatment may be a safe and effective antidepressant monotherapy for bipolar II major depression. However, the period of evaluation was too short to be

definitive and some case reports suggest possible mood switch associated with venlafaxine.[47,48] The randomised trial conducted by Vieta et al.[49] to compare the efficacy and safety of paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilisers have confirmed this possible mood switch with venlafaxine. After 6 weeks of treatment, the results have shown that paroxetine (mean of dosage: 32.3 mg/day) and venlafaxine (mean of dosage: 179.2 mg/day) are both effective and well tolerated but with a slightly higher risk for switch to mania or hypomania with venlafaxine. Despite this point, the practitioners surveyed by Sachs et al.[50] ranked venlafaxine as the best next choice for bipolar depression not responding to SSRIs or bupropion.

Currently, the experience of treating bipolar depression with other new antidepressants is limited and the risk of inducing manic switches cannot yet be estimated with confidence.

Very few studies have compared the risk of switch associated with ECT to that associated with antidepressants. Lewis and Winokur[20] found in the bipolar patient subgroup switch rates of 22% with ECT and 15% with TCAs. More recently, Angst et al.[51] reported that the risk of a switch to hypomania or mania was 37.5% in patients treated with ECT, compared with 29.5% in patients treated with an antidepressant and 28.5% in patients receiving no treatment. We found a very similar rate of switch with a frequency of 36% with ECT and 24% with an antidepressant.[30] In our study, we only took into account immediate switching from depression to hypomania or mania after the application of ECT, and not those having subsequent antidepressant treatment. The advantage of ECT is that continuation of treatment by ECT also improves mood elation.

### 3.5 Paradoxical Effects of Antidepressants: Antidepressant Withdrawal-Induced Mania or Hypomania

In a letter, Gabbay et al.[52] described the risk of mood switch induced by the use of combined antidepressant treatment in bipolar patients. This raises the issue of the need to try another type of antidepressant first rather than to give a combination to bipolar patients with persisting depression. In the letter, Gabbay et al. reported another case from Zubieta[53] to illustrate this point. The paper of Zubieta[53] reports a switch that occurred 4 days after the onset of bupropion treatment and two days after discontinuing fluoxetine. The authors speculated that the manic episode might have been caused by the combination of bupropion and fluoxetine, still present due to the long half-life of fluoxetine. Four days appears as a very short time interval as the onset of antidepressant activity and the switches induced by bupropion usually occur later.[39] Possibly, it was not the combination of the two antidepressants, but rather the discontinuation of fluoxetine that was responsible for the mood change. This effect was described by Goldstein et al.[54] who reported six cases of antidepressant discontinuation-related mania in bipolar patients, in spite of adequate concomitant mood-stabilising treatment. This phenomenon is also known for TCAs[55,56] and includes: (i) general somatic gastrointestinal distress often accompanied by anxiety and agitation; (ii) sleep disturbance; (iii) movement disorder; and (iv) hypomania or mania. This syndrome seems to be related to a withdrawal-induced cholinergic overdrive by blockade of the muscarinic receptors[57] resulting in supersensitivity of muscarinic receptors to acetylcholine.

Abrupt withdrawal of SSRIs can have similar effects: following discontinuation of SSRIs, patients presented hypomanic symptoms, sometimes resulting in a real manic episode a few days after abrupt withdrawal.[58] This phenomenon could be linked to the discontinuation syndrome and perhaps more specifically to the severe insomnia observed in some cases of antidepressant withdrawal. In spite of a poor understanding of their neuropharmacological substrate, interrupting SSRIs more slowly even after the beginning of hypomanic symptoms may help sometime to avoid the worsening of hypomania.

## 4. Atypical Antipsychotics and Possible Induction of Mania or Hypomania

Clozapine, risperidone and olanzapine are marketed for the treatment of psychotic disorder. These atypical antipsychotics have less extrapyramidal adverse effects and presumably lower risks of tardive dyskinesia than typical antipsychotics.[59,60] Various studies report preliminary evidence of antimanic or mood stabilising effects by these atypical antipsychotics.[61-65]

In spite of their documented antimanic efficacy, these drugs also could result in a paradoxical effect consisting of the induction of manic episode in bipolar subjects. Recently, Aubry et al.[66] reported cases of risperidone- and olanzapine-induced hypomania and mania based on a MEDLINE search of the literature up to 1999. We reported a recent case of bipolar patient who experienced a manic episode apparently induced by olanzapine,[67] and we have observed similar cases of apparent risperidone-induced mania in euthymic bipolar patients in whom atypical antipsychotics were given as a substitute for low doses of typical antipsychotics.

This raises questions concerning the mechanism of this apparent adverse effect of atypical antipsychotics. The pharmacological characteristics of these atypical antipsychotic drugs are a higher potency as serotonin 5-$HT_{2A}$ than dopamine $D_2$ receptor antagonists. Lane et al.[68] suggested that risperidone-induced-mania is dose-related. Low doses may result in receptor blockade of 5-$HT_{2A}$, but not $D_2$. The antagonism of 5-$HT_{2A}$ receptors would then lead to the disinhibition of frontal dopamine release, which may account for the induction of manic episodes. It would be interesting to know whether a similar mechanism is responsible for the effects of olanzapine. However, although Lane's hypothesis about the 5-$HT_{2A}$/$D_2$ receptor occupancy ratio is attractive, it only partly fits the data of the published case reports in which most of the cases were receiving high doses of risperidone.[66]

Another mechanism has recently been proposed for atypical antipsychotic-induced frontal dopamine release (Ichikawa's hypothesis):[69] combined blockade of both $D_2$ and 5-$HT_{2A}$ receptors may promote the ability of 5-$HT_{1A}$ receptor stimulation to increase frontal dopamine release. The functional status of the serotoninergic system would then be critical for the effects of these drugs on frontal dopamine release. Our case report[67] suggests that olanzapine may have diverse effects in bipolar patients, depending on the state of endogenous neurotransmitter release. Tohen[70] presented data at the European Union Bipolar Regional Neuroscience Conference showing that olanzapine mood induction rates were less than placebo when prescribed as antidepressant.

In some circumstances, changes in endogenous transmitter release may account for changes in drug effects: for instance a partial agonist may act as an agonist when endogenous transmitter release is low, and as an antagonist when endogenous transmitter release is high.[71] The balance between the activities of the dopaminergic and serotoninergic systems might be abnormal during manic episodes, resulting in an altered profile of 5-$HT_{2A}$ and $D_2$ receptor occupancies, and therefore in differences in the psychopharmacological effects of these mixed drugs according to Lane's hypothesis. Moreover, bipolar patients exhibit constitutive alterations in the serotoninergic tone and function,[72] even when euthymic. This may account for the different effects of atypical antipsychotics on serotonin signalling in bipolar and non bipolar subjects, and therefore on frontal dopamine release according to Ichikawa's hypothesis.[69]

## 5. Type of Mood Stabiliser and Mood Switching

Mood stabilisers are considered as front-line treatments for bipolar I depression. All patients with bipolar I disorder will need to receive a mood stabiliser for subsequent prophylaxis. Also, these drugs, even when prescribed as monotherapies, have acute-phase antidepressant effects. Indeed, in a review of the literature, Zornberg and Pope[1] reported that in eight out of nine placebo-controlled studies, lithium was superior to placebo for treating depression. Six of the nine studies of lithium involved administration of placebo after active treatment, in the attempt to distinguish spontaneous recoveries

from medication-related improvement. All six studies found that some patients relapsed when changed back to placebo. Finally, there is no risk of treatment-emergent mania or accelerated cycling associated with their use. For these reasons, the guidelines suggest using mood stabilisers as the initial treatment for bipolar depression. However, in many cases, an antidepressant is also required. Thus, the question is: how best to use mood stabilisers and antidepressants to avoid mood switching?

Jann et al.[73] found a significant correlation between low serum lithium levels and mood switching during antidepressant treatment. The study involved 30 patients meeting criteria for bipolar affective illness on an established lithium regimen before initiation of the antidepressant treatment. Twelve patients experienced a switch and most of these patients were taking TCAs. The results suggested that low lithium levels are unlikely to provide adequate protection against mood switch. Lewis and Winokur[74] confirmed that lithium and antipsychotic treatment significantly prevented the induction of mania. In a meta-analyses, Rouillon et al.[75] reported switching to hypomania or mania in 21% of patients receiving placebo, 51% receiving imipramine, 21% receiving lithium, and 28% receiving imipramine and lithium. Thus, the risk of switching associated with imipramine monotherapy is about double the baseline rate, and this increase in risk is almost completely abolished if lithium is also given. In a retrospective study results indicate that patients receiving a mood stabiliser had a significantly lower risk of switching than whose without these medications.[76] We compared the efficacy of lithium with that of other mood stabilisers.[30] The incidence of mood switching did not differ between patients receiving anticonvulsants (43%) and patients receiving no mood stabiliser (45%). In contrast, mood switches tended to be less frequent in patients receiving lithium only (11%) than in patients receiving no mood stabiliser (45%). They were also less frequent in patients given lithium (alone or in combination with anticonvulsants) [15%] than in patients not given lithium (44%). These results need to be confirmed with larger numbers of subjects in a randomised trial but currently no other study has been devoted to the comparison of antidepressant-induced switch as a function of the mood stabiliser.

There is no study demonstrating that divalproex is an effective acute-phase monotherapy for bipolar depression, although there is evidence for its value in depression.[77] Similarly, this is some evidence that carbamazepine has modest antidepressant effects.[62] However, these medications have been more extensively studied as an antimanic agent[78] and no well documented data about their consequences on switching is available. For example, one recent study[79] sought to determine whether patients receiving valproate plus an antidepressant had significantly lower serum valproate levels before initiation of the antidepressant than those patients receiving valproate without an antidepressant. This study also assessed if valproate provided a protective effect against antidepressant-induced mania. The mean serum valproate level just before starting antidepressant treatment was significantly lower for the group receiving antidepressant than for the group without antidepressant. Forty-four percent of patients developed antidepressant-induced mania but there was no association with the valproate titre. However, it is difficult to conclude because the samples were small in size and heterogeneous.

In contrast, lamotrigine seems to be a most promising new therapy for bipolar depression.[80,81] In a double-blind study of lamotrigine monotherapy, 195 patients were randomly assigned to placebo or either 50 or 200 mg/day of the drug. Both doses of lamotrigine were significantly more effective than the placebo and the rates of switching were low after 7 weeks of treatment (5% with placebo versus, respectively, 3% and 8% with 50 or 200mg of lamotrigine).[81] The efficacy and tolerability of lamotrigine should now be compared with those of other antidepressants, both, alone and in association with other mood stabilisers. Note that lamotrigine has to be initiated at low dose, and increased slowly for 6–8 weeks to avoid the risk of rash.[82]

A recent study confirmed that the risk of switching was significantly increased by treatment with TCAs and was reduced if a mood stabiliser was

administered.[76] However, studies comparing the efficacy of different mood stabiliser to protect against switching when associated with antidepressant would be valuable.

## 6. Clinical and Biological Characteristics of Patients Prone to Mood Switching

Little is known about the clinical features of patients prone to switching. The identification of these characteristics might be useful for predicting manic episodes. However, few studies have investigated the relationships between the characteristics of the illness and of the patient's personality, and the tendency to develop antidepressant-induced mood elevation.

Some studies have shown that bipolar I patients experience more treatment-induced mood swings than bipolar II patients.[33] Another study showed that switchers were significantly younger, had a lower mean age at onset of the illness, and tended to present with more severe illness. However, Jan et al.[73] did not find any correlation between mood changes and age, sex or racial background.

The clinical data for 11 patients who developed mania during treatment with SSRIs showed that SSRIs may induce severe mania. Mania is more likely among patients with personal or family histories of hypomania or mania.[25] Boerlin et al.[23] also reported that larger numbers of past manic episodes are associated with a higher risk of switching. Conversely, Altshuler et al.[21] found that this variable did not predict susceptibility to antidepressant-induced mania.

We found no correlation between age, sex, type of bipolar disorder, number of previous manic episodes and the risk of mania induced by antidepressant.[30] However, we did find that hyperthymic temperament was associated with a strong tendency to switch ($p = 0.008$). The number of manic episodes may have been a less indicative factor because it is more sensitive than temperament to previous drug treatment. Temperament is thus a more stable dimension. In addition, the criterion 'number of previous manic episodes' is not a good predictive factor in patients with a recent onset of the illness. There is a continuum between temperament subtypes (hyperthymic versus depressive) and the polarity of episodes.[83] Indeed, bipolar patients with a hyperthymic temperament during premorbid and intercrisis periods have a tendency to develop mania. Thus, temperament may be useful for discriminating and identifying subtypes of bipolar illness and for optimising treatment but further studies are needed to conclude.

Recently, a study has shown that bipolar patients who became depressed following a period of euthymia were more likely to respond to treatment with an antidepressant or the addition of an mood stabiliser than patients who became depressed following a period of mania or hypomania. Although not statistically significant, the ratio of switch for previously euthymic patients was more favourable.[84] The authors concluded that antidepressant agents should be considered for the treatment of patients who become depressed following a period of euthymia.

Apart from some studies about thyroid function,[85] few studies have addressed the biological characteristics of switchers. However, some authors consider the serotonin transporter (5-HTT), the selective site of action of most antidepressant treatment as a potential candidate relevant for the switchover. The 5-HTT gene has two known polymorphisms and the short form is associated with bipolar disorders. However, various studies show discordant results that may be a consequence of the existence of distinct subgroups of bipolar illnesses. For instance Mundo et al.[86] found an association between the short allele variant and the propensity to develop mood switches under antidepressant treatment, but this result was not replicated in our larger cohort.[87]

## 7. Clinical Characteristics of Depression and Mood Switching

Some authors report that certain forms of agitated depression are worsened by antidepressant.[88] The main symptoms of this agitated depression were: agitation; emotional lability; head crowded with thoughts or thoughts that vanish too quickly; sleep

disorder with initial insomnia or with frequent night awakenings; suicidal thoughts; or attempted suicide with impulsiveness. The patients were not at all slow-minded but rather were talkative and expressive. Antidepressant drugs increased agitation and insomnia, and in some cases, suicidal impulses. Benzodiazepines had limited efficacy but antipsychotics given in small doses with either anticonvulsants or lithium gave very effective results. A limited number of courses of ECT can also provide rapid improvement. We found that in one group of 50 patients referred by psychiatrists to hospital for major depressive episodes and in some cases with the diagnosis of resistant depression, only 42% really fulfilled all the diagnosis criteria for major depressive episode.[89] The others presented with the main diagnostic criteria for major depressive and criteria for manic or hypomanic states, but did not meet criteria for mixed state. These two groups of patients could not be distinguished by suicidal risk or suicide attempts, but differed greatly in their response to treatment. Thus, the group of patients with a characteristic major depressive episode with anergia, blunted affect, anhedonia responded to antidepressant medication (76.2%) or to ECT (23.8%). Conversely, patients presenting in a state of depressive mood and symptoms of exaltation recovered under treatment with a combination of a mood stabiliser and a antipsychotic, after removing antidepressant medication. This shows that in most cases this state is misdiagnosed and it is not recognised as a mixed state because DSM-IV[31] criteria for mixed state do not fit with this form of episode. These states are worsened by antidepressant treatment, which leads to increased agitation and therefore are often considered as a mood switch. Strengthening this idea, Bottlender et al.[90] found that the number of mixed depressive symptoms on admission, like flight of ideas, racing thoughts, logorrhoea, aggression, excessive social contact, increased drive, irritability and distractibility, was associated with a higher risk for and the acceleration of manic switch during inpatient treatment. To avoid this problem, it seems necessary to define more rigorously the exact characteristics of mood episodes that require antidepressant medication in bipolar patients and those that are worsened by such treatment: for these latter ones, the best treatment is the combination of a mood stabiliser with an antipsychotic.

## 8. Conclusions

### 8.1 Towards a Definition for Antidepressant-Induced Switches

Many of the studies assessing mood switches have methodological flaws such as broad diagnostic criteria and failure to control for the duration of treatment administration prior to the onset of switching. As shown in some studies, the natural course of illness may contribute to the occurrence of switches while taking an antidepressant. There is currently no consensus over the optimal definition of switching.[91] Unfortunately, most of the times, the only definition criteria proposed by the authors is the onset of mania or hypomania fulfilling the DSM-IV[31] criteria during the trial. Obviously, there is a need for an internationally recognised definition of mood switches, particularly with respect to the time interval between onset of treatment and onset of mood elation. For example, one study scores manic or hypomanic episodes when they occurred during or up 2 months following a depressive episode[23] and another when mania or hypomania occur within 2 months or less of the start of treatment because they showed that most switches occurred within 30 days with TCAs.[92] We found that switches occurred shortly after the start of antidepressant treatment, with a mean at 5.8 weeks and a range from 3–10 weeks.[30] However, in a study with SSRIs, it appears that switches occurred later (12 weeks)[26] or even later with second-generation antidepressants when associated with mood stabilisers.[93] The delay before switching can depend on the association, if any, with a mood stabiliser and also possibly on the type of bipolarity.[19]

Standardising the definition may facilitate study of this phenomenon and improve the clinical management of bipolar depression. Based on this review, we suggest a set of proposals to define antidepressant-induced mood switch.

- The manic or hypomanic episode must fulfil DSM-IV[31] criteria.
- The onset of mania or hypomania must occur within 2 months after mood improvement (for example defined by a score's reduction on depression scale). Another possibility is to take into account the duration after onset of the treatment, but in this case a delayed improvement would lead to arbitrarily reduce the time to assess the occurrence of a switch.
- There is no stable normothymic period between depressive state and manic/hypomanic state. A switch seems better defined by a biphasic episode (depressive/manic or hypomanic) rather than by a triphasic one (depressive/euthymic/manic or hypomanic). This helps to avoid considering mood elation during continuation treatment likely due to the disease process itself.
- Withdrawal of the antidepressant treatment contributes to improve this clinical status (but this usually is not sufficient for full and rapid recovery).
- Patients with a history of rapid cycling are excluded (this last item is questionable as it is possible that rapid cycling could in some cases be a consequence of drug-induced switching).

### 8.2 Towards an Improved Drug Management of Bipolar Depression

The use of antidepressants must be in combination with a mood stabiliser in all cases. The most effective mood stabiliser at preventing switches seems to be lithium. Whatever the mood stabiliser used, there is a need to ensure effective plasma levels, and if necessary to increase the dose of mood stabiliser before the onset of the antidepressant treatment. Lamotrigine seems to be an interesting alternative particularly in bipolar II patients.

SSRIs (and possibly bupropion) appear to be the first-choice drugs for treating bipolar depression because of their efficacy, and low risk of mood switch. However, there is still no study comparing the risk of mood switches between the different SSRIs available, despite some evidence for differences in their propensity to induce mood elation.

The optimal duration of continuation phase therapy for bipolar depression has not been established, and it is not certain whether depressed bipolar patients require a minimum of 6 or 9 months of treatment, as suggested for other depressive disorders. This raises the issue of removing antidepressant medication progressively in most bipolar patients following recovery, because the need for longer antidepressant treatment has not been proven.[94] However, some patients require a longer course of maintenance antidepressant pharmacotherapy to avoid depressive relapses. Thus, it is necessary to determine which bipolar patients need a prolonged association of mood stabiliser and antidepressant between the mood episodes.

Despite the few studies dealing with this issue, careful examination of mood symptoms is essential before the onset of antidepressant treatment. In bipolar patients, some 'depressive' states seem to be worsened by antidepressant treatment.[88] However, besides sadness, these states have symptomatic characteristics related to mania or hypomania (accelerated thoughts, agitation, emotional lability, affective hyperexpressivity) such that they could be seen as mixed or dysphoric manic/hypomanic episodes (although dysphoric mania/hypomania lack a DSM-IV[31] definition). Antidepressant treatment would obviously worsen their manic/hypomanic symptoms, but this inappropriate drug treatment – a consequence of the misdiagnosis of the mixed mood episode – does not correspond to a drug-induced switch. It seems important to better study what kind of depression needs treatment with an antidepressant (perhaps depression associated with blunted emotions and cognitive or motor retardation) and to be very careful when patients have mixed symptoms. However it is necessary to be careful in restricting the use of antidepressant in bipolar patients because of the risk of depression-related suicidal behaviour, and also because of the risk of chronicity of depressive symptoms due to under-treatment.[95]

## 9. Concluding Remarks

We are still waiting for comprehensive data from both clinical and basic research to elucidate the brain mechanisms underlying mood disorders. Neuroscience will probably help elucidate the mechanisms of action of antidepressants and mood stabilisers, and lead to an improved knowledge of brain mechanisms of mood control and its pathological alterations. However, current views are mainly based on clinical data, and as a consequence their reliability is highly dependent on the relevance of the clinical definitions used for both mood switches and for bipolar depression.

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