To control the symptoms of bipolar disorder effectively and to reduce relapse, polytherapy has become exceedingly common (Kupfer et al., J Clin Psychiatry 2002; Frye et al., J Clin Psychiatry 2000; Freeman & Stoll, Am J Psychiatry 1998). Despite the frequency of polytherapy in clinical practice, the evidence to support this approach is limited.

Acute mania
Several studies have shown that lithium, valproate (e.g. Orfiri® long, Orfiri®), carbamazepine (e.g. T(r)imonil®) and antipsychotics are effective as monotherapy to treat acute mania. A number of recent studies suggest that a combination of lithium or valproate and an atypical antipsychotic is the most effective polytherapeutic approach for this acute condition, with approximately 20% more patients responding to polytherapy than monotherapy. For example, a randomised, double-blind trial with 344 patients who did not respond adequately after two weeks treatment with valproate or lithium showed a significantly greater reduction in manic symptoms, a more marked response, and longer remission with additional treatment with olanzapine (started at 10 mg/day) than with placebo, i.e. valproate or lithium alone (Tohen et al., Arch Gen Psychiatry 2002). However, patients receiving polytherapy were more likely to discontinue the study due to treatment-emergent adverse events such as somnolence, dry mouth and weight gain. In a further study in 156 patients with a current manic or mixed episode of bipolar disorder, combination therapy with risperidone (mean modal dose 3.8 mg/day) or haloperidol (6.2 mg/day) and lithium or valproate was significantly more effective than monotherapy with a mood stabilizer in terms of response and remission rates (Sachs et al., Am J Psychiatry 2002). Patients receiving haloperidol experienced more extrapyramidal symptoms (EPS). In another study in 30 patients experiencing manic or mixed symptoms, a combination of valproate and quetiapine was superior to valproate alone, with a significant advantage as early as day 14 (Delbello et al., J Am Acad Child Adolesc Psychiatry 2002).

Fewer findings have been published for combinations of lithium or valproate and an antiepileptic drug. Lithium combined with carbamazepine was found to be as effective in acute mania as haloperidol, but with haloperidol, higher EPS rates and with lithium plus carbamazepine, higher rates of non-compliance and need for rescue medication were observed (Small et al., Psychopharmacol Bulletin 1995). In general, combination therapy with lithium or valproate and carbamazepine is complicated due to the numerous drug interactions of carbamazepine.
Acute bipolar depression

Despite the profound comorbidity and mortality associated with depression, very few studies have investigated this phase of bipolar illness. As monotherapy, lithium and valproate may be adequate for mild to moderate bipolar depression, in the same way as several studies have shown that lithium and lamotrigine are effective against depressive symptoms without increasing manic symptoms, and that these drugs alone have some ability to decrease the rate of recurrence of depressive episodes (Srisupanant et al., Can J Psychiatry 1995; Calabrese et al., J Clin Psychiatry 2003; Bowden et al., Arch Gen Psychiatry 2003; Burgess et al., Cochrane Database Syst Rev 2001). Valproate and carbamazepine may reduce depressive symptoms without triggering a switch into mania (Yatham et al., Bipolar Disord 2003). Monotherapy with antidepressants has not been studied systematically due to their ability to induce high rates of manic or hypomanic switch and cycle acceleration (Peet et al., Br J Psychiatry 1994).

There is limited evidence that the best approach to treat bipolar depression may be combination therapy with lithium and an antidepressant in patients with low lithium levels, especially with novel antidepressants. In a randomised study, 184 patients with bipolar I depression were treated with bupropione, venlafaxine or sertraline on top of lithium, valproate, carbamazepine, lamotrigine or other antipsychotic drugs (Post et al., Br J Psychiatry in press). Efficacy and attrition were the same in each group, but significantly more patients switched to mania or hypomania with venlafaxine. One study, which directly compared combination therapy of a mood stabilizer plus an antidepressant with a mood stabilizer alone, showed that the addition of paroxetine or imipramine result in significantly greater benefit than with placebo in patients with low lithium levels (Nemeroff et al., Am J Psychiatry 2001). Addition of a second mood stabilizer or paroxetine in patient already receiving lithium or valproate resulted in similar improvements in both groups, but the attrition rate was higher in the group with two mood stabilizers.

Although the antidepressant effect of lamotrigine is known, the efficacy of lamotrigine plus an antidepressant has not been investigated in a randomised, double-blind study. In an open label trial, patients with refractory bipolar depression improved when lamotrigine was added to ongoing therapy with valproate (Kusumaker et al., Psychiatry Res 1997). An 8-week, placebo-controlled double-blind randomised study in n=633 patients with bipolar I depression showed that olanzapine alone is more effective than placebo, and that the combination of olanzapine plus fluoxetine is better than placebo or olanzapine alone, without increasing the risk of developing manic symptoms (Tohen et al., Arch Gen Psychiatry 2003).

Maintenance therapy

Up to 70–75% of patients without maintenance treatment after acute treatment will relapse within the year following an acute episode (Sachs & Rush; J Clin Psychiatry 2003). For maintenance therapy, commonly used agents, such as lithium, valproate or olanzapine appear to be most effective in preventing manic relapses, and lamotrigine in preventing depressive relapses. However, there have been few systematic studies into whether combinations such as lamotrigine and lithium, valproate or olanzapine control mood stability more effectively.

Combination therapy with olanzapine and lithium or valproate introduced after patients responded to lithium or valproate alone did not result in a difference in overall rate of relapse during maintenance therapy (Tohen et al., Br J Psychiatry 2004). Some small studies suggested that there might be a role for combination therapy with lithium and an antidepressant, but up until now, no final conclusions could be drawn. Altogether 12 patients who received the combination of lithium plus valproate had a lower risk of relapse than patients who received lithium alone, but they experienced more adverse events (Solomon et al., J Clin Psychiatry 1997). Combination therapy with lithium and carbamazepine showed inadequate responses for monotherapy with these drugs and for them in combination; only patients with a history of rapid cycling responded better to combination than to monotherapy (Denicoff et al., J Clin Psychiatry 1997).

Conclusions of the authors: Treatment of bipolar disorder remains challenging. As monotherapy often leads to relapses, polytherapy is required in most cases to reduce the affective symptoms and improve the quality of life. Evidence for supporting combination therapy differs according to the phase of illness, i.e. acute mania, acute depression and maintenance therapy, and is very limited in some phases. Studies on combination therapy are therefore urgently needed, above all long-term efficacy and safety studies. Until adequate findings are available, physicians must focus on the individual needs of the patient.

New Studies

Clinical course of children and adolescents with bipolar spectrum disorder

Birmaher et al., Arch Gen Psychiatry 2006; 63:175-183

Design: prospective, longitudinal study with interviews on average every 9 months for an average of 2 years using the Longitudinal Interval Follow-up Evaluation

Setting: Outpatient and inpatient units at University of Pittsburgh, Brown University, and University of California at Los Angeles

Objective: To assess the longitudinal course of bipolar (BP) spectrum disorders (BP-I, BP-II, and not otherwise specified BP-NOS) in children and adolescents

Patients: 263 children and adolescents, mean age of 13 years, with BP-I (n=152), BP-II (n=19) and BP-NOS (n=92)

Results: approx. 70% of the subjects recovered from their index episode and 50% had at least 1 syndromal recurrence, particularly depressive episodes. For 60% of the follow-up period, patients had syndromal or subsyndromal symptoms with numerous changes in symptoms and shifts in polarity, and psychosis 3% of the time. Early onset, BP-NOS, long duration of mood symptoms, low socio-economic status, and psychosis were associated with poorer outcomes and rapid mood changes. Compared to adults with BP-I, children and adolescents with BP-I are symptomatic for a significantly longer time and have more mixed/cycling episodes, mood symptom changes, and polarity switches.

Conclusions: Children and adolescents with BP spectrum disorders experience frequent changes in symptom status and polarity with a fluctuating course, showing the whole
BP spectrum from subsyndromal to mood syndromes meeting full DSM-IV criteria. Younger patients showed more severe mood changes than adults.

There have been very few prospective studies and clinical samples that have investigated the outcome of paediatric bipolar disorder. And it has not been known whether onset of BP in early life has the same clinical course as onset of BP in adult life. The collaborative COBY study (Course and Outcome of Bipolar Illness in Youth) is the first study to describe the psychopathological course of each major clinical phenotype of BP among children and adolescents, and it is the largest cohort of paediatric subjects with BP described in the literature to date.

To describe the early clinical course and relevant predictors of outcome in children and adolescents with BP-I, BP-II, and BP-NOS, 263 patients between 7 and 17 years 11 months were recruited into the COBY study: 57% had BP-I, 8% BP-II, and 35% BP-NOS. The patients were prospectively interviewed every 35.5 weeks for a mean of 94.8 ± 51.5 weeks, using assessments such as the K-SADS-PL (Schedule for Affective Disorder and Schizophrenia for School Age Children-Present and Lifetime Version), LIFE (Longitudinal Interval Follow-up Evaluation), and Peterson Pubertal Development Scale.

At the start of the study, children with BP-I (13.2 years) and BP-NOS (12.1 years) were significantly younger than children with BP-II (15.1 years). Fewer BP-I patients were living with both biological parents and they had significantly more lifetime psychoses than those with BP-II and BP-NOS. Although two-thirds of the children recovered from the index episode, half of them had at least one syndromal recurrence. BP-I and BP-II patients recovered and relapsed more frequently, but BP-NOS patients had more protracted illness. On average, the patients had 1.5 syndromal recurrences per year, particularly depressive episodes. For 60% of the follow-up period, patients had syndromal or subsyndromal symptoms, with numerous changes in symptoms and shifts in polarity. For 22% of the time, full syndromal episodes were present, subsyndromal symptoms 38% of the time.

The results of the COBY study are comparable with studies in adult BP patients, in whom polyphasic episodes and interepisodic symptoms of subthreshold intensity are frequent. But the children and adolescents with BP-I were symptomatic for significantly more of the time, and had more mixed and cycling episodes, mood changes, and polarity switches than adults with BP-I.

Due to the enduring and rapid changeability of symptoms from very early in life and at crucial stages of their lives, the normal emotional, cognitive, and social development of children and adolescents with bipolar disorder is impaired. The authors therefore emphasize that early recognition and accurate acute and maintenance treatment are of utmost importance, not only to improve syndromal and subsyndromal symptoms, but also to prevent the serious psychological morbidity that usually accompanies this condition.

Books
The bipolar child – The definitive and reassuring guide to childhood’s most misunderstood disorder


“ADHD”, “depression”, “oppositional defiant disorder”, or “generalized anxiety disorder” – bipolar disorder in children and adolescents is often misdiagnosed and mistreated due to the overlapping symptoms with other childhood psychiatric disorders. And too often, the children are treated with stimulants or antidepressants – medications which actually worsen the bipolar disorder.

The first edition of “The bipolar child” was published in January 2000, and when it was discussed on TV, thousands of parents phoned or mailed: They were stunned...
Bipolar Disorders – Keystones of acute and long-term management

Bipolar disturbances are at least now gradually receiving the attention this affective disorder has long deserved because of their high prevalence, poor prognosis, devastating (and even existential) consequences for those affected, and their effects on the economy as a whole. This change in attitude has resulted in a considerable increase in available treatments. The role of valproate as a keystone in acute antimanic treatment and mood-stabilising long-term therapy has remained unaffected by this. Whilst the WHO has long listed this substance amongst its ‘essential drugs’ for the treatment of bipolar disturbances [1], the German BIArM did not agree to a long-overdue extension of its indications until 2005. This new legal status was taken as an occasion to critically appraise the importance of sustained-release valproate in the management of bipolar patients on the occasion of an expert meeting in mid-2006. A résumé of the main points covered was first presented at the 6th Annual Conference of the German Society for Bipolar Disturbances (Deutsche Gesellschaft für Bipolare Störungen; DGBS).

Mood stabilisation with valproate – established in clinical practice and indispensable

The ‘ideal’ antimanic agent has yet to be found, because it would have to satisfy extraordinarily high demands. The ideal qualities are not only a rapid onset of action, but a multidimensional efficacy profile that would cover emotional, cognitive and motor agitation/disinhibition, and at the same time, in addition to euphoric states, dysphoric, psychotic and mixed affective states. Reliable tolerability and uncomplicated treatment regimens with a wide therapeutic window and a low degree of interactions in combination regimens are equally important for acute and long-term management. That valproate has proven to largely meet this profile under the very different situations encountered in the everyday clinical setting is demonstrated by the high degree of acceptance it has achieved throughout the world.

After decades of relative quiet, about ten years ago, we witnessed the start of a veritable ‘boom’ in publications with guidelines or recommendations for the treatment of bipolar disturbances. This was accompanied by a sudden increase in treatment alternatives, particularly for the management of acute mania. Despite the multitude of options – or perhaps because of these – Martin Schäfer, university Essen, Germany, is still convinced that there will never be adequate, ‘evidence-based’ data to assist in finding the right treatment for every situation. This means that those who treat bipolar disturbances must develop their own concept regarding which type of antimanic agent best suits which type of patient. Equally important when deciding upon the best agent are psychopathological aspects (table 1) and tolerance/safety.

Mania with psychotic components triple the risk of recurrence

The first attempts at treating acute manic patients with valproate left a great impression on Prof. Peter Bräunig, Berlin. Until then, at his hospital, patients in this situation were generally treated with a standard neuroleptic. Patients usually suffered such severe extrapyramidal-motoric side effects, and especially akathisia, that their willingness to comply with treatment was permanently impaired. Valproate was as successful as a standard neuroleptic in these patients – but was much more patient-friendly.

The status quo of the treatment of mania changes only very slowly, however: 80-90% of all bipolar patients still routinely receive a highly potent, first-generation neuroleptic as first-line treatment, and often as maintenance treatment [2]. In Bräunig’s opinion, this is not only incomprehensible because of the considerable problems with tolerance, but also because of the low success rate. A response can be expected in only one third of patients [3]. One reason for the continuing preference of highly potent neuroleptics may be the difficulty to find a distinct diagnosis. More than 60% of bipolar patients also have individual psychotic symptoms during acute mania [4], and more than 20% also have severe, mood-incongruent psychotic symptoms [5]. This are these patients, however, who require special attention from the physician, because the psychotic component means that there is a 2-3-fold higher risk of recurrence [6], and also renders compliance poorer than it already is [7].

Valproate is effective in treating the entire spectrum of manic states

However, the dominance of psychotic symptoms cannot be allowed to serve as an ‘excuse’ for continuing to use conventional neuroleptics. ‘De-escalation’ can be achieved just as well with valproate, and especially just as quickly as with haloperidol, for example [8]. Although this study was only conducted in a relatively small sample, the findings were nevertheless significant, because it had a prospective randomised design and it is the only study of this type that has so far been conducted in this patient population.

In current guidelines, such as those published by the World Federation of Societies of Biological Psychiatry, lithium is recommended as first-line treatment for mania before valproate and second-generation neuroleptics [9]. Bräunig assumes that lithium is so high on the list, because it was the first ever mood-stabilising agent, and not because there is absolutely convincing evidence for its use. Direct comparisons with valproate have not shown any advantage for lithium [10, 11]. The chance of a response is even partly worse if it is not being used to treat isolated episodes of euphoric mania, but – as it is very often the case – patients with:

- dysphoric or mixed affective states [12],
- rapid cycling [13],
- concomitant substance
abuse [14],
• other concomitant psychiatric disorders (especially anxiety states) [15].

Unlike with lithium, the antimanic efficacy of valproate does not decrease with the duration of the illness or the number of previous exacerbations [16].

Complete and durable remission of great prognostic relevance

The most recent findings are from the ‘New Deli’ Study [17]. The study confirmed once again that the onset of the antimanic effects with valproate is rapid. After 3 weeks, the responder rate in the valproate arm was almost 10 percent points higher than in the lithium arm (47.3% versus 37.9%). Of greater importance for the long-term prognosis and the chance of successful professional and social reintegration was, however, that the antimanic effects of valproate were not only maintained throughout the observation period, but continuously increased. At the end of the study, valproate showed a trend to more frequently leading to complete remission than lithium.

Only relatively few controlled studies have been published on the prophylaxis of episodes with valproate, as for other mood stabilisers. Protection against recurrence of up to one year has been shown in open studies. Only one double-blind study has been published so far, and this showed no significant difference from lithium or placebo for the primary outcome variable of a recurrent manic or depressive episode [18]. Possible reasons for this were methodological problems and a response rate in the placebo group twice as high as in comparable investigations [19]. However, valproate was statistically significantly superior to placebo for many of the secondary variables, such as the duration of the recurrence-free period. And valproate exerted a prophylactic effect not only on manic exacerbations, but also depressive episodes. Also, valproate had the lowest rate of treatment withdrawals at 62%, compared with 76/75% under lithium/placebo, which indicates a favourable benefit-risk relationship.

A prerequisite for prophylaxis is compliance – and valproate treatment also offers good conditions for this. The sustained-release formulation (which is actually the formulation for which the approval for the indications bipolar disturbances was granted in Germany) has the advantage that when taken daily, the blood concentrations remain at a consistently effective level. The range of available dosage forms (e.g. of Orliril® long), from sustained-release minitablets with 150 or 300 mg valproate in capsules up to 500 and 1000 mg sachets with sustained-release minitablets should suit the preferences of every person affected.

Polypharmacy is the rule rather than the exception

Under the premise of ‘evidence-based medicine’, the efficacy of a drug is primarily assessed when it is used as monotherapy. This is of limited relevance, however, to patients with bipolar disturbances. This is because, in the everyday clinical setting, treatment with only one psychotherapeutic agent is the exception rather than the rule, according to the many years of experience made by Dr. Heinz Grunze in Munich. He drew attention to a prospective investigation by the ‘Stanley Foundation Bipolar Network’ (n=258). Amongst the patients treated for more than one year, only 7% required single-agent therapy for sustained mood stabilisation, whilst 75% needed three agents or more.

On the one hand, combinations are used for the specific support of acute effects of monotherapy, but, on the other, they are unavoidable when choosing adequate prophylactic regimens to prevent recurrences and cover all affective aspects of the disease, in Grunze’s opinion. The benefits of ‘add-on’ valproate in acute management with neuroleptics (haloperidol or perazine) were shown by the ‘European Valproate Mania Study’, amongst others. In comparison with ‘add-on’ placebo, the mean decrease in the Young Mania Rating Scale score was not only greater and more rapid (p=0.0042) with valproate: this clinical advantage also meant that lower doses of neuroleptics (p=0.0007) were required or that comedication with benzodiazepines was less frequent (p=0.0304) [20].

The converse, i.e. the effect of adding a modern neuroleptic or placebo to existing treatment with valproate or lithium, has also been investigated in many studies [21]. In Grunze’s opinion, however, the study designs used mean that only limited conclusions can be drawn on the usefulness of such a measure. What became obvious, however, is that combinations of olanzapine, risperidone and quetiapine with valproate are well tolerated and do not imply a greater safety risk. Synergism with regard to efficacy can also be expected with combination of valproate and lithium. This is supported by the results of open studies, but above all by many years of clinical experience with both mood stabilisers. Grunze takes this approach very often if breakthrough mania occurs under prophylaxis with lithium. In his opinion, ‘valproate loading’ of this sort usually leads to rapid subsidence of the exacerbation.

Favourable tolerability profile

Valproate is generally well tolerated by patients with bipolar disturbances. This applies to both initial rapid saturation and maintenance therapy in the upper region of the therapeutic window. The side effect profile is not altered when combined with other psychotherapeutics such as mood stabilizers, neuroleptics or antidepressants. Interactions are rare and can be corrected by adjusting the dosage.

Troublesome side effects may take the form of dizziness, gastrointestinal disturbances, tremor, and transient hair loss. Weight gain can also be expected, but less frequently than under lithium. Although changes in laboratory levels such as thrombopenia or an asymptomatic increase in liver enzymes are frequent, they are usually reversible. According to Grunze, these levels should be monitored, but if abnormalities are seen, this does not necessarily mean that valproate has to be discontinued. When using valproate in female bipolar patients with childbearing potential, the benefit-risk situation should be very carefully considered, particularly if used for long-term prophylaxis.

Compliance saves resources

Extrapolated to one year, bipolar patients who discontinue their mood-stabilising medication in the first three months of treatment consume three times as many medical resources as patients who are compliant for longer. The chance of patients remaining compliant to valproate therapy is about twice as high as with lithium. Viewing these two observations together leads to the conclusion that prophylaxis of episodes with valproate not only corresponds to the wishes of patients, but also avoids unnecessary expenditure in the healthcare sector. The data supporting this conclusion were obtained in a practice-based investigation at 33 centres in the USA in 201 inpatients with bipolar I disorder under treatment for an acute manic or mixed affective episode [22]. They were randomised to acute treatment with
Effects on ability to drive and use machines: concentration of valproic acid may be increased with concomitant treatment of cimetidine, erythromycin and felbamate. Concomitant use of sodium valproate and anticoagulants or acetylsalicylic acid may increase the tendency to bleed. As sodium valproate is partly metabolised to ketones, the possibility of false-positive results for tests of ketone-body excretion should be borne in mind in diabetics with suspected ketoacidosis.

Indications: sodium valproate. Prescription only.

Step-wise increase up to the most effective dose is recommended. When taking sodium valproate on its own (monotherapy), the starting dose is generally 5-10 mg/kg body weight, increasing by approximately 5 mg/kg body weight every 3-7 days. The dosage should be determined individually by the physician.

Children: Children are usually treated with doses of 20-30 mg/kg body weight per day. The dosage should be determined individually by the physician.

Pregnancy and lactation: Valproic acid passes into breast milk. As placental barrier and concentrations in foetal plasma are higher to those in the mother, there is an increased risk of malformations. The use of sodium valproate in pregnancy is therefore not recommended. Valproate may rise the phenobarbital concentration and the free fraction of phenytoin.

Interactions with other medicaments and other forms of interaction: Valproate may rise the phenobarbital concentration and the free fraction of phenytoin without increase of total phenytoin concentration. Valproic acid inhibits the metabolism of lamotrigine and felbamate. The plasma concentration of theophylline is increased when theophylline is coadministered with sodium valproate. Concurrent treatment of sodium valproate with valproate or lithium is not associated with safety problems in the clinical setting [24]. A meta-analysis of three double-blind studies with determination of valproate blood concentrations (n=574) confirmed that the onset of the antimanic effect occurs at levels of about 50 µg/mL, that an evident response can be expected from levels of about 80 µg/mL, and that the optimum therapeutic range starts at 94 µg/mL. The maximum effect level of 1.06 corresponds to a decrease in 12 points on the "Young Mania Rating Scale" [25]. The pooled data also showed that in the acute management of patients with manic or mixed affective exacerbations. With regard to the onset of action, rapid saturation is clearly superior to slow titration [23]. The recommended "loading dose" of 20-30 mg/kg body weight is not associated with safety problems in the clinical setting [24].

Rapid up-titration – linear increase in efficacy

With its wide therapeutic window and linear relationship between serum concentrations and mood-stabilising efficacy, valproate offers excellent conditions for the acute management of patients with manic or mixed affective exacerbations. With regard to the onset of action, rapid saturation is clearly superior to slow titration [23]. The recommended "loading dose" of

Table 1: Suggestions for tailoring mania therapy to individual needs (modified from Schäfer M. Essen, Lecture at the 6th DGBS Annual Conference 2006)

<table>
<thead>
<tr>
<th>Type of mania</th>
<th>LIT</th>
<th>VPA</th>
<th>CBZ</th>
<th>PRZ</th>
<th>HAL</th>
<th>OLZ</th>
<th>RIS</th>
<th>QUE</th>
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<td>mild</td>
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• intake independent from meals
• once daily = improved compliance
• convenient 1,000 mg dosage

Value at the 6th Annual Conference of the German Society for Bipolar Disturbances, 16 September 2006, Nuremberg, Germany.

Sources

Satellite Symposium ‘Update on valproate in the treatment of bipolar affective disorders’ supported by DESITIN ARZNEIMITTEL GMBH and Sanofi-Aventis Deutschland GmbH, and other scientific symposiums at the 6th Annual Conference of the German Society for Bipolar Disturbances, 16 September 2006, Nuremberg, Germany.
In 2005, the Canadian Network for Mood and Anxiety Treatments (CANMAT) revised their bipolar disorder guidelines of 1997. The first annual update has now been published. This update reviews new evidence for the treatment of different phases of bipolar disorder, and is designed to be used in conjunction with the 2005 CANMAT Guidelines (Yatham et al., Bipolar Disord 2005; 7 (Suppl. 3): 5-69).

**Acute management of bipolar mania**

The recommendations for the treatment of acute bipolar mania have remained mostly unchanged (tab. 2).

The management of acute bipolar mania is divided into 5 steps with lithium, valproate and several atypical antipsychotics continuing to be the choice for first-line treatment; for second-line therapy, new data confirm the efficacy of the extended release formulation of carbamazepine and open-label data the efficacy of adjunctive oxcarbazepine; from third-line treatment onward, treatments remain the same with no novel or experimental drugs.

**Acute management of bipolar depression**

For this phase of bipolar disorder first line options are still lithium and lamotrigine monotherapy, valproate or lithium plus SSRI/bupropion or olanzapine plus SSRI continue to be the other first-line options, new data support quetiapine monotherapy as a first-line option (tab. 3).

**Maintenance therapy for bipolar disorder**

Valproate, lamotrigine, lithium, and olanzapine remain first-line options for maintenance therapy, and new data support the combination of olanzapine and fluoxetine, with gabapentin as a third-line option (tab. 4).

**Management of bipolar disorder with rapid cycling**

Valproate and lithium and remain the choices for first-line therapy in the long-term management of rapid cycling, and lamotrigine is second-line; adjunctive therapy to lithium or valproate, and olanzapine are now second-line choices.

The update of the CANMAT-guidelines also covers special populations such as women, children, patients with bipolar disorder II, and those with morbid medical conditions, as well as safety issues such as monitoring patients for obesity, metabolic syndrome, dyslipidaemia and type 2 diabetes.
Relapse prevention in bipolar disorder: a critical review of current guidelines

McAllister-Williams RH 2006, J Psychopharm 20 (2: 12-16)

Although bipolar disorder is a severe mental illness – it is one of the worldwide top 10 leading causes of disability (Murray & Lopez 1996) – according to Hamish McAllister-Williams, Newcastle upon Tyne/UK, the evidence-based regarding treatment is less than satisfactory. He therefore reviewed the methodology of the guideline produced by the British Association of Psychopharmacology (BAP; Goodwin GM, J Psychopharm 2003) and its recommendations regarding the long-term treatment of bipolar disorder, and compared it with the guidelines of the American Psychiatric Association (APA; APA, J Am Psychiatry 2002), the Canadian Network for Mood and Anxiety Treatments (CANMAT; Yatham et al., Bipolar Disorders 2005), and the Texas Implementation of Medication Algorithms (TIMA; Suppes et al., J Clin Psychiatry 2005).

The recommendations of the BAP guidelines are based on the strength of the underlying evidence: The highest level A and B recommendations require controlled data, and only the recommendations for level D are based on clinical opinion. The algorithms of the TIMA guidelines are based on the same system, but without level D. In contrast, the APA recommendations are rated on the degree of clinical confidence, combining lack of confidence and clinical conviction. The CANMAT guidelines classify the treatments as “first”, “second” and “third” on the basis of evidence, but also on costs and safety.

All four guidelines are broadly consistent with regard to initiation of long-term treatment, and suggest starting after just one single episode of mania, also incorporating psychological and social support. There is less evidence to support prophylaxis of depressive episodes and the recommendations in this area are therefore less robust. The BAP still considers lithium to be the gold standard of long-term treatment (A), and if lithium fails or is not tolerated, valproate and olanzapine are recommended (A). For failing long-term monotherapy, the recommendation is to combine drugs (D). The APA recommends lithium (I) and valproate (I) as the main options for long-term treatment, with lamotrigine (II) and carbamazepine or oxcarbazepine (II) as possible options. The main difference between the BAP and APA guidelines is the addition of antipsychotics for rapid cycling disorder (III), or for sub-threshold or breakthrough mood episodes in addition to long-term treatment (III). The CANMAT and BAP guidelines are very similar for first-line treatment. For second- and third-line the CANMAT recommend drugs not recommended by the other guidelines (see also “guidelines” in this issue page 7 above). The most recent TIMA guidelines take the form of explicit algorithms. The recommendations for long-term therapy depend upon the pole of the patient’s most recent episode, although most long-term data are based on studies with patients with recently manic or hypomanic episodes. Beyond first-line treatment for patients with hypomanic, manic or mixed episodes, the TIMA differs from the other guidelines in recommending more atypical antipsychotics.

Conclusions of the author: The guidelines reviewed – BAP, APA, CANMAT and TIMA – recommend lithium and valproate (e.g. Orfiri® long, Orfiri®) at the top of the list of recommended drugs for long-term treatment. All guidelines show a similar trend to an increasing prominence of lamotrigine.

For patients who have experienced depressive symptoms, lamotrigine (e.g. Plexox®, Lamotrigin Desitin®) is seen as the main option for relapse prevention. The BAP guidelines continue to be a reasonable set of recommendations, although new data have become available since their publication.