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Concepts in the treatment of bipolar disorder

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Objective: Concepts in the treatment of bipolar disorder are discussed considering clinical practice.
Method: Results of the Multicenter Study of Long-term Treatment of Affective and Schizoaffective Psychoses (MAP) study, a controlled maintenance trial, are interpreted with respect to treatment concepts.
Results: The spectrum of patients diagnosed as bipolar has become more heterogeneous. It now comprises subtypes requiring differentiated treatment. The MAP study confirms that prophylactic efficacy of lithium seems to be specific to classic manic-depressive illness, whereas carbamazepine might be more efficacious in non-classic bipolar patients. With respect to clinical practice, treatment evaluation should also consider antisuicidal effects, inter-episodic morbidity and compliance. In these respects, results are in favour of lithium. Furthermore, data indicate that adherence to lithium clearly depends on illness concepts. This encourages efforts to supplement pharmacotherapy by psychoeducation and psychotherapy.
Conclusion: With the broadening of diagnostic criteria, the treatment of bipolar disorder has become more complex. Patients need an integrated approach, including differentiated mood-stabilizing pharmacotherapy and psychotherapeutic measures.

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Introduction

The prevalence and the clinical spectrum of patients diagnosed as bipolar have changed considerably over recent decades. Until recent years, lifetime prevalence of bipolar affective disorders was about 0.5–1.5% according to most epidemiological studies (e.g. 1–3). Recent studies indicate, however, that the prevalence of bipolar disorders is much higher than thought previously. A major reason for the rise in prevalence of bipolar disorder is a diagnostic shift resulting from evolution of diagnostic manuals and diagnostic practice. For example, many patients diagnosed formerly as schizophrenic, as unipolar depressive or diagnosed as presenting a borderline personality are now supposed to belong to a 'bipolar spectrum' (4–6). According to a review on epidemiological studies the median lifetime prevalences are 0.5% for both bipolar I and bipolar II disorders, but 5.1% for bipolar spectrum disorder (7) (see Fig. 1).

In consequence, the clinical picture of patients diagnosed as bipolar has changed significantly over the last two or three decades. Treatment concepts that have proved to be suitable for the small group of manic-depressive patients as diagnosed in the 1970s have to be reconsidered. New subtypes of bipolar illness may require new treatment strategies.

The first part of this paper deals with the concept of mood stabilization and with differential responses to preventive treatments. In the second part, we present data from a controlled clinical trial Multicenter Study of Long-term Treatment of Affective and Schizoaffective Psychoses (MAP) on inter-episodic morbidity, non-compliance and suicidal behaviour – aspects which are clearly understudied.

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Mood stabilization

Outcome in the treatment of bipolar illness has many different aspects – cycling frequency, duration

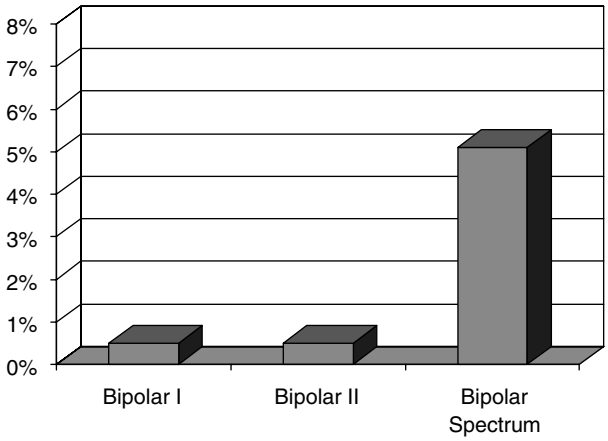

Fig. 1. Median lifetime prevalences for different subtypes of bipolar disorder. Adapted from (7).

of episodes, depressive, manic and subthreshold symptomatology. As treatment should take care of all these different aspects, mood stabilization has become one of the prevailing concepts in the treatment of bipolar disorder. According to Sachs (8), a mood stabilizer is a drug that benefits at least one of the major aspects of bipolar disorder without worsening any other major aspect of the illness. Other, more rigorous definitions essentially require prophylactic efficacy, i.e. the drug has been shown to be effective in the acute and continuation phases as well as in the maintenance phase of treatment [see (9, 10); for an explanation of the treatment phases see Fig. 2].

The concept of mood stabilization is of special interest in the treatment of bipolar depression (i.e. a depressive episode of a bipolar patient) including (pseudo-) unipolar patients presenting signs of bipolarity such as family history of bipolar disorder or an abrupt onset in the 2nd or 3rd decade of life, i.e. an early illness onset (12). The self-evident pharmacological therapy of bipolar depression is an antidepressant. However, as has been pointed out by Kukopulos (13) and Wehr and Goodwin (14), antidepressants may induce mania; and it is also discussed whether antidepressants worsen the course of the illness by increasing the cycling frequency (14, 15). These risks are reflected in several expert opinions and guidelines which recommend avoidance of antidepressants in less severe bipolar depression (e.g. 8, 16) or – if antidepressants are considered necessary in severe cases – to discontinue them as early as possible (8). When reviewing recommendations concerning treatment of bipolar depression, Möller and Grunze (15) have found many guidelines overemphasizing the risk of inducing mania or rapid-cycling and neglecting other important aspects, especially suicidality, which is clearly the most critical outcome. The authors conclude that although it is necessary to keep the risk of switch into mania in mind, modern antidepressants with a lower switch-rate, especially selective serotonin reuptake inhibitors (17), should be the first choice in the treatment of acute bipolar depression. Another recommendation is to combine the antidepressant with a mood stabilizer because this combination has been shown to diminish the risk of a switch into mania in bipolar patients (18) (see Fig. 3).

At present, lithium, carbamazepine and valproate are usually considered as mood stabilizers. Further substances such as olanzapine and lamotrigine are tested currently in large clinical trials involving bipolar patients [see Table 1; for an overview, also see (9, 19, 20)].

Differential response

With respect to long-term treatment, a mood stabilizer is the backbone of pharmacological treatment in bipolar disorders; but which mood stabilizer is best for a specific patient? Are there identifiable characteristics from which a response

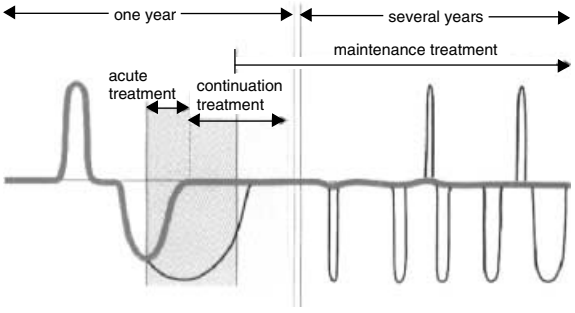

Fig. 2. Phases in the treatment of bipolar disorder: Acute treatment alleviates the symptoms. Continuation treatment prevents relapses into the episode under treatment. Maintenance treatment prevents the occurrence of new episodes (11).

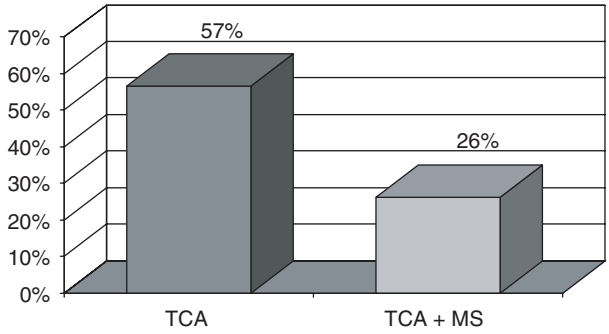

Fig. 3. Switch rates in $n = 92$ bipolar depressive patients treated with a tricyclic antidepressant (TCA). Adapted from Bottlender et al. (18).

to different mood stabilizers can be predicted? The interest in differential response is rising with the rising prevalence and heterogeneity of bipolar disorders. None the less, knowledge on differential efficacy is still to be considered as preliminary. Table 1 gives an overview regarding the spectrum of efficacy of established and of putative mood stabilizers.

To what extent optimal treatment strategy is influenced by diagnostic criteria is shown by the results in differential response to prophylactic lithium and carbamazepine by the MAP study (21). A total of 171 bipolar patients [Diagnostic and Statistical Manual (DSM-IV)] were subdivided into a classical subgroup (bipolar I patients without mood-incongruent delusions and without comorbidity; $n = 67$) and a non-classical subgroup including all other patients ($n = 104$). Classical bipolar patients had a lower re-hospitalization rate under lithium than under carbamazepine prophylaxis ($P = 0.005$). In contrast, a trend in favour of carbamazepine was found in the non-classical group. This indicates that lithium is highly efficacious in the relatively small group of classic manic-depressive illness. For the larger group of patients with atypical features, other prophylactic drugs such as mood-stabilizing anticonvulsants might be more efficacious.

Recent empirical evidence [cf. (22)] supports the notion that different mood stabilizers might have a different spectrum of efficacy (see Fig. 4) with some having marked effects on the depressive pole (such as lamotrigine), on the manic pole (such as valproate) or having marked antipsychotic effects (such as atypical antipsychotics) or having anti-suicidal effects, as has been shown for lithium (see below). The consequences could be to combine two or more mood stabilizers, e.g. lamotrigine and lithium, in order to achieve full protection against the different aspects of bipolar illness (23–25). Combination therapy is common in clinical practice, although the empirical evidence on safety and efficacy of combination of mood stabilizers is still limited (25).

Table 1. Monopharmacological treatment strategies in the prophylaxis of bipolar disorder

Substance	Remarks
Lithium	Prophylactic efficacy established by several controlled studies Prophylactic efficacy seems to be affected negatively by: • mood-incongruent delusions • rapid cycling • psychiatric comorbidity • secondary affective disorders Prophylactic efficacy seems to be influenced positively by: • a typical clinical picture • an episode sequence of mania – depression – free interval Some evidence of antisuicidal efficacy Acute antimanic effects in patients with euphoric mania Augmentation of the antidepressant effects of an antidepressant
Carbamazepine	Evidence of prophylactic efficacy from controlled studies Seems to have a broader spectrum of efficacy than lithium Acute antimanic effects
Valproate	Some evidence of prophylactic efficacy from open studies and from clinical experience Acute antimanic effects in patients with euphoric, dysphoric and mixed mania Possibly efficacious in the acute and preventive treatment of rapid and ultra-rapid cycling
Lamotrigine	Evidence of prophylactic efficacy from controlled clinical trials Might be especially helpful in rapid cycling Antidepressive effects
Olanzapine	Evidence of prophylactic efficacy from controlled large clinical trials Acute antimanic effects Possibly augmentation of the antidepressant effects of an antidepressant
Oxcarbamazepine/Clozapine/Risperidone/ Topiramate/Nimodipine/Gabapentine?	The current evidence regarding efficacy of oxcarbazepine, clozapine, risperidone, topiramate, nimodipine, gabapentine, and other substances is limited Oxcarbazepine has less pharmacokinetic interactions than carbamazepine but might have a similar efficacy profile Clozapine might be especially helpful in schizoaffective disorders Nimodipine might be helpful in ultra-rapid cycling bipolar disorder

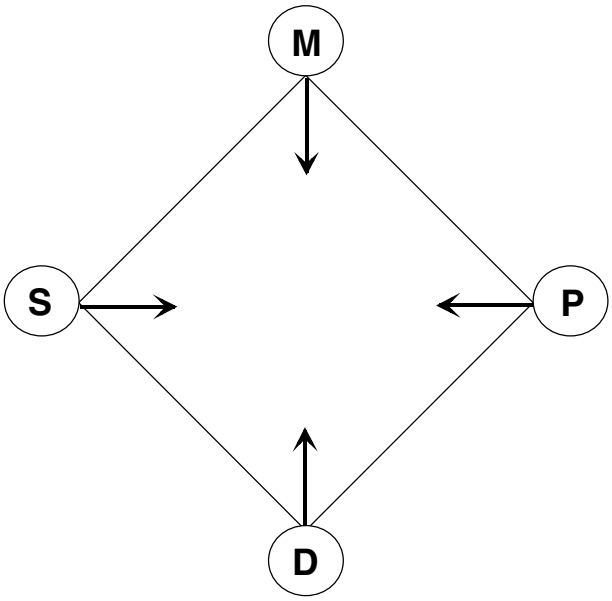

Fig. 4. Major targets for mood-stabilizing drugs: M = manic pole, D = depressive pole, S = suicidality, P = psychotic features.

Inter-episodic morbidity and non-compliance

Efficacy defined as the potential of a treatment under optimal conditions (26) is essential, but it is useless if the medication is discontinued by the patient who is discontent with the medication for any reason, e.g. for inter-episodic subsyndromal morbidity. Hence, the choice of the optimal treatment is to be supplemented by additional criteria such as non-compliance and inter-episodic morbidity. This has been neglected for many years, although research has shown its significance in many respects (27–29). For example, inter-episodic symptoms may be associated with a poor prognosis (30) and a considerable impairment of social functioning (31).

Regarding non-compliance to medication, most authors agree that it is one of the most limiting factors in the long-term treatment of bipolar disorders (26, 32–34). Moreover, discontinuation of treatment following non-compliance is usually abrupt. This presents a further peril, as clinical research has found that rapid discontinuation of lithium is related to an increased risk of a rapid recurrence (35–37).

For both inter-episodic morbidity and non-compliance the few studies available concentrate on patients treated with prophylactic lithium and little is known on inter-episodic symptoms and treatment discontinuation under other mood stabilizers. Recent results from the MAP study (38) suggest, however, a clear difference between lithium and carbamazepine at these respects. Although the rates of re-hospitalization were similar under treatment with lithium and carbamazepine (31% vs. 28%), the response rate in bipolar patients (DSM-IV) was higher under prophylactic lithium than under carbamazepine (40% vs. 24%) when extending definition of a treatment failure to inter-episodic morbidity and drop-out (Fig. 5). This is due mainly to a significantly higher rate of drop-outs under carbamazepine. The risk of drop-out was significantly correlated to inter-episodic morbidity for both drugs. According to recent analyses from the MAP study, the probability of dropping-out under lithium was related to patients' illness concepts (Kleindienst N, Greil W, unpublished data). Positive attitudes towards treatment and the treating physician clearly favour adherence to prophylactic lithium. This result encourages efforts to supplement pharmacotherapy by intensive psychiatric management, psychoeducation or psychotherapy [see also (39)].

Suicidality

The data from the MAP study on differential response, inter-episodic morbidity and non-compliance are supplemented by data on suicidal behaviour (see Table 2). Considering all patients who had been randomized to lithium or carbamazepine (i.e. all bipolar and schizoaffective patients according to the International Classification of Diseases (ICD)-9, $n = 234$) (40, 41), one completed suicide and five suicide attempts were observed. All the six suicidal acts occurred in the carbamazepine group (see Table 2). These data refer to the controlled treatment period. When additional data from the time before and after the controlled study period are taken into account, three more suicidal acts were observed. Again, all

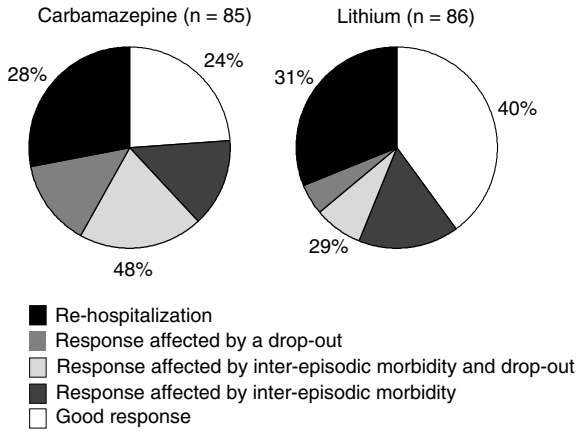

Fig. 5. Levels of treatment response under lithium and carbamazepine (38). Reproduced with the kind permission of Cambridge University Press.

Table 2. Suicidal behaviour under lithium or carbamazepine in the MAP study ($n = 285$)*

	Lithium	Carbamazepine
Study period ($n = 234$)**		
Suicides	0	1
Suicide attempts	0	5
Open period		
Suicides	0	3

*All bipolar and schizoaffective patients who consented to randomization to either lithium or carbamazepine (40, 42).
**$n = 117$ under lithium and $n = 117$ under carbamazepine.

three patients were under carbamazepine and none under lithium at the time they committed suicide (42). All in all, no suicidal acts under lithium contrast to nine under carbamazepine (see Table 2). For the subsample of patients with a diagnosis of bipolar disorder according to DSM-IV ($n = 171$; $n = 86$ under lithium and $n = 85$ under carbamazepine), four suicide attempts were observed during the treatment period in the carbamazepine group and none under lithium. These data from our controlled trial are in line with several naturalistic studies reporting antisuicidal effects of lithium [for an overview, see (43, 44)].

Summary

In sum, options in the treatment of bipolar disorders have expanded greatly over recent years. Bipolar disorder has become more heterogeneous and there is increasing evidence that different subtypes of the disorder need different pharmacotherapeutical approaches. Lithium efficacy seems to be specific to classic bipolar illness. Other types of the bipolar spectrum that are diagnosed more frequently in recent years might respond better to an alternative mood stabilizer or to a combination therapy (23, 45).

Efficacy of medication should, however, be just one aspect when selecting a treatment strategy. Recent results from the MAP study show that various medications may differ substantially regarding further aspects of relevance, such as inter-episodic morbidity or unscheduled discontinuation of treatment. As the best medication is useless if not taken, the prescription of medication has to be complemented by active measures to support compliance. This includes intensive psychiatric management, comprising co-operation with patients' relatives and elicitation of the patient's illness concepts, psychoeducation regarding illness and its treatment and, if possible, specific psychotherapy (46, 47). Only a comprehensive treatment approach will have a beneficial effect on the long-term course of the illness and might even help bipolar patients to profit from the surplus energy characteristic for bipolar patients (48).

Conclusion

Diagnostic concepts and prevalence of bipolar disorders have changed substantially over the last decades. This asks for adaptation of treatment concepts. An integrated treatment approach is required, including differentiated pharmacotherapy with mood-stabilizing drugs, intensive psychiatric management and psychotherapeutic measures.

Acknowledgements

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