

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part III: Maintenance Treatment

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Summary

As with the two preceding guidelines of this series, these practice guidelines for the pharmacological maintenance treatment of bipolar disorder 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 relating to maintenance treatment. The data used for these guidelines were extracted from a MEDLINE and EMBASE search, from recent proceedings from key conferences and various national and international treatment guidelines. The scientific justification of support for particular treatments 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 reviewed by the experts of the task force to ensure practicality.

Key words: bipolar disorder, maintenance, prophylaxis, evidence-based guidelines, pharmacotherapy, antipsychotics, mood stabiliser, electroconvulsive therapy.

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Acknowledgements

We would like to specially thank the following individuals for their valuable help in preparing these guidelines: Jacqueline Klesing and Dorothea Bode, Munich, for general and editorial assistance.

1. Introduction

Parts I and II of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders (Grunze et al. 2002a; Grunze et al. 2003) concerned the acute treatment of mania and bipolar depression. Although it is of great importance to control these acute manifestations of illness as rapidly and effectively as possible, the real key to treatment of bipolar disorder is successful maintenance treatment. Starting with Kraepelin (1921), several long-term observational studies have demonstrated that the duration of the symptom-free interval tends to decrease sharply with a growing number of episodes (Zis et al. 1980; Angst 1981; Roy-Byrne et al. 1985; Kessing 1998). The central aims of long-term treatment are the prevention of new clinically significant episodes, and the maintenance of full remission without subsyndromal symptoms. Subsyndromal symptoms and chronicity contribute significantly to long-term disability of individual patients (Coryell et al. 1993; Angst and Preisig 1995a, b) and thus also have a strong socio-economic impact (Begley et al. 2001). Since it may be over-optimistic to expect any single mood stabilising agent to be effective enough on all symptoms of bipolar disorder, an evidence based and skilful combination of two or more medicines may increasingly become the strategy of choice (Post et al. 1996; Frye et al. 2000). Unfortunately, controlled data on different combination strategies are still very limited. Combination treatment rests on informed choices of medicines, the properties being usually established only as monotherapy. Thus, in the following section we will mainly focus on the published evidence for individual medicines, as confirmed by controlled trials or large-scale naturalistic studies. When data are available, consideration will be given to combination treatment strategies.

2. Methods

A detailed description of the methodology is provided in the previously published guidelines on bipolar depression (Grunze et al. 2002a). In brief, the WFSBP set up a task force on the biological treatment of bipolar affective disorders including 55 members and a board with a chairman, two co-chairmen and a secretary. A first draft of these guidelines was compiled by the board and sent out to all 55 members to collect their comments on, additions to and corrections of this first draft. A second draft was compiled incorporating the members' suggestions. In order to ensure that the guidelines were as up-to-date as possible, a second MEDLINE query and a search in abstract volumes of international key conferences was conducted to include the latest information on treatment strategies up to January 2004. In addition, other

recently published expert statements and guidelines were searched for additional references, e.g. the Austrian (Kasper et al. 2003), German (Grunze et al. 2002b), US (Zarin et al. 2002), British (Goodwin 2003), Danish (Licht et al. 2003) and Australian and New Zealand (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder 2004) guidelines. The final version of this WFSBP guideline tries to incorporate the input of all the members of the task force, although areas of uncertainty and different emphasis may remain.

To grade evidence for any specific treatment recommendation a modified version of the PORT recommendations (Lehman and Steinwachs 1998) was used in these guidelines, similar to the previous parts on acute treatment. Four different levels of evidence were defined:

Level A: Good research-based evidence. This means that evidence for efficacy has been supported 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 and concealed distribution to either treatment and double-blind conditions should have been met.

Level B: Fair research-based evidence. On the basis of trials, this includes evidence from at least two randomised, double-blind (RDB) controlled trials which, however, 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 randomised, double-blind (RDB) study with comparator and one prospective open-label (POL) study, or two POL studies with >10 participants.

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

Classical bipolar I disorder is a severe, often psychotic and usually intermittent disorder. Most existing data relates to Bipolar I patients. However in recent years the better recognition of less severe related states has expanded our definition of bipolar disorder to include a broad range of milder but still clinically significant cases. This bipolar spectrum also represents a challenge for maintenance treatment. The following different longitudinal courses of the illness will be considered here:

- bipolar I disorder without rapid cycling
- bipolar I disorder with rapid cycling
- bipolar II disorder without rapid cycling
- bipolar II disorder with rapid cycling
- schizoaffective disorder, bipolar type

These categories are not without controversy.

However, despite belonging to the same spectrum, the longitudinal course of Bipolar I and II disorder is distinct enough to allow separation as separate entities (Judd et al. 2003), and while it is becoming apparent that to define rapid cycling in a separate category is to some degree artificial (Kupka et al. 2003, 2004), it is still consistently applied in prophylactic treatment trials. It was also decided to include schizoaffective disorder in these guidelines because it may have more in common with bipolar disorder than with schizophrenia as far as maintenance treatment is concerned (Marneros 2001). These over-simple categorisations, however, cannot do justice to the clinical complexity of treating bipolar disorder. When finally choosing the first choice mood stabiliser or other maintenance medication, characteristics such as the following should also be considered:

- Predominance of mania or hypomanic episodes versus depressive episodes over the course of illness
- Severity of episodes
- Associated psychotic symptoms and the number of episodes in which they occurred
- Whether previous episodes were or were not related to concurrent treatment with antidepressants or use or misuse of psychostimulants
- Long-term tolerability of the medication considered
- Patient preferences

The term mood stabiliser needs some clarification. No single agent shows equally good efficacy for all mood disturbances throughout the bipolar spectrum. Following the suggestions of Ketter and Calabrese (2002), we have here included, as mood stabilisers, medicines that preferentially act on and prevent relapse to only one pole of the illness (e.g., mania or depression, without ill effect on the other).

A note of caution has to be entered concerning the duration of clinical trials. Studies following strict scientific criteria do not usually last longer than 12-18 months. Thus it is to a certain degree problematic to claim prophylactic rather than subacute maintenance properties for agents such as olanzapine or lamotrigine.

A further limitation of these international guidelines is the fact that, because not all medicines are licensed and marketed in every country, the reader has to take this into consideration in personal clinical practice.

3. Bipolar I disorder without rapid cycling

Recommendations for bipolar I disorder without rapid cycling are the most evidence-based because, until recently, maintenance studies had been conducted only in this type of illness.

Lithium

The prophylactic efficacy of lithium became evident as early as the 1960s and early 1970s (Baastrup and Schou 1967; Prien et al. 1973a); for recent reviews, see Goodwin (2002) and Müller-Oerlinghausen et al. (2002). Unfortunately, the prophylactic effect of lithium was probably over stated, especially in trials where responsive patients were re-randomised from lithium to placebo, due to discontinuation effects of lithium. A meta-analysis applying the Cochrane methods, and controlling for withdrawal studies, identified a total of nine studies in unipolar and bipolar affective disorder (Burgess et al. 2001): pooled analysis indicated that lithium is nevertheless effective in preventing new episodes in mood disorder. Although some aspects of the methodology of the early trials can be questioned, their positive findings have been independently supported recently by two positive large-scale placebo controlled double-blind randomised trials where lithium was used as a comparator to lamotrigine (Bowden et al. 2003; Calabrese et al. 2003a). Another recent large-scale controlled study (Bowden et al. 2000a), in which lithium served as a comparator to valproate and placebo, failed to show efficacy of lithium in the primary outcome criterion (time to any mood episode) due to a combination of methodological shortcomings and inadequate power. The secondary analysis demonstrated lithium to be effective for mania prevention. A further meta-analysis of bipolar only trials, including five trials totalling 770 patients, indicated that lithium is effective in preventing new episodes in bipolar disorder, being preferentially more effective against new manic episodes (Geddes et al. 2004). Regarding optimal maintenance blood levels, Gelenberg et al. (1989) found that relapse rates were higher among patients with plasma levels maintained at 0.4-0.6 mEq/L than among patients with plasma levels maintained at 0.8-1.0 mEq/L. However, tolerability problems may limit the use of higher lithium doses for long-term treatment. Together with other reasonably well-designed trials against comparators (e.g., carbamazepine (Greil et al. 1997b, 1998; Hartong et al. 2003) or imipramine (Prien et al. 1973b) **the evidence for prophylactic efficacy in bipolar I disorder for lithium can be clearly graded as Level A. It is probably more effective against manic than depressive relapse, so where the illness course is primarily driven by manic episodes (more likely when manic episodes show classical uncomplicated euphoria) it may be preferred.**

In clinical use, however, the effectiveness of prophylactic lithium across the clinical spectrum appears to be less than suggested by these controlled trials (Dickson and Kendell 1986; Harrow et al. 1990; Goldberg et al. 1996; Keck and McElroy 1996; Maj et al. 1991, 1998). This efficacy-effectiveness gap may exist not

only for lithium, but for all agents used in maintenance treatment. Cohorts in clinical studies may not be fully representative of the clinical population with bipolar disorder (Licht et al. 1997), since co-morbidity (Suppes et al. 2001) or poor adherence (Johnson and McFarland 1996; Scott 2002) complicate treatment. Moreover, the structure of clinical trials probably improves patient care and outcomes generally. Therefore, putative predictors of favourable response to lithium (family history of bipolar disorder, Mania-Depression-Free interval course, no rapid cycling, no alcohol or drug abuse and, especially, good adherence) should also be considered when recommending treatment with lithium (Abou-Saleh and Coppen 1986; Maj 1992). In the case of partial responsiveness to lithium, adding low doses (400 µg) of folic acid has been suggested to improve the outcome (Coppen et al. 1986). However, this suggestion remained a point of controversy within the task force, as its scientific rigour is low.

Especially for lithium, an increased relapse risk after its sudden discontinuation has been described (Mander and Loudon 1988) and re-instituting lithium may not always be effective (Post et al. 1992; Goodwin 1994). If necessary, it is strongly recommended that lithium maintenance is always tailed off slowly over some weeks or even months (Suppes et al. 1993). Informed adherence to treatment plans is clearly necessary in bipolar patients, and formal psychoeducation can improve outcomes (Colom et al. 2003). Attention to patient information and adherence should be mandatory for patients selected for long-term prophylactic treatment.

Antiepileptic medications

As already mentioned, several antiepileptic medicines have also been studied for maintenance efficacy in classical bipolar I disorder.

Lamotrigine

Recent guidelines have recommended lamotrigine for the acute treatment of bipolar depression (Zarin et al. 2002; Calabrese et al. 2004), despite the absence of unambiguous proof in controlled studies (Calabrese et al. 1999b). In contrast, two recent studies (Bowden et al. 2003; Calabrese et al. 2003a) have demonstrated the prophylactic efficacy of lamotrigine. Both studies (in patients recovering from mania or from depression respectively) were conducted under double-blind conditions using a three-arm design with placebo and lithium as comparators. The patient sample was moderately enriched for likely lamotrigine response and tolerability. They were stabilised during an open run-in phase with lamotrigine in addition to any other indicated psychotropic agents. Patients were required to maintain

stability on lamotrigine alone after withdrawal of other acute treatments. Thus, patients experiencing side-effects with lamotrigine or who were unresponsive to acute treatment with lamotrigine may not have been randomised.

The main result of both studies was that lamotrigine was statistically superior to placebo (as was lithium) for the primary outcome – “time to intervention for a mood episode”. Secondary analysis revealed that this overall outcome was mostly due to a preventative effect of lamotrigine against depressive relapse independent of whether the index episode was manic or depressive. Lamotrigine was less effective in preventing new manic episodes, but in a combined analysis it was still significantly better than placebo (Goodwin et al. 2004). In contrast, lithium was more effective in preventing new manic episodes, but less effective in preventing bipolar depression. These apparently complementary properties may support the combination of lithium with lamotrigine in clinical practice although, so far, there are no controlled studies supporting this approach.

In addition to these controlled trials there exist data from open, successful long-term lamotrigine treatment (Walden et al. 1996, 2000; Calabrese et al. 1998; Suppes et al. 1999a; Bowden et al. 1999). In summary, **we would grade lamotrigine as Level A concerning prophylactic efficacy, with its main strength being the prevention of new depressive episodes** (Goodwin et al. 2004).

Valproate

Expectations for valproate as prophylactic medication were quite high because several open, but in part, randomised studies (Lambert 1984; Denicoff et al. 1997a; Hirschfeld et al. 1999; Emrich and Wolf 1992; Hayes 1989; Vencovsky et al. 1984; Solomon et al. 1998) appeared positive. However, the only randomised double-blind placebo-controlled study failed to demonstrate a statistical benefit. The prophylactic efficacy of neither valproate, nor lithium, which was used as an active comparator, could be shown for the primary outcome parameter (“time to any mood episode”) (Bowden et al. 2000a). Secondary analysis (time to a specific mood episode) suggested efficacy of valproate, especially in preventing a new depressive episode. This finding is also discussed in a recent Cochrane analysis (Macritchie et al. 2001). Extension of an acute mania trial (Tohen et al. 2003) over 47 weeks permitted comparison of two small parallel groups who had remitted on valproate or olanzapine (Tohen et al. 2002a). Double-blind conditions were maintained throughout the study. At endpoint, there was no significant difference between groups in the number of manic relapses (olanzapine 41 %, valproate 50 %), or in the median time to

relapse. There were, however, differences in secondary outcomes such as affective stability and measures of cognitive function in favour of olanzapine.

Thus, together with the evidence from open long-term studies we would grade the level of evidence for prophylactic efficacy for valproate as B. It may be especially helpful for preventing new depressive episodes, although further evidence on this point is needed.

Carbamazepine

Carbamazepine has been widely used as a first-line alternative to lithium maintenance treatment in patients not responding sufficiently to or not tolerating lithium, especially in Europe and Japan. There is some evidence that carbamazepine is superior to placebo in controlled trials (Okuma et al. 1981) and it has also been claimed that its usefulness may be comparable to lithium (Placidi et al. 1986; Lusznat et al. 1988; Denicoff et al. 1997b). However, these studies employed methodology that would not now be supported, and very small numbers of patients, so the results are difficult to interpret (Dardennes et al. 1995). There have been two more recent impressive head-to-head comparisons of carbamazepine with lithium. The key finding of the MAP-Study was that for patients with a history of classical euphoric mania, lithium was superior to carbamazepine (Greil et al. 1997b). This was confirmed in a recently published study of patients receiving maintenance treatment for the first time. Hartong et al. (2003) compared lithium and carbamazepine under double-blind randomised conditions for two years. At the endpoint, lithium was outperforming carbamazepine on dropout rates due to relapse. In fact, there was a linear decline of the efficacy of carbamazepine, whereas lithium patients tended to either relapse early (carbamazepine appeared superior for the first six months) or remain stable for the duration of the study. The lower efficacy of carbamazepine in the second year cannot be explained by autoinduction of the metabolic pathway of carbamazepine, because dosages of both lithium and carbamazepine were based on plasma levels throughout the study.

A significant number of the patients not responding to lithium may have atypical features – for example, dysphoria rather than euphoria, bipolar II or ‘not otherwise specified’ diagnoses, mood incongruent delusions and comorbidities. In a secondary analysis of the MAP data, this atypical group showed a better outcome with carbamazepine compared to lithium (Greil et al. 1998).

Thus, on a formal level, carbamazepine would fulfil the study requirements to be graded as Level B. Carbamazepine may be more

useful in atypical manifestations but will usually show poorer long-term efficacy than lithium. As a significant disadvantage, it can also induce the metabolism of antidepressants, antipsychotics and other antiepileptic agents used as mood stabilisers, thus leading to a loss of efficacy of co-medications (Spina et al. 1996; Hesslinger et al. 1999). Thus, its use is impractical in certain combination treatment regimens.

Atypical antipsychotics

Controlled evidence that antipsychotics show long-term efficacy is currently available only for olanzapine (Kasper et al. 2002). Olanzapine showed prophylactic efficacy compared to placebo in a 12-month study in patients who remitted from mania under olanzapine treatment. Although both the prevention of new manic and depressed episodes was significantly better for olanzapine than placebo, the effect was more pronounced for the prevention of manic relapses (Tohen et al. 2004). In a large, one-year randomised double-blind comparator study versus lithium, olanzapine showed at least comparable efficacy to lithium – perhaps even superiority in preventing a manic relapse (Tohen et al. 2002c). Remembering the valproate maintenance study (Bowden et al. 2000a), the absence of a placebo arm limits the interpretation of this trial. Olanzapine as an add-on to lithium or valproate also performed significantly better in relapse prevention compared to placebo in a double-blind, 18-month extension of the respective acute mania study (Tohen et al. 2002b). Thus, **olanzapine may be rated as having Level A evidence for prophylactic treatment with a probably greater efficacy against the manic pole of the illness.** Its profile is thus similar to lithium. The only qualification must be that the key maintenance studies were targeting a population of patients acutely responsive to olanzapine, a selection bias even more pronounced than in the lamotrigine studies. Accordingly, the relative prophylactic efficacy of olanzapine in a non-selected sample remains unclear.

Clozapine has been in use as an off-label agent in refractory bipolar disorder for more than 30 years. In this indication it has shown efficacy mostly in small, investigator-initiated trials for both acute and maintenance treatment (Suppes et al. 1999b). In addition, several case reports (Puri et al. 1995; Hummel et al. 2002; Kurz et al. 1998; Zarate et al. 1995b; Banov et al. 1994) support long-term efficacy of clozapine. Despite its widespread clinical use, **the published evidence for clozapine for prophylactic treatment of classical bipolar I disorder is limited (Level C).**

Risperidone, at least as an add-on medication, may be useful in bipolar disorder for

long-term use, despite the absence of randomised controlled trials (Level D). It has been added to mood stabilisers in symptomatic patients under open conditions (Vieta et al. 2001). This regimen not only improved manic and depressive symptoms significantly, but also appeared to reduce recurrence for the next six months.

Antidepressants

In bipolar patients where recurrent depressive episodes dominate the clinical course, the long-term use of antidepressants in combination with a mood stabiliser may be considered. On the other hand, monotherapy, especially with a tricyclic antidepressant, should be discouraged. In the Prien study (Prien et al. 1973b, 1984) comparing lithium and imipramine, imipramine was effective in preventing new depressed episodes but was associated with a high switch risk into mania. The situation may be different with newer antidepressants such as SSRIs, or combined norepinephrine and serotonin reuptake inhibitors, e.g. venlafaxine and milnacipran, and bupropion. Naturalistic data from the Stanley Foundation Bipolar Network (SFBN) support the long-term continuation of antidepressants in patients previously stabilised on one of these antidepressants. Patients were partly recruited from a previous double-blind randomised control trial comparing the efficacy of sertraline, venlafaxine and bupropion in the acute treatment of bipolar depression, and partly from patients who responded to an antidepressant introduced as routine treatment.

After remission, unblinded continuation treatment was offered to patients, all of whom were simultaneously treated with a mood stabiliser. It should be noted that only 15% of patients originally receiving antidepressants remained in remission for two months; thus the sample studied during follow-up is highly selective both for antidepressant responders and a relatively low switch risk into mania. During the one-year follow-up, patients continuing on an antidepressant had a significantly lower relapse rate to new depressive and also numerically, manic episodes (Altshuler et al. 2003). This finding is in line with a previous smaller study conducted by Altshuler et al. (2001). A retrospective chart review by Ghaemi et al. (2000) only partially supported these results. Patients again had fewer depressive relapses but there was an elevated risk of switch into mania with antidepressant continuation. Thus, at this stage, **the option of long-term continuation of a non-tricyclic antidepressant should primarily be considered in patients who were good acute responders and who are at risk mainly from severe recurrent depressive episodes in the long term (Level D).**

Further treatment options

Other treatment options, e.g. calcium antagonists, are usually only considered for patients with a rapid cycling course of bipolar disorder (Post et al. 1990). Despite the high risk of persistent tardive dyskinesia (Mukherjee et al. 1986), long-term use of typical neuroleptics, especially as a depot formulation, is sometimes considered in non-compliant bipolar I patients, but is mostly reserved for patients with pronounced psychotic symptoms or schizoaffective disorder. Littlejohn et al. (1994) compared the duration of affective episodes in periods on or off depot antipsychotics for 18 bipolar patients who had been treated for a mean of 8.2 years. Patients in this naturalistic study suffered fewer relapses and spent significantly less time in hospital ($P = 0.001$) for treatment of manic, depressive or mixed affective illness during treatment with depot antipsychotics. However, a recent double-blind, placebo-controlled trial showed significantly greater rates of emerging depression when a typical neuroleptic was maintained after remission from mania (Zarate and Tohen 2004).

Maintenance ECT is believed to be effective on the limited evidence of single case reports and small case series in bipolar disorder (Kramer 1999; Gupta et al. 1998; Rabheru and Persad 1997; Vanelle et al. 1994; Shapiro et al. 1989), but it is also associated with a moderate switch risk when given without concomitant mood stabiliser treatment (Angst 1985).

Patient psychoeducation through group, individual or family approaches can play a crucial part in the long-term success of maintenance treatment with medicines. Increased adherence, improved awareness of relapse prodromes and effective action planning are central components of such interventions. A detailed review of psychological interventions is beyond the scope of this review, but the key issue is how the lessons from quite specialised interventions can be generalised to good clinical care.

4. Classical bipolar I disorder with rapid cycling

Lithium

Dunner and Fieve (1974) found that patients with four or more episodes per year were on the whole less responsive to lithium than those with fewer episodes, and coined the term "rapid cycler" for this subgroup. In non-selected populations rapid cyclers may constitute 15-20% of all bipolar patients; however, in specialised clinics they may make up more than 50% (Suppes et al. 2001). Thus, rapid cycling especially constitutes a particular challenge for expert settings rather than for general practitioners.

After Dunner and Fieve's study, opinion hardened that lithium is not useful in rapid cycling bipolar patients. However, this may have been premature, and rapid cycling patients may be less responsive to most treatments. In fact, in Dunner and Fieve's study, lithium appeared to prevent new manic episodes in rapid cycling patients but it had no effect on new depressive episodes. In other small open trials in rapid cycling patients (e.g., Walden et al. 2000), a small prophylactic effect of lithium was again observed (although it was inferior to the active comparator, lamotrigine). Thus, **we may grade the efficacy of lithium for the prevention of new manic episodes in rapid cycling bipolar disorder as C, and it may not be efficacious in preventing new depressions.**

Valproate

Evidence for the efficacy of valproate in bipolar I rapid cycling comes purely from open studies. The largest study by Calabrese et al. (1993) showed prophylactic efficacy in rapid cycling patients against new episodes of typical mania, mixed states and to some degree also bipolar depression. This impression is also supported by other smaller open studies (Jacobsen 1993; Sharma et al. 1993; Walden and Grunze 2002). The only randomised, double-blind study so far, comparing valproate and lithium in bipolar I and II rapid cycling, failed due to a lack of power (Calabrese et al. 2003b): only one in four patients was successfully stabilised at baseline and thus eligible to enter the randomised study phase. Numerically, valproate was superior to lithium. **Thus we may conclude evidence for valproate is, at best, Level C in the maintenance treatment of bipolar I rapid cycling.**

Lamotrigine

The most reliable controlled data in rapid cycling are available for lamotrigine. In a large randomised, placebo-controlled six-month study lamotrigine was significantly superior to placebo for survival in study. However, it was not positive for the primary efficacy measure (time to intervention). Secondary analysis also showed the effect to be confined to bipolar II patients and not bipolar I (see related section). Another as yet unpublished controlled trial failed to show a significant improvement with lamotrigine compared to placebo. Open data appear to support a beneficial effect of lamotrigine in preventing bipolar I rapid cycling (Kusumakar and Yatham 1997; Fatemi et al. 1997; Bowden et al. 1999; Walden et al. 2000). We may therefore conclude that **lamotrigine monotherapy has Level D evidence for treating bipolar I rapid cycling.**

Carbamazepine

The evidence for a prophylactic efficacy of carbamazepine in rapid cycling is contradictory. The only controlled study comparing lithium and carbamazepine failed to show a better effect

of carbamazepine (Okuma 1993). Some open trials gave positive hints (Di Costanzo and Schifano 1991; Strömngren and Boller 1985), while others did either not or only partially replicate this finding (Joyce 1988; Post et al. 1990). None of these studies was performed under controlled conditions so that **the use of carbamazepine in bipolar I rapid cycling relies on case studies and expert opinion (Level D).**

Calcium antagonists

Two studies (Pazzaglia et al. 1993, 1998) conducted under double-blind conditions with an on-off-on design supplied evidence for a prophylactic efficacy of the calcium antagonist nimodipine, even in previously refractory bipolar I rapid cycling patients (Level B). The clinical usefulness may be limited by the short half-life - a daily dosage of more than 240 milligrams is usually needed, corresponding to eight tablets given in three doses. Nevertheless, this option should be considered in patients where other treatment attempts have failed.

Atypical antipsychotics

As already mentioned, there is some evidence for prophylactic efficacy of clozapine in rapid cycling patients (Hummel et al. 2002; Frye et al. 1996; Suppes et al. 1994; Calabrese et al. 1991). Again, these studies are rather small and questionable from a methodological point of view. However, given that these patients are difficult to treat, **the option of clozapine in refractory rapid cycling patients should always be considered, although the grading according to the level of evidence is currently D.** For other atypical antipsychotics, data are still not adequate to make any judgement concerning prophylactic efficacy.

Combination treatment

Especially in rapid cycling, combination of mood stabilisers is the clinical rule, not the exception. This reflects the generally disappointing response to monotherapies. Most data on combination treatments for prophylaxis of bipolar disorders come from open studies, but blinded, prospective studies have also been conducted (Denicoff et al. 1997b; Solomon et al. 1997). In the landmark, albeit underpowered, study by Denicoff et al. the prophylactic efficacy of lithium, carbamazepine and their combination was compared. Fifty-two outpatients who met DSM-III-R criteria for bipolar illness were randomly assigned in a double-blind design either to start with lithium or carbamazepine, followed by a crossover to the opposite medication and to the combination with each treatment lasting one year. The percentage of the evaluable patients who had marked or moderate improvement on the Clinical Global Impression scale was 33.3% on lithium, 31.4% on carbamazepine and 55.2% on the combination treatment (not significantly

different). Patients with a past history of rapid cycling did poorly on monotherapy (28.0% responded to lithium; 19.0% responded to carbamazepine), but significantly better on the combination (56.3%, $p < .05$). A small study by Solomon in 12 non-rapid cycling bipolar I patients tested the efficacy of lithium plus valproate versus the efficacy of lithium alone in continuation and maintenance treatment over one year (Solomon et al. 1997). Patients treated with the combination of lithium and valproate were significantly less likely to suffer a relapse or recurrence ($p = .014$), but were also significantly more likely to suffer at least one moderate or severe adverse side effect ($p = .041$). Thus, clinicians prescribing combination treatment must weigh any benefit against this potential cost.

With the studies available, the evidence for combination treatment may be graded as Level C. The choice of combination will often depend on a clinical judgement as to the balance of morbidity between the poles of the illness.

5. Bipolar II disorder without rapid cycling

Bipolar II disorder has just recently become a focus of research interest, especially with the emergence of new agents such as lamotrigine. This interest is also due to increasing awareness of the high prevalence of bipolar II and, especially, spectrum disorders (Akiskal et al. 2000; Angst and Gamma 2002). Unfortunately, this new interest in bipolar II disorder is not so far reflected in large randomised and placebo-controlled studies (Suppes et al. 2002). Current treatment guidelines for bipolar II disorder, including the American Psychiatric Association guidelines (American Psychiatric Association 2002) and the Texas Implementation of Medication Algorithms (in earlier phases known as the Texas Medication Algorithm Project; Rush et al. 1999) do not include recommendations specific to the treatment of bipolar II disorder.

Due to a lack of evidence, it has been suggested that lithium may not be as effective in bipolar II disorder as it is in bipolar I disorder. However, this seems not to be confirmed in large-scale naturalistic studies (Tondo et al. 1998; Peselow et al. 1982; Dunner et al. 1976; Fieve et al. 1976). One placebo-controlled trial versus imipramine (Kane et al. 1982) and one randomised trial versus carbamazepine (Greil and Kleindienst 1999) also showed superiority (against imipramine) and equality (against carbamazepine) of lithium prophylaxis.

Long-term data for other anticonvulsants or atypical antipsychotics are only available for bipolar II patients with a rapid cycling course (see relevant section).

As long as clear evidence is lacking that a specific mood stabiliser is superior to others in bipolar II disorder without rapid cycling, a general rule may be to continue the mood stabiliser that was effective in acute treatment. For those patients receiving a mood stabiliser for the first time, general illness features may also guide the selection of a treatment. Bipolar II disorder is characterised not only by more inter-episodic (Benazzi 2001) and episodic morbidity, and mostly severe depressive episodes (Vieta et al. 1997b; Tondo et al. 1998), but also by a high degree of suicidality (Vieta et al. 1997a; Rihmer and Pestaloty 1999). Thus, those mood-stabilisers which show preventive effects mainly on depression in bipolar I disorder, such as lamotrigine, or suicidality, such as lithium (Tondo and Baldessarini 2000), may be the agents of choice. In addition, lithium seems to be of equal efficacy in uncomplicated bipolar II patients compared to bipolar I disorder.

The use of tricyclics in maintenance treatment is discouraged due to their probable propensity to induce rapid cycling (Altshuler et al. 1995), however, long-term treatment with modern antidepressants should not be ruled out, although the evidence is still preliminary (Altshuler et al. 2003). Switch rates into mania for bipolar II patients treated with modern antidepressants are still a subject of controversy (Ghaemi et al. 2001), but if switches occur they are more likely of moderate severity (Benazzi 1997).

Currently, only lithium reaches a Level C classification, and the evidence for carbamazepine is no better than Level D criteria.

6. Bipolar II disorders with rapid cycling

Secondary analysis of a placebo-controlled, double-blind, randomised study with lamotrigine in rapid cycling patients suggested that it may be of special value in bipolar II patients (Calabrese et al. 2002). For the 52 patients with bipolar II disorder, the median time to intervention was significantly greater in those receiving lamotrigine (17 weeks vs. seven weeks). However, the positive effect of lamotrigine in bipolar II disorder was a *post hoc* finding and related to reduction of depression only. Together with supporting evidence from open case series (Calabrese et al. 1999; Suppes et al. 1999a; Fatemi et al. 1997) **a Level C grading may be appropriate for lamotrigine.**

For valproate, some evidence of usefulness comes from the trial by Calabrese and Delucchi (1990) already cited. Thirty of the 55 individuals with rapid cycling had a bipolar II disorder. Interestingly, **responsiveness to valproate appeared to be slightly better in those bipolar II patients compared to bipolar I (Level D).**

7. Schizoaffective disorder

The positioning of schizoaffective disorder, bipolar type, between schizophrenia and affective disorders has always been a matter of controversy and threatens to shift with every new diagnostic manual. Furthermore, the diagnosis of schizoaffective disorder, even in good studies, is not reliable: e.g., the inter-rater reliability in Maj's study (2000) for schizoaffective disorder had a kappa of 0.22. It is also of some concern that schizoaffective treatment data are almost exclusively provided as sub-group analyses from schizophrenia trials. However, in order not to overlook this patient group, we will briefly summarise the evidence.

Referring to trials primarily addressing relapse in schizophrenia, from atypical antipsychotics, namely, risperidone, olanzapine, ziprasidone and aripiprazole, schizoaffective patients showed prophylactic efficacy to a similar degree. However, the primary outcome was almost exclusively focused on emerging psychotic, not mood symptoms, which makes the findings hard to interpret fully. Given the acute antimanic efficacy of all atypical antipsychotics, however, it appears likely that positive effects on mood symptoms can also be observed in schizoaffective patients.

The efficacy of both lithium (Tress and Haag 1979) and carbamazepine (Vovin et al. 1984) has been investigated in open trials showing efficacy for both agents. In an open, randomised, multicentre study (the MAP study), the prophylactic efficacy of lithium and carbamazepine was also compared (Greil et al. 1997a). A total of 90 ICD-9 schizoaffective patients were included in the maintenance phase (2.5 years). They were diagnosed according both to Research Diagnostic Criteria (RDC) and DSM-III-R and classified into subgroups. Outcome criteria were hospitalisation, recurrence, concomitant psychotropic medication and adverse effects leading to discontinuation. There were more non-completers under carbamazepine than under lithium ($p = 0.02$). Survival analyses demonstrated no significant differences between lithium and carbamazepine in treatment outcome. Patients' ratings of side effects ($p = 0.003$) and treatment satisfaction ($p = 0.02$) favoured carbamazepine. Following the RDC criteria, patients of the schizodepressive and non-classifiable type did better with carbamazepine than lithium ($p = 0.055$ for recurrence), whereas in the schizomanic patients, they were equipotent. Applying DSM-III-R, carbamazepine demonstrated superiority in the patient group with more schizophrenia-like or depressive disorders ($p = 0.040$ for recurrence), but not in patients fulfilling the DSM-III-R criteria for schizoaffective disorder,

bipolar type. This is the best evidence currently available for prophylactic efficacy of mood stabilisers in schizoaffective disorders. Lithium and carbamazepine seem to be equal alternatives in the maintenance treatment of broadly defined schizoaffective disorders. However, in subgroups with depressive or schizophrenia-like features, and in long-term tolerability, carbamazepine may be superior. These findings are in line with previous reports that lithium may be more effective in schizoaffective disorder, mood-dominant type (Müller-Oerlinghausen et al. 1989), than in schizophrenia-dominant patients (Lenz et al. 1989).

In patients not responding sufficiently with lithium prophylaxis, augmentation with carbamazepine may be successful (Bocchetta et al. 1997).

Both carbamazepine and lithium in these indications may be ranked as Level C.

Valproate has also demonstrated prophylactic usefulness in schizoaffective disorder, but only on the basis of case series and open trials (Puzynski and Klosiewicz 1984; McElroy and Keck 1993; Keck et al. 1996) (Level D).

Despite the positive findings with mood stabilisers, concomitant treatment with an antipsychotic as well often appears prudent in schizoaffective disorder. Most experience derives from open studies where atypical antipsychotics appear to be a more promising treatment than typical neuroleptics (Ghaemi and Goodwin 1999). Clozapine has traditionally been used in the prophylaxis of schizoaffective disorder (Suppes et al. 1999b; Ciapparelli et al. 2000; Hummel et al. 2002) (for a review of the earlier literature, see also Zarate et al. 1995a). A subgroup analysis of a large controlled Phase III trial revealed that olanzapine is more efficacious than haloperidol in relapse prevention of schizoaffective disorder (Tran et al. 1999). Similarly, risperidone appears more effective and tolerable than haloperidol as demonstrated by a double-blind, large-scale prospective maintenance trial for schizophrenia and schizoaffective disorder (Csernansky et al. 2002). However, these two controlled trials lasted only one year, and more clinical, long-term experience is needed for a definite judgement. For example, a recent report on quetiapine treatment raised the question of loss of efficacy and rebound psychosis over three years (Margolese et al. 2002).

When combining a mood stabiliser and antipsychotics, lithium or valproate may be the primary choice as the mood stabiliser. The induction of cytochrome P450-dependent metabolism by carbamazepine often leads to insufficient serum levels of antipsychotics (Spina et al. 1996; Hesslinger et al. 1999; Yatham 2000).

In addition to the range of medicines discussed above, maintenance ECT may also be an effective treatment (Swoboda et al. 2001).

8. Additional psychopharmacological treatment options

Besides the cited pharmacological treatment options, there is a wide range of additional experimental treatments or nutritional agents currently under investigation for mood stabilising properties. This includes, e.g., thyroid supplementation in patients with rapid-cycling bipolar disorder (Bauer and Whybrow 1990), novel anticonvulsants like oxcarbazepine (Grunze and Walden 2002) or nutritional supplements, e.g. omega-3 fatty acids (Severus et al. 1999). For reasons of space and the currently limited quality of available study data, we will not discuss these options further. We note that they may, nevertheless, prove important in the future.

9. When is maintenance treatment indicated?

There is no controlled prospective study to indicate when maintenance treatment should start. Several retrospective chart analyses suggest that with every episode the length of the subsequent symptom-free interval decreases (Kessing 1998; Roy-Byrne et al. 1985; Angst 1981; Zis et al. 1980). For lithium, there is also some recent evidence that prophylactic efficacy may decrease with a longer delay between onset of illness and initiation of treatment (Franchini et al. 1999; Garcia-Lopez et al. 2001). However, there are also contradictory data (Baldessarini et al. 1999b) and it remains unclear whether this phenomenon is only true for lithium or also for other treatment modalities. These findings justify starting maintenance treatment as soon as possible after the diagnosis has been established. However, not all patients would suffer from an additional episode (Goodwin 2002), and the acceptance of long-term treatment by many patients is low at this early stage so to prescribe lithium at all risks its premature discontinuation. Sudden discontinuation, especially of lithium, may harm patients more than having never been on prophylactic treatment (Baldessarini et al. 1999c; Goodwin 1994) and increase suicide risk (Baldessarini et al. 1999a).

Whereas many European guidelines usually recommend waiting for at least a second episode of illness, and only recommend maintenance treatment if these episodes occur within a rather short time interval (e.g. three years), US guidelines favour commencement of maintenance treatment with the first manic episode (Sachs et al. 2000; Bowden et al. 2000b). Compromising between these recommendations, the Dutch guidelines consider the number

of episodes and variables such as severity and positive family history of bipolar disorder suggesting an increased genetic risk (Nolen et al. 2001). Thus, if the first episode is manic, of disruptive severity, and there is a family history, they recommend to consider seriously the start of maintenance treatment. Otherwise, with two episodes (one of them manic), maintenance treatment should be initiated if at least one is of particular severity or the patient has a positive family history. With the third episode, prophylaxis should always be considered (Figure 1). Whatever the advice from doctors may be, the limiting consideration at this stage is often the attitude of patient and family.

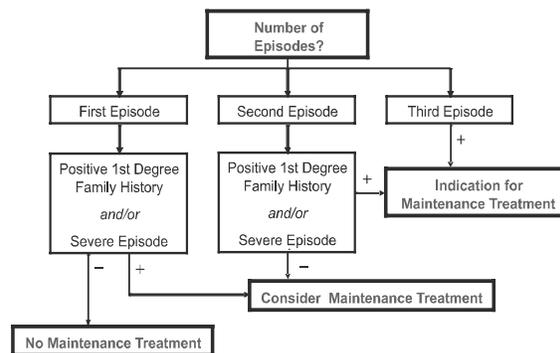


Figure 1 Algorithm for indication for maintenance treatment (Dutch guidelines, from Nolen et al. 2001)

Concerning the duration of prophylactic treatment, there is a consensus among experts that it should be continued life long whenever possible, although there are no discontinuation studies targeting this question.

10. Conclusions

Both the broadening of the bipolar spectrum and the increasing awareness of the limitations of lithium (Maj et al. 1998), and the rest of our current treatment portfolio (Frye et al. 2000), especially with respect to bipolar depression (Akiskal et al. 2000), gave rise to the development of new treatment strategies. Some anti-epileptic medications and atypical antipsychotics may be helpful alternatives, either in monotherapy or combination treatment. In other than classical manifestations, they may even be the first choice treatment. However, more controlled data, especially beyond two years (similar to what is available for lithium and carbamazepine) and long-term clinical experience are needed, and several important questions, e.g. anti-suicidal properties, still have to be addressed (Goodwin et al. 2003). Table 1 summarises current, but only to some extent evidence based, recommendations for maintenance treatment of the different forms of bipolar disorder. It depicts a suggested sequence

of use of medications. With a severe and refractory course of bipolar disorder, combination treatment should be initiated early in some instances, e.g. often in schizoaffective disorder and rapid cycling patients, right from the beginning.

We can reasonably claim to have identified

rational approaches to long-term treatment in bipolar patients, based loosely on evidence, albeit of varying strengths. The future development of combination treatments will only be optimised if we move beyond mere reason to high quality evidence from large scale trials in representative patient samples.

Table 1

Treatment choices of medicines for maintenance and prophylactic treatment of bipolar disorder. With severity and/or refractoriness, combinations are recommended at an early treatment stage. The level of evidence for efficacy is shown in brackets after each agent; however, in clinical practice, other aspects such as tolerability and interaction need at least the same careful consideration. (-) **only based on case reports or expert opinion in the absence of data sufficient for Level D**

<i>Bipolar I disorder without rapid cycling</i>	<i>Bipolar I with rapid cycling</i>	<i>Bipolar II disorder without rapid cycling</i>	<i>Bipolar II with rapid cycling</i>	<i>Schizoaffective disorder (bipolar type)</i>
Lithium (A)	Combination of lithium and carbamazepine (C) or valproate (C)	Lithium (C)	Lamotrigine (C)	Lithium(C) In schizo-dominant type: Atypical antipsychotics (A)
Mania-dominant type: Atypical antipsychotics (especially olanzapine (A)), Depression-dominant type: lamotrigine (A)	Mania-dominant type: lithium (C), olanzapine (D) Depression-dominant type: lamotrigine (D)	Carbamazepine (D)	Valproate (D)	Carbamazepine (C)
Valproate (B)	Carbamazepine (D); clozapine (D)	Lamotrigine (-), valproate (-) with prominent depressions: modern antidepressants (-)	Carbamazepine (-), lithium (-)	Valproate (D), Atypical antipsychotics (-)
Carbamazepine (B), with severe manias: classical antipsychotics, clozapine, risperidone (D) with prominent depressions: modern antidepressants in combination with a mood stabilizer (D), maintenance ECT (D)	Nimodipine (B)	Atypical antipsychotics (-), maintenance ECT (-)	Nimodipine (-), atypical antipsychotics (-)	Typical neuroleptics (-), maintenance ECT (-)

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