# WFSBP Guidelines for Biological Treatment of Bipolar Disorders
## Part I – Treatment of Bipolar Depression

*a report by*
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Bipolar disorder is an under-diagnosed and, when insufficiently treated, devastating illness.[1–3] In contrast to unipolar depression, bipolar disorder seems to have a worldwide prevalence within a relatively narrow range. Multinational studies have revealed a lifetime prevalence rate of approximately 1.6% for bipolar I disorder,[4] and for the spectrum of bipolar disorders classified as bipolar I and II, a prevalence of 5.5%.[5] Some groups, such as young patients with psychotic depression, are especially likely to be misdiagnosed at index episode; up to 50% of patients hospitalised with an index episode of depression may turn out to be bipolar in the long run.[6] Together with increasing evidence of associated genetic polymorphism, e.g. in the expression of genes encoding for transporters and receptors of biogenic amines,[7,8] the epidemiological figures support the assumption that bipolar disorder has a strong hereditary component and that prevalence is relatively insensitive to variations in personal or social adversity. Thus, it will be assumed that an optimised biologic, mostly psychopharmacological, treatment may bring similar benefits across cultures.

Despite this argument, there are multiple guidelines and strategies for the treatment of bipolar disorder worldwide that place different emphases on different kinds of treatments. Obviously, this is not due to inherent biological diversities, but to different traditions in treatment and different attitudes towards particular agents. Accordingly, the evidence on which different approaches are based is relatively limited. For the bipolar spectrum, these treatment guidelines may differ even more, as even the nosological issue is far from solved.[9,10]

## Methods

The aim of these guidelines is to bring together different views on the appropriate pharmacological treatment of bipolar disorder from scientifically well-respected experts and representatives of all continents. In order to achieve this aim, an extensive literature search was conducted up to February 2002, using Medline, EMBASE and other sources, e.g. book articles and abstract volumes of recent key conferences. Additionally, several national treatment guidelines from 1997 onwards were analysed for additional references. The evidence found was summarised and categorised to reflect its susceptibility to bias.[11] Each pharmacological treatment suggestion was evaluated with respect to its efficacy, safety (side effect profile and, particularly for bipolar depression, switch risk), practicability of use and availability in different countries. In view of the large diversity in pricing for medications worldwide, daily treatment costs were not taken into consideration.

Given the existing paucity of scientifically well-designed studies in bipolar affective disorders,[12] it was decided, in contrast to existing guidelines for more rigorously studied disorders, that less rigid criteria would be used and that any long-term clinical experience with a drug would be taken more into account. After a vigorous discussion at the World Congress of Biological Psychiatry in Berlin in July 2001, grading of evidence was based on the Schizophrenia Patient Outcome Research Team (PORT) treatment recommendations.[13]

## Grading of Evidence

These recommendations combine evidence-based elements and clinical experience and have been used in the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on unipolar affective illness.[14,15]

### *Level A – Good Research-based Evidence*

Good research-based evidence means that evidence for efficacy has been proven by at least three methodologically sound trials, including at least one placebo-controlled trial and at least two comparison trials with another standard treatment. In these trials, criteria such as sufficient sample size, duration of trial, randomised distribution to either treatment and double-blind conditions should have been followed.

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### Level B – Fair Research-based Evidence

On the basis of trials, fair research-based evidence includes evidence from at least two randomised double-blind controlled trials, which may fail to fulfil all the criteria above (e.g. small sample size or no placebo control), or from one randomised double-blind study and at least one prospective large-scale naturalistic study.

### Level C

This level includes one randomised double-blind study with comparator, one prospective open-label study or two prospective open-label studies with more than 10 participants.

### Level D

Level D includes a recommendation based on prospective case studies with a minimum of 10 patients or large-scale retrospective chart analyses and support by expert opinion.

## The Road to Final Approval

Once a draft of this recommendation had been prepared by the Secretary and Chairman of the WFSBP Task Force, it was sent out to the 55 members of the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders for critical review and addition of remarks about specific treatment peculiarities in their respective countries. A second draft, revised according to the respective recommendations, was then distributed for final approval.

To minimise potential bias, these guidelines were established without any support from pharmaceutical companies. Experts of the task force were selected according to their expertise with the aim of covering a multitude of different cultures.

Although the authors are aware that bipolar disorder is a changeable condition that also shows common overlap of the different poles of mood (i.e. mixed mania and mixed depression), for practical reasons, the treatment recommendations are initially divided into the traditional categories of acute treatments for bipolar depression and mania and prophylaxis. This article concentrates on the treatment of bipolar depression.

## Acute Treatment of Bipolar Depression

### Antidepressants

Numerous clinical studies support the efficacy of the different available antidepressants in treating symptoms of unipolar depression, even in refractory patients.[16–18] Especially with new antidepressants, trials are methodologically sophisticated and every single antidepressant that has been registered during the last two decades would gain a clear Level A for efficacy. However, this is unfortunately only true for unipolar depression. Bipolarity has regrettably been an exclusion criterion in most antidepressant trials of the last two decades. Older trials on tricyclic antidepressants (TCAs) sometimes included bipolar depressed patients; however, a separate sub-analysis was either not performed or failed to provide sufficient evidence due to the small number of bipolar patients. Thus, on the level of controlled trials, the authors can only refer to several small trials, most of which tested new drugs such as selective serotonin re-uptake inhibitors (SSRIs), non-selective and selective A-type mono-amine oxidase (MAO-A) inhibitors or bupropion against TCAs – mostly imipramine – or placebo. They suggest that at least the irreversible, non-selective MAO inhibitors,[19,20] SSRIs (fluoxetine and paroxetine)[21–23] and bupropion[24] are superior to placebo and/or similarly efficacious or more efficacious than imipramine or desipramine.

The controlled evidence alone is unimpressive. Practice is guided by the indistinguishable similarity of depressive episodes with a unipolar and bipolar course. What is true for acute treatment of unipolar depression seems likely to be true also for bipolar depression. Some evidence for comparable efficacy of TCAs in unipolar and bipolar depressed patients is provided by a large retrospective analysis of 2,032 in-patients recruited between 1980 and 1992 at the Department of Psychiatry of the University of Munich.[25] When the routinely recorded clinical global impression (CGI), the Association for Methodology and Documentation in Psychiatry (AMDP) items for depressed mood and the length of stay in hospital were compared, no difference could be detected between unipolar and bipolar depressed patients.[26] Analysis of the co-administration of mood stabilisers also failed to give any hint for different treatment results. The authors regard this as important Level D evidence underpinning the use of antidepressants in moderate to severe bipolar depression.

For new antidepressants, small trials also suggest comparable efficacy in unipolar and bipolar depression, e.g. fluoxetine[22] and venlafaxine.[27] One exception was an add-on trial to high-serum-level lithium treatment of paroxetine compared with a TCA (imipramine) and placebo. No treatment effect could be established in the primary analysis.[28] This may be best regarded as a failed trial, although secondary analyses have led to additional interpretations of the findings. For example, in patients with low-lithium plasma levels, both paroxetine and imipramine were significantly better than placebo, and paroxetine was better tolerated

than imipramine. In summary, it can be concluded from, at best, Level B evidence but also from Level C and D that antidepressants – both traditional TCAs and antidepressants of the new generation – are effective in treating traditional depressive symptoms in bipolar patients.

From the safety and side effect profile, new-generation antidepressants are believed to be better tolerated by patients, and are less toxic when taken in overdose.[29–31] It has to be added, however, that a Cochrane library meta-analysis established only a slight advantage for SSRIs compared with TCAs when looking at drop-out rates in clinical trials.[32] Adherence to treatment is often a highly critical issue, particularly in bipolar patients, so even a trend of better tolerability has favoured the use of new-generation antidepressants.

There is no evidence for differential efficacy when one antidepressant is compared with another. Thus, treatment can be symptom-orientated, e.g. using a sedative drug when there is major sleep disturbance or an alerting drug when patients are retarded. However, there is preliminary evidence that venlafaxine (a new antidepressant with both a noradrenergic and a serotonergic component of action) may more easily induce a switch into mania than an SSRI.[23] Thus, the risk of inducing a switch with any given antidepressant should be critically considered. As far as practicability is concerned, the majority of the new antidepressants can be administered once or twice a day; thus, they can be conveniently combined with the administration of a mood stabiliser. As far as access is concerned, most new antidepressants are available worldwide, but while 'on patent', they remain more expensive than older drugs whose patents have expired. While economic considerations are especially important, less expensive TCAs with a better tolerability, e.g. nortriptyline, may be considered if the switch risk is adequately controlled by a mood stabiliser.

In summary, given the small number of controlled trials (often with insufficient sample sizes) but large retrospective chart analyses, the authors grade the level of evidence for the efficacy of antidepressants as a class in bipolar patients as Level B only. Individual agents merit a lower grading.

## Mood Stabilisers

Due to the state of research and the available evidence regarding mood stabilisers, the authors concentrate on lithium, valproate, carbamazepine and lamotrigine only. In general, this area is understudied; thus, prior to the lamotrigine trial published in 1999,[33] no placebo-controlled randomised parallel-group monotherapy study in bipolar depression had been undertaken.

### Lithium

There is limited evidence that lithium may be more effective in bipolar compared with unipolar depression.[34,35] Eight of nine double-blind trials versus placebo suggest that lithium is superior to placebo in treating bipolar depression.[36] However, only a meta-analysis of these studies has sufficient patient numbers to confirm the efficacy of lithium.[37] The strength of the antidepressant effect of lithium monotherapy compared with that of other antidepressants also remains rather unclear. Five rather small double-blind trials have been documented.[38–40] In particular, the authors are not aware of published controlled trials comparing the antidepressant efficacy of lithium with that of antidepressants of the new generation head to head. Furthermore, lithium has no sedating effects, although these may actually be desirable in patients with severe depression and suicidal impulses. The putative antisuicidal effect of lithium is not acute but develops over time.

The acute antidepressant efficacy of lithium may be supported at Level B. Although lithium is also used as an augmentation strategy in refractory depression, lithium monotherapy by itself may not be sufficient in patients with moderate to severe bipolar depression.

### Valproate

There is even less evidence for an acute antidepressant effect of valproate. A systematic, placebo-controlled double-blind study in 19 patients with bipolar II disorder, depressed phase that was recently published demonstrates an antidepressant effect of valproate.[41] Lambert, however, showed a response in only 24% of 103 depressed bipolar patients;[42] this was an open-label study of mainly bipolar I patients. This 24% response rate is probably not different from an expected placebo response. Thus, there is, to date, no strong evidence for the efficacy of valproate as a sole antidepressant acute treatment, at least not for bipolar I patients. Its potential for preventing depressive episodes, however, is more positive. A large-scale placebo-controlled maintenance study showed that valproate, but not lithium, was significantly better than placebo in preventing a depressive relapse.[43] However, this was a secondary analysis of a trial that failed on its primary outcome measure. In conclusion, the rationale to use valproate in acute bipolar depression is effectively inferred from considerations concerning long-term maintenance and from the prevention of a switch into mania.

An adjunctive treatment with an antidepressant or a mood stabiliser with intrinsic antidepressant action is definitely merited if there is no acute response. At best, valproate may reach Level C as an acute antidepressant treatment.

### Carbamazepine

Similar to valproate, carbamazepine has been much less studied in the treatment of acute bipolar depression than in mania and prophylaxis.[44–46] The majority of studies mixed unipolar and bipolar depressed patients. Some trials suggested moderate efficacy,[47–50] including one placebo-controlled trial,[51] but others did not replicate this.[52] In the latter trial, the response rate for carbamazepine did not appear to be better than that expected for placebo. Thus, similarly to valproate, carbamazepine is not to be recommended as a monotherapy for bipolar depression (Level C), although it may be helpful to prevent a switch into mania. However, in contrast to valproate, carbamazepine may increase the metabolism of several antidepressants, which can make treatment monitoring difficult. If a patient has already received carbamazepine as a prophylactic treatment and has, thus far, responded well to it, continuation of this treatment may be justified. Otherwise, if prophylactic treatment is about to be started, other treatment options, e.g. lithium, valproate or lamotrigine, should be considered.

### Lamotrigine

Of all available so-called mood stabilisers, lamotrigine use is supported by the largest trial undertaken, which suggests acute antidepressant efficacy. Strictly speaking, however, it failed to show significance for the primary outcome variable, namely the Hamilton Depression Scale, against placebo,[33] but other ratings (the Montgomery-Asberg Depression Scale and CGI) were significantly in favour of lamotrigine. Unfortunately, no controlled trial has yet been published comparing lamotrigine with a standard antidepressant. Thus, together with the considerable number of open trials of uncertain validity, the authors would grade the evidence for antidepressant efficacy of lamotrigine as Level B.

## Tolerability

As always, tolerability and side effects pose distinct advantages and disadvantages for individual drugs in individual patients. Compared with lithium, valproate and carbamazepine, it appears that patients are most satisfied with lamotrigine as far as efficacy and side effects are concerned,[53] although the risk of allergic reactions with lamotrigine and carbamazepine especially should not be underestimated.

### Switch Risk

Many physicians, especially in North America, appear more concerned about the risk of a switch into mania than about maximal efficacy in treating depression. On the one hand, manic episodes can be devastating for patients and their occupational and family life. On the other hand, insufficient treatment of depression may severely reduce the patients' functional capacities and put them at an increased risk of suicide. With regard to the switch rates reported with mood stabiliser monotherapy, they appear to be between 0% and 5%, with lithium probably being the most effective in switch prevention.[54] The natural risk of a switch into mania during recovery from a bipolar depression has been estimated to be between 4% and 8%,[55,56] and antidepressant monotherapy without an accompanying mood stabiliser may increase this switch risk significantly.[57,58] However, the highest reported switch rates (up to 70%) originate from a time when treatments with a TCA or irreversible MAO inhibitor were the only options. When new antidepressants are used, especially SSRIs, the switch risk may not be much different from the natural switch risk,[59] and can be sufficiently controlled with the addition of a mood stabiliser,[60] although a mood stabiliser cannot totally eliminate it.[61,62]

Switch rates reported for SSRIs administered in combination with a mood stabiliser are of the same order as the switch rate for mood stabiliser monotherapy. However, since a switch can still occur with SSRIs, those with a long half-life, such as fluoxetine, may not be considered ideal. A low risk of switch appears to hold for bupropion,[24,63] but not all studies have confirmed this.[64] In addition, the small size of these studies reduces confidence in their conclusions.

When antidepressant treatment with a new-generation antidepressant, e.g. an SSRI, venlafaxine or bupropion, is effective, it should be continued together with a mood stabiliser as maintenance treatment.[65] In the only randomised double-blind prospective trial on the issue of long-term continuation with modern antidepressants in bipolar depression, the risk of a depressive relapse is significantly lower in patients continuing the antidepressant than in those discontinuing after remission, with no statistically significant difference for breakthrough manic episodes.[66]

This observation clearly conflicts with the recommendation of previous guidelines to discontinue antidepressants as early as possible.[67,68]

## Recommendations

Considering the different aspects of efficacy, tolerability and safety, it appears that antidepressants are probably the most efficacious treatment, whereas mood stabilisers are the safest or most conservative treatment. There is probably not much difference between the tolerability of the new generation of

antidepressants and that of the new generation of mood stabilisers, such as lamotrigine. When the central inherent risks of bipolar depression are kept in mind, i.e. switch into mania and suicide, it appears that a combination of antidepressants and mood stabilisers should usually be the treatment of choice from the beginning. First-line antidepressants are SSRIs and, perhaps, bupropion, depending on availability. First-line mood stabilisers are lithium (which may additionally have antisuicidal effects)[69] and lamotrigine. However, the main practical problem with lamotrigine treatment is that rapid dose increase is unacceptable because it may lead to severe allergic complications. In a phase III multicenter lamotrigine study,[33] the first antidepressant effects were seen at a dosage of 50mg, which is not reached before week three if lamotrigine dosage is increased according to the manufacturer's recommendations. However, the time to the development of an antidepressive action of lithium is probably not much different, which clearly limits its use as monotherapy in bipolar depression.[70]

Conventional antidepressants also have a delay of two weeks or more before they show full beneficial action, so additional symptomatic treatment with tranquilisers, e.g. lorazepam, may be needed to bridge this time gap and may even accelerate response.[71]

If there is pre-existing treatment with a mood stabiliser that has shown efficacy in preventing relapses in the past, physicians should continue with it, optimise the dosage and add an antidepressant if necessary. Optimisation of mood stabiliser treatment does not imply simply a predefined plasma level, but an optimal balance between efficacy and tolerability. If this initial treatment is not sufficient, there is little controlled evidence on which to base a further treatment decision. Some advocate the addition of a second mood stabiliser but, equally, substitution of the antidepressant may be considered. There is limited evidence that adding a second mood stabiliser to pre-existing mood stabiliser treatment may be as efficacious as adding an antidepressant.[72] However, as far as tolerability is concerned, the addition of a modern antidepressant may be better tolerated than combination treatment with two mood stabilisers. (In the study by Young et al.,[72] a combination of lithium and valproate was used.)

When the decision to add either a second mood stabiliser or an antidepressant has to be made, analysis of the patient's history concerning previous switches or rapid cycling may be helpful. This recommendation may be slightly varied in patients with severe and psychotic depression and in depression within a rapid-cycling course of illness. In uncomplicated unipolar depression, the efficacy of SSRI and TCA appears the same.[73] In severe and psychotic depression, however, a traditional TCA or an irreversible MAO inhibitor may be required as, at least in unipolar depression, they appear superior to SSRI in these conditions.[74] Additionally, augmentation with an atypical antipsychotic may be beneficial. Besides treating psychotic symptoms and having good tolerability, trials with both olanzapine[75–77] and risperidone[78] suggest reasonable antidepressant effects with these atypicals by themselves.

For depression within a rapid-cycling course, the role of antidepressants is controversial. Some highlight the potential of antidepressants to not only induce a switch, but also cause an increase in the number of episodes,[79] although the likelihood of the latter has been questioned.[80] Given the negative view of antidepressants, in rapid-cycling patients with mild to moderate depression without suicidal risk, mono- or combination therapy with two mood stabilisers may be considered. In more severe depression within a rapid-cycling course, however, the addition of an antidepressant appears entirely reasonable. If an antidepressant is added, some authorities believe it should be discontinued as early as possible; in practice, this may be difficult.

### *Additional Treatment Modalities*

If insufficient treatment response is obtained despite sufficient trials with mood stabilisers and antidepressants, high-dose thyroxine may be an augmentative treatment of choice (Level C).[81] Additionally, when continued, thyroid augmentation may have a beneficial effect on rapid cycling. However, somatic, especially cardiovascular, side effects may vary considerably and this strategy should only be applied under informed medical surveillance.

Several other augmentation studies (e.g. pindolol and pramipexole) have been suggested by case reports or deduced from positive results in controlled trials in unipolar patients, so their evidence base is currently still poor and does not reach Level D criteria.

As a chronobiologic intervention strategy, sleep deprivation combined with sleep phase advance protocol is as efficacious in bipolar depression as in unipolar depression (Level C).[82] When not combined with a mood stabiliser, the switch risk is approximately 10%.[83] Thus, after starting the patient on a mood stabiliser, sleep deprivation should be considered in patients with a past history of refractoriness to antidepressant treatment or low tolerability of pharmacological treatment.

Although controlled data are limited for bipolar depression, the most successful non-pharmacological treatment modality in depression is still electro-

convulsive therapy (ECT) (Level B).[84,85] Especially in very severe and psychotic depression or in depression with severe psychomotor retardation, ECT has its major role. The switch risk is relatively high (approximately 7%)[55], but protective lithium co-administration may increase the risk and duration of a transient post- ECT delirium. The readiness to use ECT varies between different countries and mainly reflects public opinion and not its usefulness. Thus, ECT is used in some countries at an early stage of treatment, whereas in others, it is usually only applied in selected, mostly treatment-refractory patients.

Transcranial magnetic stimulation (TMS) is currently undergoing extensive evaluation in unipolar depression, but little is known about its effects in bipolar patients.[86]

Combining pharmacological treatment with psychotherapy, especially those following a standardised procedure or manual, e.g. cognitive-behavioural therapy (CBT)[87] or interpersonal psychotherapy (IPT),[88] is always an option, especially in mildly ill patients. Beneficial effects may include better compliance and adherence to pharmacological treatment as well as avoidance of a stress-inducing lifestyle.[89]

## Conclusions

The treatment of bipolar depression has raised some controversy, especially in weighing the impact of switch risk versus suicide risk.[90] Recent guidelines show a relative convergence of different views.[91–96] Consensus seems to be emerging that combined treatment with a mood stabiliser and antidepressant – preferably a modern, non-TCA antidepressant – is the first-line approach, at least for patients with moderate and severe bipolar depression.

In severe and/or psychotic depression, SSRIs may be less effective, and traditional antidepressants such as TCAs or irreversible MAO inhibitors may be needed. ■

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