Bipolar disorder is a severe and recurrent, and often chronic psychiatric disorder with a lifetime prevalence of up to 6.5% in the population of the USA (Angst, J Affect Disord 1998). Alcohol and other substance abuse and dependence are also very common, with lifetime prevalences of up to 17% (Grant et al., Arch Gen Psychiatry 2004). The prevalence of substance abuse disorders in patients with bipolar disorder is much higher than in the general population. In the Epidemiologic Catchment Area (ECA) study in more than 20,000 people, 61% of patients with bipolar I disorder and 48% of patients with bipolar II disorder had comorbid substance abuse or dependency (Regier et al., JAMA 1990). In this study, bipolar disorder had the highest lifetime prevalence compared to other psychiatric illnesses such as schizophrenia (47%), unipolar major depression (27%), and anxiety disorder (24%). The most recent survey (National Epidemiologic Survey on Alcohol and Related Conditions; NESARC) with more than 43,000 respondents showed a 12-month prevalence of substance abuse disorders of 27.9% in patients with a history of mania and 26.6% in patients with hypomania, compared to 9.4% in persons without a mood disorder (Grant et al., Arch Gen Psychiatry 2004).

Why more substance abuse in bipolar disorder?

There are only hypothetical explanations why patients with bipolar disorder abuse substances more than other people – the reasons are still not well known yet. Possible explanations for some, but not all findings are misdiagnosis of bipolar disorder due to overlapping symptoms, “self-medication” of symptoms, substance abuse causing bipolar disorder, greater impulsivity of patients, and a common genetic vulnerability (Strakowski & DelBello, Clin Psychol Rev 2000; Brown et al., J Affect Disord 2001; Müller et al., Am J Psychiatry 2001). Patients suffering from bipolar disorder and substance abuse show, at least, greater impulsivity than individuals with each disorder alone (Swann et al., Bipolar Disord 2004).

Substance abuse worsens bipolar disorder

The main barrier for treating dual-diagnosed patients successfully is their poor treatment adherence. Non-adherence is well documented in patients with both diagnoses (Keck et al., Am J Psychiatry 1998; Sajatovic et al., Psychiatr Ser 2006). Non-adherence to medication is associated with delayed symptomatic and functional recovery in patients with bipolar disorder and may be the cause of higher relapse rates (Tohen et al., Arch Gen Psychiatry 1990; Strakowski et al., Arch Gen Psychiatry 1998; Colom & Vieta, Clin Approaches in Bipolar Disorder 2002). Bipolar patients with past or current substance abuse are more likely to attempt suicide, are more often hospitalised, and tend to be more violent (Scott et al., Br J Psychiatry 1998; Saxon et al., Am J Addict 1994; Goldberg et al., Am J Psychiatry 1998; Potash Am J Psychiatry 2000).

Best approach to treat concurrent disorders

Although substance abuse or dependence and bipolar disorder often...
occur together, to date only three randomized, double-blind, placebo-controlled studies have been conducted.

One trial investigated the efficacy of carbamazepine in cocaine-dependent individuals with bipolar disorder (n=57) and without affective disorder (n=87), who were randomised to carbamazepine or placebo for 12 weeks (Brady et al., Exp Clin Psychopharmacol 2002). In the group of patients with bipolar disorder, carbamazepine tended to result in fewer cocaine-positive urine drug screens tests and in a reduction in the severity of depressive symptoms compared to placebo. In the study participants without affective disorder, carbamazepine had no effect on cocaine use compared to placebo.

In another 6-week trial, 25 adolescents with substance abuse and bipolar I or II disorder or recurrent major depressive disorder with adolescent predictors of future bipolar diagnosis received lithium or placebo (Geller et al., Psychiatry 1998). Compared to placebo, adolescents taking lithium had significantly fewer positive urine drug screens and their illness also improved better according to the Children’s Global Assessment Scale.

The most recent double-blind, placebo-controlled trial in dual-diagnosed patients evaluated the efficacy of valproate in 59 alcohol-dependent bipolar I patients (Salloum et al., Arch Gen Psychiatry 2005). Patients were randomised to receive either valproate or placebo on top of the usual treatment, whereas the usual treatment consisted of lithium and psychosocial intervention. After 24 weeks, patients on valproate had significantly fewer heavy drinking days and fewer drinks per drinking day compared to the placebo patients, and this was independent of improvements in mood (concerning manic or depressive symptomatology). The secondary analysis of this study showed that in the 25 bipolar patients with marijuana abuse and alcohol abuse, valproate resulted in less alcohol consumption compared to the dual-diagnosed patients not consuming marijuana (Salloum et al., Addict Behav 2005).

To date there are only few small, open-label studies investigating atypical antipsychotics in bipolar patients with substance abuse: these drugs may be associated with a reduction in substance use and craving as well as an improvement in psychiatric symptoms (Brown at al., Bipolar Disord 2002; Brown et al., J Clin Pharmacol 2003; Brown et al., J Clin Pharmacol 2005). A preliminary open study with lamotrigine suggests that it may also be a promising drug in cocaine-dependent patients (Brown et al., J Affect Disord 2006).

**Psychotherapy must address both disorders**

An integrated psychotherapeutic approach to the treatment of co-occurring bipolar disorder and substance-use disorder is appropriate (Mueser et al., Behav Modif 2003).

Comprehensive counselling and treatment includes case management, vocational rehabilitation services, family counselling, housing, and medication, incorporating motivational strategies.

**Conclusions of the authors:** Three randomised, double-blind, placebo-controlled clinical trials in dual-diagnosed patients showed that carbamazepine (e.g. Timonil®, Trimonil®), lithium and valproate (e.g. Orfiril®, Orfiril® long) are effective. Future randomised, double-blind, controlled trials will show whether similar conclusions can be drawn with atypical antipsychotics in dual-diagnosed patients.

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**NICE clinical guideline: Bipolar disorder**

**The management of bipolar disorder in adults, children and adolescents, in primary and secondary care**

**NICE clinical guideline 38; www.nice.org.uk/CG038**

The National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Mental Health launched in July 2006 a clinical guideline on the identification, treatment and management of bipolar disorder in children and adults. This new guideline calls for more action to ensure that bipolar disorder is correctly identified by health professionals and sets out the criteria, when a patient should be referred to a specialist psychiatric assessment and treatment.

**The NICE clinical guideline on bipolar disorder covers:**

> what treatment people with bipolar disorder can expect to be offered, including medication and psychological therapies with key priorities for implementation,
> advice on self-help,
> the services that may help people with bipolar disorder, including psychiatric or specialist mental health services, and
> how families and carers may be able to support people with bipolar disorder, and get support for themselves.

A quick reference guide for this bipolar disorder guideline contains treatment algorithms like the one for managing episodes of mania and hypomania (fig. 1, page 2) and comprehensive lists for drug treatment, e.g. long-term management of bipolar disorder:

Valproate (e.g. Orfiril®, Orfiril® long), lithium or olanzapine should be considered for long-term treatment of bipolar disorder. The choice should depend on:

> response to previous treatments
> the relative risk, and known precipitants, of manic versus depressive relapse
> physical risk factors, particularly renal disease, obesity and diabetes
> the patient’s preference and history of adherence
> gender
> a brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people.

Additionally schedules for monitoring physical parameters like blood tests, blood pressure and ECG as well as monitoring for specific drugs be-
Managing episodes of mania and hypomania

**Stop antidepressant (if taking) – abruptly or gradually, depending on clinical need and risk of discontinuation/withdrawal symptoms**

**Is patient already taking antimanic medication?**

- No
- Yes

**If taking an antipsychotic, check the dose and increase if necessary. If the response is inadequate, consider adding lithium or valproate**

**If taking lithium, check plasma levels:**

- if below 0.8 mmol/l, increase dose to a maximum blood level of 1.0 mmol/l
- if the response is not adequate, consider adding an antipsychotic

**If taking valproate, increase the dose until:**

- symptoms start to improve, or
- side effects limit dose increases

- If there is no improvement, consider adding olanzapine, quetiapine, or risperidone. Monitor carefully if the valproate dose is higher than 45 mg per kilogram.

- If taking lithium or valproate and mania is severe, consider adding an antipsychotic while gradually increasing the dose of the original drug.

- If taking carbamazepine, do not routinely increase the dose. Consider adding an antipsychotic. Drug interactions are common with carbamazepine – adjust doses as needed

**Advises all patients on:**

- avoiding excessive stimulation
- calming activities
- delaying important decisions
- a structured routine with a lower activity level

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**New Studies**

**Adjunctive lamotrigine treatment for adolescents with bipolar disorder: a retrospective report on five cases**

Soutullo C. A. et al., J Child and Adolescent Psychopharmacol; vol. 16, 3: 357-364

**Design:** Open, non-controlled retrospective case reports

**Objective:** To evaluate the effectiveness, safety, and tolerability of adjunctive lamotrigine in the treatment of adolescents with bipolar disorder

**Patients:** 5 patients aged 14-17 years, diagnosed with bipolar I and II, and not otherwise specified (NOS) bipolar disorder, who were treated with lamotrigine... adolescent outpatient clinic of the Department of Psychiatry and Medical Psychology, University of Navarre, Pamplona, Spain.

**Results:** All patients had a depressive episode at baseline and were treated with 100 ± 87.5 lamotrigine mg/day as an adjunct to a mood stabilizer and an antipsychotic for a mean of 28 ± 28 weeks; the Clinical Global Impression-Severity scale (CGI-S) improved from 5 at baseline to 3 ± 1 at end of study (p=0.011). Improvement was marked to moderate in 4 patients and minimal in 1 patient; 1 patient reported dizziness as an adverse event.

**Conclusions:** The present retrospective case reports suggest that lamotrigine (e.g. Plexxo®) may be effective and well tolerated as an adjunctive treatment in adolescents with bipolar disorder. In adult patients with bipolar disorder, lamotrigine can act as a mood stabilizer since it is effective in the prevention of mood episodes, especially depressive episodes. Several studies have been conducted in adult bipolar patients, but only one study has been published, which investigated lamotrigine as monotherapy in adolescents or are planning a pregnancy, and another chapter the special consideration on children and adolescents.

The full text guideline, quick reference guide and slides with the key messages can be downloaded from the internet www.nice.org.uk/CG038
During this trial the Clinical Global Impression (CGI) improved in 8 out of 9 adolescents with lamotrigine treatment. Lamotrigine can interact with other psychotropic medications used as mood stabilizers, e.g. adding lamotrigine to an existing valproate therapy leads to a decrease of valproate serum concentrations and results in lamotrigine serum levels above the therapeutic range. Carbamazepine and other cytochrome-P450 inducers may induce the metabolism of lamotrigine, with a higher risk of dizziness and double blurred vision for the patient.

To evaluate the effectiveness, safety, and tolerability of adjunctive lamotrigine in the treatment of adolescents with bipolar disorder, Soutullo and his colleagues included all patients under the age of 18 with bipolar disorder according to DSM-IV treated at the University of Navarre with lamotrigine and retrospectively evaluated the response based on the CGI-S. They identified one male and four female adolescents: one had bipolar I disorder, one had bipolar II disorder, and three had bipolar disorder NOS. All patients had a depressive episode at baseline and affective symptoms, which impaired their functioning. When lamotrigine was added, the patients were already on treatment with mood stabilizers (lithium, carbamazepine and/or valproate) and antipsychotics. The dose of lamotrigine was titrated over several weeks from 25 mg/day up to a maintenance dose of 200 mg/day, depending on the concurrent medication and clinical outcome. The mean dose of lamotrigine was 100 ± 87.5 mg/day (range 75-200 mg/day), and the mean duration of treatment was 28 ± 28 weeks (range 8-56 weeks).

With adjunctive lamotrigine, the CGI-S improved from 5 (minimally worse) at baseline to 3 ± 1 (minimally improved) at endpoint (p=0.011). The improvement was marked in three patients, moderate in one patient, and minimal in one patient. Lamotrigine was well tolerated. Only one patient reported dizziness; no other adverse events occurred.

Conclusions of the authors: Despite the limitations of these retrospective data, the study showed that the patients responded to lamotrigine (e.g. Plexxo®) after being non-responders to adequate therapy with a mood stabilizer and an antipsychotic drug alone. Controlled trials are needed to evaluate the efficacy, safety and tolerability of lamotrigine in adolescent patients with bipolar disorder.

New Studies

Metabolic syndrome in bipolar disorder: findings from the bipolar disorder centre for Pennsylvanians

Fagiolini A. et al., Bipolar Disorders 2005; 7: 424-430

Design: Cross-sectional study
Objective: To evaluate the presence of metabolic syndrome and each of its criteria in a group of bipolar patients consecutively recruited into the study
Patients: 171 adult patients aged ≥ 18 years with bipolar I, bipolar II, and bipolar not otherwise specified (NOS), entering the multicentre randomized controlled Bipolar Disorder Centre for Pennsylvanians study
Results: 30% of the patients met the NCEP criterion (see below) for metabolic syndrome, 49% for abdominal obesity, 41% for hypertriglyceridaemia, 48% for hyperglycaemia, 48% for hypertriglyceridaemia taking a cholesterol lowering medication, 23% for LDL-cholesterol, 39% for hypertension, and 8% for high fasting glucose or antidiabetic medication. Patients with metabolic syndrome and patients, who met the obesity criterion or were evidently obese, were more likely to report a lifetime history of a suicide attempt or attempts.

Conclusions: The prevalence of the metabolic syndrome in patients with bipolar disorder is as alarmingly high as in the general population in the USA, and the prevalence of obesity is even higher. These findings are of great concern considering the difficulty of implementing programmes to prevent and treat metabolic syndrome in bipolar patients.

Some studies have evaluated the prevalence of obesity, diabetes, dyslipidaemia and hypertension alone in patients with bipolar disorder. But, to date, no study has investigated the clustering of these risk factors for cardiovascular disease, described as metabolic syndrome.

The present study analysed the findings in 171 bipolar patients for the prevalence of the metabolic syndrome, as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (NCEP ATP III). This panel suggested that people have metabolic syndrome if three or more of the following characteristics exist: abdominal obesity (waist circumference), hypertriglyceridaemia, low HDL-C, high blood pressure, and fasting hyperglycaemia.

The ongoing Bipolar Disorder Centre for Pennsylvanians study is comparing the clinical outcome in subjects who receive enhanced clinical intervention (ECI) with the outcome of subjects who do not receive ECI, both groups on drug regimens. For this analysis, the diagnostic and demographic data and baseline measurements of blood pressure, anthropometrics and body fat distribution of 171 patients recruited from November 2003 to August 2004 were analysed regarding the prevalence of metabolic syndrome and each of its criteria. 44% of the patients were taking lithium, 34% atypical antipsychotics, 9% valproate, 20% lamotrigine, and 54% antidepressants. Overall, 74% of the patients were either obese (45%) or overweight (29%). 45% of the study patients were obese at baseline compared to 30.5% in the general population in the USA based on body mass index, and 49% compared to 44%, based on waist measurements. 30% of the patients met the NCEP ATP III criterion for metabolic syndrome. And the analysis revealed a correlation between the metabolic syndrome in general, and obesity in particular, and a history of suicide attempts.

Due to the cross-sectional design of this study, Fagiolini and her colleagues were unable to determine whether the suicide attempts preceded or followed the development of metabolic syndrome. Nor could the researchers evaluate a relationship between the use of specific medication and the metabolic syndrome or obesity. But medication alone does not influence the weight. The disease-specific symptoms of bi-
Oxcarbazepine is effective in treating acute mania and can be used as an adjunctive treatment for refractory bipolar disorder. Oxcarbazepine has fewer drug interactions and better pharmacology with fewer interactions compared to its active metabolite monohydroxy derivative (MHD). It is generally well tolerated, but carbamazepine has significant side effects and induces enzymes of the cytochrome-P450 system, resulting in numerous drug interactions. Oxcarbazepine is an anticonvulsant compound with a slightly different chemical structure from carbamazepine.

Several causes of cognitive deficits have been reported during manic, depressive and euthymic episodes of bipolar disorder. Amongst these are the side effects of the pharmacological intervention. The cognitive side effects of anticonvulsants are generally mild. The impact of lamotrigine on cognitive function has mostly been studied in epilepsy patients and healthy control subjects. Cognitive testing showed a significantly better outcome for patients on lamotrigine concerning verbal fluency (p<0.008), and a trend towards an improvement in verbal memory (p<0.052).

The authors propose two different explanations for the difference. One is that this study confirmed the favourable cognitive profile of lamotrigine. Some studies have even suggested that lamotrigine has neuroprotective effects. However, they also felt that the difference may not only be due to either lamotrigine, valproate or carbamazepine, as the latter two also do not induce major cognitive deficits. Other variables such as type of bipolar disorder, number of manic, depressive and mixed episodes could explain the difference. Larger studies are needed to further investigate these preliminary observations.

**New Studies**

**Cognitive functioning in bipolar patients receiving lamotrigine**

Daban C. et al., J Clin Psychopharmacol 2006; 26: 178-181

**Design:** Open-label, non-randomized pilot study

**Objective:** to determine the effect of lamotrigine on attention, verbal learning, memory and executive functions on euthymic bipolar I and II patients receiving lamotrigine for at least 6 months and compare it with the cognitive functioning of patients receiving other anticonvulsants.

**Patients:** n=33 patients with bipolar I and II disorder, recruited from the Bipolar Disorder Programme of the University Hospital Clinic of Barcelona/Spain. 15 patients received lamotrigine and the other 18 patients received carbamazepine or valproate.

**Results:** Patients treated with lamotrigine were generally diagnosed with bipolar II and had experienced more depressive episodes, but fewer episodes of hospitalization, and had better verbal fluency compared to the patients on the other anticonvulsants.

**Conclusions:** These preliminary results suggest that lamotrigine (e.g. Plexx®) may improve, or at least does not impair, verbal fluency and immediate memory.

Several causes of cognitive deficits have been reported during manic, depressive and euthymic episodes of bipolar disorder. Amongst these are the side effects of the pharmacological intervention. The cognitive side effects of anticonvulsants are generally mild. The impact of lamotrigine on cognitive function has mostly been studied in epilepsy patients and healthy control subjects. No cognitive performance deficits are observed with this drug in healthy volunteers. One small study showed that depressed patients with bipolar I disorder had improved sustained attention, verbal fluency, and concentration.

Daban and her colleagues investigated the development and testing of interventions specifically designed to prevent and treat the metabolic syndrome in patients with bipolar disorder.
Effects on ability to drive and use machines: a rule it is not necessary to avoid or stop breast-feeding. Should generally be treated with 20–30 mg sodium valproate/kg body weight/day. If seizure control cannot be achieved, the dose can be increased up to 40 mg/kg/day.

Indications:
Sodium valproate. Prescription only.

Dosages and administration:

Posology and method of administration.
Interactions with other medicaments and other forms of interaction:
Mefloquine and enzyme-inducing antiepileptics such as carbamazepine and oxcarbazepine may lead to increased plasma levels of these drugs. The use of anticonvulsants should be carefully controlled and monitored. Other central nervous system depressants should be given with care.

Undesirable effects:
- occasional or rare, dose-related side effects, such as somnolence, dizziness, depression, memory disturbances, ataxia, nausea, vomiting, abdominal cramps, diarrhoea, coughing, tiredness, abnormal dreams, nightmares, aggressiveness, agitation, tremor, skin rash, etc., or rarely, encephalopathy of unknown pathogenesis
- occasionally, dose-related increases or decreases in weight, increased or reduced appetite, drowsiness, transient hair loss, tremor, thrombocytopenia, leucopenia, paraesthesias or amenorrhoea
- rare hypersalivation, diarrhea, hallucinations

Special precautions for storage:

Pregnancy and lactation:
- hypersensitivity to sodium valproate or other constituents of the drug (see excipients),
- previous or present liver disease and/or severe current dysfunction of the liver or pancreas,
- a history of a sibling having died from liver dysfunction during valproic acid treatment of other forms of seizures,
- acute mania.

Contraindications:
- generalised seizures in the form of absences, myoclonic and tonic-clonic seizures,
- partial and secondary generalised seizures, combination treatment with sodium valproate and lamotrigine,
- previous or present liver disease and/or severe current dysfunction of the liver or pancreas,
- a history of a sibling having died from liver dysfunction during valproic acid treatment of other forms of seizures,
- acute mania.

In an on-off-on design, one open-label trial investigated the efficacy of oxcarbazepine in 12 patients with mild to moderate mania (Hummel et al., Bipolar Disord 2002). The patients received oxcarbazepine for 14 days followed by 7 days with no drug, and then a further 14 days on drug. Titratin in the first week resulted in a final range of 900–2100 mg oxcarbazepine per day. One third of the patients responded to therapy, defined as a 50% reduction in the Young Mania Rating Scale (YMRS) score. A single-blind, active-comparator trial assessed the efficacy and safety of oxcarbazepine and valproate (Reinstein et al., Clin Drug Investigation 2003). The trial included 57 patients with manic or schizoaffective bipolar disorder and suggested that oxcarbazepine and valproate have similar effects in the treatment of mania. Similar results were first seen in an earlier study with 11 acutely ill patients with affective and schizoaffective disorder (Emrich et al., Pharmaco Biochem Behav 1983; Emrich et al., J Affect Disord 1985).

Effective in treatment of acute mania: double-blind studies

Two double-blind studies compared the efficacy of oxcarbazepine and haloperidol. In the first trial, 20 patients with acute mania received 900–1200 mg oxcarbazepine daily or 15–20 mg haloperidol daily for two weeks (Muller et al., Excerpta Medica 1984). The mean Bech and Rafelson Mania Rating Scale (BRMRS) scores decreased from 20 to 8, with a slightly faster onset with oxcarbazepine. In the second comparative double-blind trial, 38 patients with acute mania received a mean dosage of 2400 mg oxcarbazepine per day or 42 mg haloperidol per day (Emrich et al., Int Clin Psychopharmacol 1990). Oxcarbazepine was as effective as haloperidol based on the reduction of the BRMRS score, but the incidence of side effects was 3.5 times higher in the haloperidol group. A similar approach was used in a third double-blind trial in which oxcarbazepine was compared to lithium in 52 patients with acute mania (mean daily dosage 1400 mg and 1100 mg respectively). Both treatments showed similar improvements (Emrich et al., Int Clin Psychopharmacol 1990).

Generally well tolerated
Oxcarbazepine and its metabolite
MHD have fewer side effects than carbamazepine. Side effects of oxcarbazepine in psychiatric patients were usually transient, occurred mostly at the beginning of treatment, and consisted mainly of sedation, vertigo, tremor, nausea, vomiting, constipation, fatigue and hyponatraemia. It had minimal effects on cognitive function and none on the haematological system (Curran & Java, Eur J Clin Pharmacol 1993). In the comparator trial versus haloperidol, 10% of the patients taking oxcarbazepine and 35% taking haloperidol reported side effects; in the trial versus lithium, the rates were 28% and 19% respectively. Rash occurred in 3-10% of patients taking oxcarbazepine. Hyponatraemia generally remained asymptomatic, but elderly patients and patients taking diuretics have a higher risk of developing hyponatraemia. Effects on body weight were inconsistent.

Conclusions of the authors: Oxcarbazepine (e.g. Apydan®) is recommended as monotherapy or as an add-on therapy in refractory mania. In other phases of bipolar disorder, oxcarbazepine should be preferred as add-on treatment in patients who have not improved on well-established treatments or in patients who cannot tolerate adequate dosing of these treatments.

New data on the use of lithium, divalproate, and lamotrigine in rapid cycling disorder

Calabrese J. R. et al., European Psychiatry 2005; 20: 92-95

According to DSM-IV, rapid cycling is defined as the occurrence of four or more either manic or depressive episodes within 12 months. The prevalence of rapid cycling in bipolar I disorder is estimated to be 4%, and in bipolar II disorder 31% (Calabrese et al., Bipolar Disorder 2000). Treatment still has to be optimised for patients with this subtype. In general, the response to lithium is poor. The findings of a preliminary open-label trial in which 55 rapid cyclers received valproate as monotherapy or in combination suggest that valproate has marked antimanic and mixed state efficacy, but only minimal to moderate antidepressant efficacy (Calabrese et al., Am J Psychiatry 1990). To increase awareness of this problem, the authors discuss two double-blind studies which investigated lithium compared to valproate and lamotrigine compared to placebo in patients with rapid cycling.

The first study was a randomized, double-blind, parallel-group comparison of valproate and lithium (Calabrese et al., Am J Psychiatry 2005). Altogether 254 bipolar patients with rapid cycling first received a combination of valproate and lithium for a six-month stabilization phase. 60 patients with stable disease then entered a 20-month randomized, double-blind maintenance phase receiving either lithium or valproate as monotherapy. The rate of relapse into a mood episode was 56% with lithium and 51% with valproate, and the number of relapses into mania or a mixed episode was 22% for each. 16% of the patients discontinued lithium and 4% valproate prematurely. The median time to initiation of additional pharmacotherapy to treat emerging symptoms was 18 weeks on lithium and 45 weeks on valproate (fig. 3) and the median time to dropping out of the study was 26 and 14 weeks respectively (fig. 4). Significantly more patients on lithium than on valproate experienced tremor (28 versus 45%; p=0.001), polyuria and polydipsia (22 versus 0%; p=0.009).

In the second randomized, double-blind study, while their current psychotropic medication therapy was tapered, 324 bipolar patients with rapid cycling first received increasing doses of lamotrigine for 12 weeks until a clinical effect was observed (Calabrese et al., J Clin Psychiatry 2000). 182 patients stabilized and they were randomized to receive lamotrigine or placebo for 6 months. In bipolar I patients, the time before additional medication was started and the time to dropping out of the study was only marginally different. There were distinct differences in bipolar II patients, however: they started additional pharmacotherapy after 17 weeks on lamotrigine and 7 weeks on placebo (fig. 5), and it took longer before patients in the lamotrigine group dropped out compared to placebo. Lamotrigine was well tolerated. During the stabilization phase, 11% of the patients experienced intolerable side effects.

Conclusions of the authors: Valproate (e.g. Orfiri®, Orfiri® long) and lithium are effective in the long-term treatment of rapid cycling, but valproate should be preferred because of its favourable safety profile. Both drugs are well tolerated when combined. Lamotrigine (e.g. Plexxo®) can be useful due to its antidepressant effects in some bipolar patients with rapid cycling and can therefore extend the treatment spectrum of valproate and lithium in patients with more marked depressive than manic symptoms. Combination therapy is emerging as the most viable option for the treatment of rapid cycling.