



World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorders, Part I: Treatment of Bipolar Depression

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To cite this article: Heinz Grunze, Siegfried Kasper, Guy Goodwin, Charles Bowden, David Baldwin, Rasmus Licht, Eduard Vieta, Hans-Jürgen Möller & WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2002) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorders, Part I: Treatment of Bipolar Depression, The World Journal of Biological Psychiatry, 3:3, 115-124, DOI: [10.3109/15622970209150612](https://doi.org/10.3109/15622970209150612)

To link to this article: <https://doi.org/10.3109/15622970209150612>



Published online: 12 Jul 2009.



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World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Bipolar Disorders, Part I: Treatment of Bipolar Depression

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Summary

These practice guidelines for the biological, mainly pharmacological treatment of bipolar depression were developed by an international task force of the World Federation of Societies of Biological Psychiatry (WFSBP). Their purpose is to supply a systematic overview of all scientific evidence pertaining to the treatment of bipolar depression. The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, and from recent proceedings of key conferences and various national and international treatment guidelines. Their scientific rigor was categorised into four levels of evidence (A-D). As these guidelines are intended for clinical use, the scientific evidence was not only graded, but also commented on by the experts of the task force to ensure practicability.

Key words: bipolar disorder, depression, acute treatment, evidence-based guidelines, pharmacotherapy, antidepressants, mood stabiliser, electroconvulsive therapy.

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Acknowledgements

We would like to thank especially the following individuals for their valuable help in preparing these guidelines: David Baldwin, Rasmus Licht and Eduard Vieta for their extensive scientific input that also justified co-authorship; Jacqueline Klesing and Ilka Lachmair, Munich, for general and editorial assistance.

Introduction

Bipolar disorder is an under-diagnosed (Ghaemi et al 2000b; Kasper et al 2002a) and, when insufficiently treated, devastating illness (Simpson and Jamison 1999). 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 about 1.6 % for bipolar I

disorder (Weissman et al 1996), and for the spectrum of bipolar disorders classified as Bipolar I and II a prevalence of 5.5 % (Angst 1995). 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 (Goldberg et al 2001) (Figure 1). Together with increasing evidence of associated genetic polymorphism, e.g. in the expression of genes encoding for transporters and receptors of biogenic amines (Kelsoe et al 1996; Waldman et al 1997), 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 biological, mostly psychopharmacological, treatment may bring similar benefits across cultures.

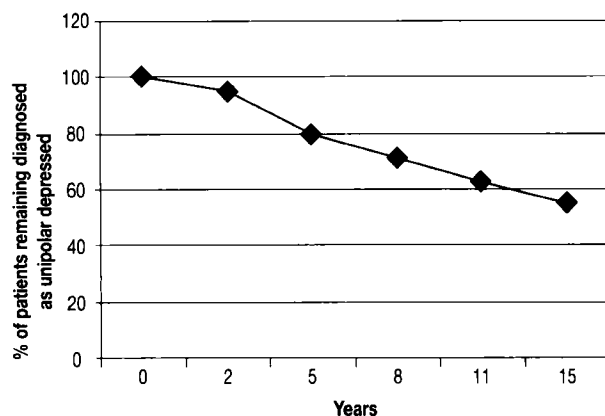


Figure 1

The Chicago follow-up study. Within 15 Years, almost 50 % of patients initially hospitalised for unipolar depression experienced at least one hypomanic or manic episode (Goldberg et al 2001)

Despite this argument, there are multiple guidelines and strategies for the treatment of bipolar disorder worldwide which place different emphases on different kinds of treatments. Obviously, this cannot be due to inherent biological diversities but to different traditions in treatment and different attitudes towards particular agents. Accordingly, the evidence upon 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 being solved (Akiskal and Pinto 1999; Baldessarini 2000)

Methods

The aim of this guideline is to bring together different views on the appropriate pharmacological treatment of bipolar disorder from scientifically well-respected experts and repre-

sentatives of all continents. In order to achieve this aim, an extensive literature search was conducted up to February 2002, using MEDLINE and EMBASE, as well as 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 (Shekelle et al 1999). 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 (Ghaemi et al 2000a), it was decided, in contrast to existing guidelines for more rigorously studied disorders, to use less rigid criteria and also to take any long-term clinical experience with a drug more into account. After a vigorous discussion at the World Congress of Biological Psychiatry in Berlin, July 2001, grading of evidence was based on the Schizophrenia Patient Outcome Research Team (PORT) treatment recommendations (Lehman and Steinwachs 1998). These recommendations combine evidence-based elements and clinical experience and have also been used in the WFSBP guidelines on unipolar affective illness (Bauer et al 2002a,b):

Level A: Good research-based evidence. This 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 (DB) conditions should have been followed.

Level B: Fair research-based evidence. On the basis of trials, this includes evidence from at least two randomized, DB-controlled trials which may fail to fulfil all the criteria above (e.g. small sample size or no placebo control), or from one RDB study and at least one prospective, large-scale naturalistic study.

Level C: One RDB study with comparator, one prospective open label study, or two prospective, open-label studies with >10 participants.

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

Once a draft of this recommendation had been prepared by the Secretary and Chairman of the 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 and with the aim to cover a multitude of different cultures.

Although the authors are aware that bipolar disorder is a changeable condition which 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 classical categories of acute treatments for bipolar depression and mania and prophylaxis. This article will concentrate on the treatment of bipolar depression.

The acute treatment of bipolar depression

• Antidepressants

There is a large body of clinical studies that support the efficacy of the different available antidepressants in treating symptoms of unipolar depression, even in refractory patients (McConville et al 1998; Nelson 1998a,b). 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 is regrettably an exclusion criterion in most antidepressant trials of the last two decades. Older trials on tricyclic antidepressants (TCA) sometimes included bipolar depressed patients, however, a separate sub-analysis was either not performed or does not provide sufficient evidence due to the small number of bipolar patients. Thus, on the level of controlled trials, we 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 MAO-A-inhibitors, or bupropion against tricyclic antidepressants (TCAs) - mostly imipramine - or placebo. They suggest that at least the irreversible, non-selective MAO-inhibitors (Baumhackl et al 1989; Himmelhoch et al 1991), SSRI (fluoxetine (Cohn et al 1989; Amsterdam et al 1998), paroxetine (Vieta et al 2000)) and bupropion (Sachs et al 1994) are superior to placebo and/or similarly 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 very likely to be true also for bipolar depression. Some evidence for comparable efficacy of tricyclics in unipolar and bipolar depressed patients is provided by a large retrospective analysis of 2032 inpatients recruited in the years 1980 to 1992 at the Department of Psychiatry of the University of Munich (Möller et al 2001). When the routinely recorded CGI, the AMDP items for depressed mood (Pietzcker and Gebhardt 1983) and the length of stay in hospital were compared, no difference could be detected between unipolar and bipolar depressed patients. At that time, antidepressants other than tricyclics were seldom administered. Analysis of the co-administration of mood stabilisers (almost exclusively lithium) also gave no hint for different treatment results. We 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 (Amsterdam et al 1998) and venlafaxine (Amsterdam 1998). One exception was an add-on trial to high serum-level lithium treatment of paroxetine compared to a TCA (imipramine) and placebo. No treatment effect could be established in the primary analysis (Nemeroff et al 2001). 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 at Level C and D, that antidepressants, both classical TCAs and antidepressants of the new generation, are effective in treating classical depressive symptoms in bipolar patients.

From the safety and side effect profile, antidepressants of the new generation are believed to be better tolerated by patients, and are less toxic when taken in overdose (Lader 1996; Barbey and Roose 1998; Frey et al 2000) (Figure 2). It has to be added, however, that a Cochrane library meta-analysis established only a tendency, but no significant advantage for SSRI compared to TCA (Barbui et al 2000) when looking at drop-out rates in clinical trials. 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 the new generation antidepressants.

There is no evidence for differential efficacy when one antidepressant is compared with another. Thus, treatment can be symptom oriented, e.g. using a sedative drug when there is

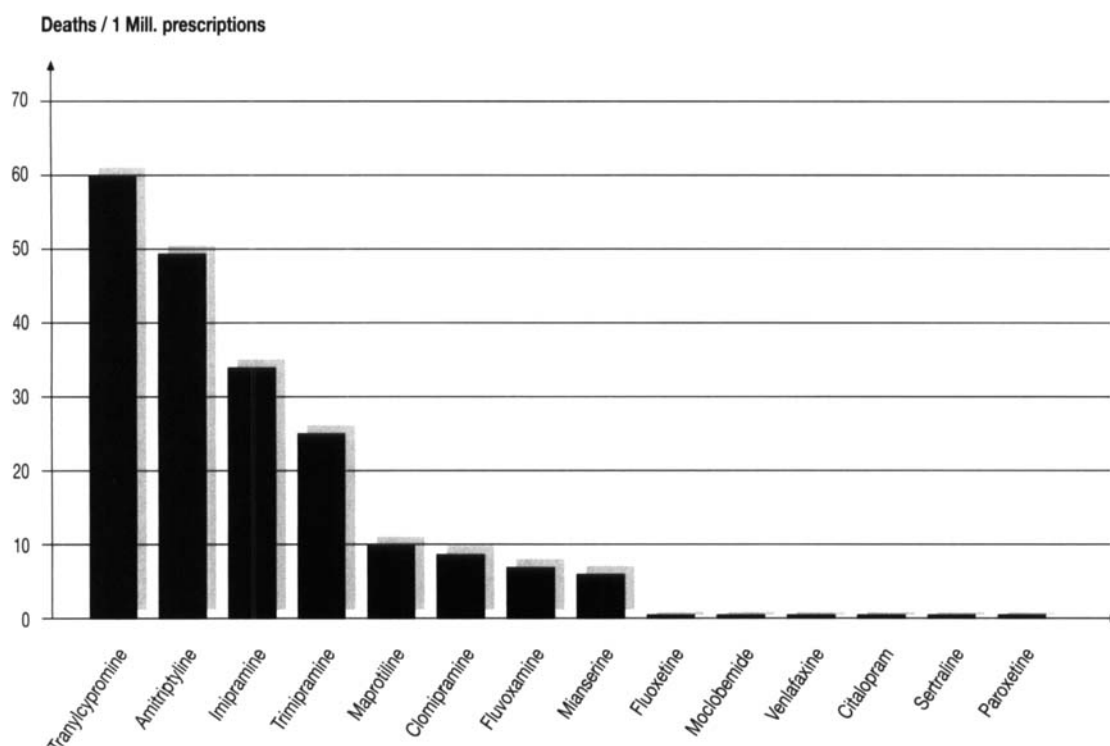


Figure 2
Comparative safety of antidepressants

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 (Vieta et al 2000). Thus, the risk of inducing a switch with any given antidepressant should be critically considered (see section on switch). 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. However, while 'on patent' they remain more expensive than older drugs whose patents have expired. When 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, we grade the level of evidence for the efficacy of antidepressants as a class in bipolar patients as only Level B. Individual agents merit a lower grading.

• Mood stabilisers

Due to the state of research and the available evidence we will concentrate here on lithium, valproate, carbamazepine and lamotrigine only. In general, this area is understudied: thus, prior

to the lamotrigine trial published in 1999 (Calabrese et al 1999a), 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 to unipolar depression (Goodwin et al 1972; Baron et al 1975). Eight of nine double-blind trials versus placebo suggest that lithium is superior to placebo in treating bipolar depression (Zornberg and Pope 1993). However, most of these trials are methodologically questionable. Only a meta-analysis of these studies (Souza and Goodwin 1991) has sufficient patient numbers to confirm the efficacy of lithium. The strength of the antidepressant effect of lithium monotherapy compared to that of other antidepressants also remains rather unclear. Five rather small double-blind trials have been documented (e.g., Mendels et al 1972; Arieli and Lepkifker 1981; for a review, see: Adli et al 1998)). In particular, we 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. Thus, 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, has just been published (Winsberg et al 2001) demonstrating an antidepressant effect of valproate. Lambert, however, showed a response in only 24 % of 103 depressed bipolar patients (Lambert 1984); 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 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 (Bowden et al 2000). 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 (Stromgren and Boller 1985; Shelton 1999; Schou 1997). The majority of studies again mixed unipolar and bipolar depressed patients. Some trials suggested moderate efficacy (Matkowski and Rybakowski 1992; Ballenger and Post 1980; Neumann et al 1984; Maj et al 1991), including one placebo-controlled trial (Ballenger 1988), but others did not replicate this (Small 1990). In the latter trial, the response rate for carbamazepine did not appear to be better than that expected for placebo. Thus, similar 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 so far responded well to it, continuation of this treatment may be justified. Otherwise, if prophylactic treatment is about to be commenced, other treatment options such as lithium, valproate or lamotrigine should be considered.

Lamotrigine

Of all available so-called mood stabilisers, lamotrigine is supported by the largest trial suggesting acute antidepressant efficacy. Strictly speaking, however, it failed to show significance for the primary outcome variable, namely the Hamilton Depression Scale, against placebo (Calabrese et al 1999a). However, other ratings (Montgomery-Asberg-Depression-Scale, CGI) were significantly in favour of lamotrigine. Unfortunately, at present there is no controlled trial published comparing lamotrigine with a standard antidepressant. Thus, together with the considerable number of open trials of uncertain validity, we would grade the evidence for antidepressant efficacy of lamotrigine at 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 (J. Goldberg, data presented at the APA 2000). However, especially the risk of allergic reactions with lamotrigine and also carbamazepine 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 the patient and his 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. As far as the switch rates reported with mood stabiliser monotherapy are concerned, they appear to be between 0 and 5 %, with lithium probably being the most effective in switch prevention (Calabrese et al 1999b). The natural risk of a switch into mania during recovery from a bipolar depression has been estimated to be between 4 and 8 % (Angst 1985; Bunney et al 1972). Antidepressant monotherapy without an accompanying mood stabiliser, however, may increase this switch risk significantly (Lewis and Winokur 1982; Wehr and Goodwin 1987). However, the highest reported switch rates (up to 70 %) originate from a time when treatment 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 (Peet 1994), and can be sufficiently controlled with the addition of a mood stabiliser (Boerlin et al 1998), although a mood stabiliser cannot totally eliminate it (Bottlender et al 1998; Quitkin et al 1981). 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 (Haykal and Akiskal 1990; Sachs et al 1994), but not all studies have confirmed this (Fogelson et al 1992). 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 (Post et al *In Press*). 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 AD compared to those discontinuing after remission, with no statistically significant difference for breakthrough manic episodes (Altshuler et al *In Press*). This observation clearly conflicts with the recommendation of previous guidelines to discontinue ADs as early as possible (e.g., American Psychiatric Association 1994; Sachs 1996).

• 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 in the tolerability of the new generation of antidepressants compared to that of the new generation of mood stabilisers like 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 (Thies-Flechtner et al 1996)) 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 the phase III multicenter study (Calabrese et al 1999a), first antidepressant effects were seen at a dosage of 50 mg, 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 (Montgomery et al 2000). Conventional antidepressants also have a delay of two weeks or more before they show full beneficial action, so additional symptomatic treatment with tranquilizers, e.g. lorazepam, may be needed to bridge this time gap, and may even accelerate response (Furukawa et al 2002).

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 (Young et al 2000). 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, 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 (Geddes et al 2000). In severe and psychotic depression, however, a classical TCA or irreversible MAOI may be required as, at least in unipolar depression, they appear superior to SSRI in these conditions (Perry 1996). Additionally, augmentation with an atypical antipsychotic may be beneficial. Besides treating psychotic symptoms and having good tolerability, trials both with olanzapine (Vieta et al 2001b; Rothschild et al 1999; Tohen et al 2000) and risperidone (Vieta et al 2001a) 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 not only to induce a switch, but also to cause an increase in the number of episodes (Altshuler et al 1995), although the likelihood of the latter has been questioned (Coryell et al 1992). Given the negative view of ADs, 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 no sufficient treatment response is observed

despite sufficient trials with mood stabilisers and antidepressants, high dose thyroxine may be an augmentative treatment of choice (Bauer et al 1998) (Level C). 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, 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 chronobiological intervention strategy, sleep deprivation combined with sleep phase advance protocol is as efficacious in bipolar depression as in unipolar depression (Riemann et al 2002) (Level C). When not combined with a mood stabiliser, the risk of switch is around 10 % (Colombo et al 1999). 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 (Abrams 1992) is still electroconvulsive therapy (ECT) (Kalin 1996) (Level B). 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 (around 7 %, Angst 1985), but protective lithium co-administration may increase the risk and duration of a transient post-ECT delirium. The readiness to use ECT is quite different in different countries and mainly reflects public opinion and not its usefulness. Thus, ECT may be 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 only little is known about its effects in bipolar patients (Yaroslavsky et al 1999).

Combining pharmacological treatment with psychotherapy, especially those following a standardised procedure or manual, e.g. cognitive-behavioural therapy (CBT, (Zaretsky et al 1999)) or interpersonal psychotherapy (IPT, (Weissman 1997)) 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 (Miklowitz et al 1996).

Conclusions

The treatment of bipolar depression has raised some controversy, especially in weighing the impact of switch risk vs. suicide risk (Möller and Grunze 2000). Recent guidelines show a relative convergence of different views (Sachs et al 2000; Nolen and Bloemkolk 2000; Kasper et al 2000, 2002b; van Calker and Berger 2000; Grunze et al 2002; American Psychiatric Association 2002). 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, SSRI may be less effective, and classical antidepressants such as TCAs or irreversible MAOI may be needed. Suggestions for a pharmacological treatment algorithm are summarised in Figure 3.

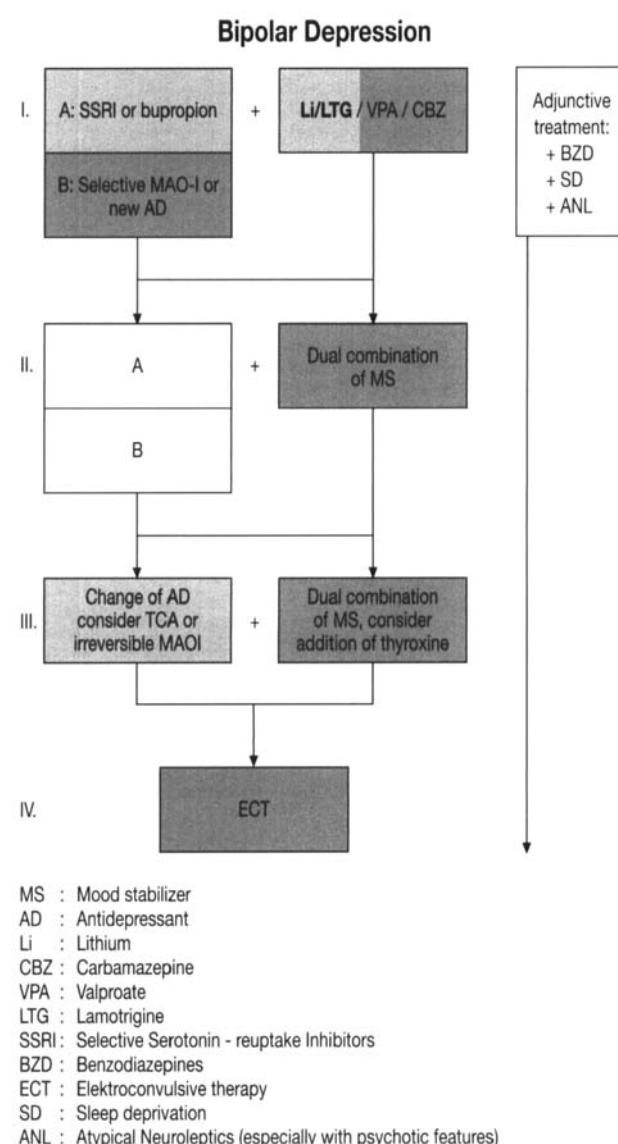


Figure 3
Suggestions for a pharmacological treatment algorithm

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