

Conference Report

Brief notes from the APA

In May 2006, more than 20,000 participants met for the annual meeting of the American Psychiatric Association (APA) in Toronto, Canada, to discuss the latest outcomes of research and to benefit from the wide-ranging further education programme. The following summarises just a few of the numerous symposia, lectures, workshops and poster sessions about bipolar disorder.

Compliance in bipolar patients

Adherence to medication – and above all to long-term prophylaxis – is crucial in bipolar disorder: remission or recovery is almost impossible if patients are not compliant or only partially compliant. Meera Narasimhan, Columbia, US, and her colleagues did a retrospective analysis of 2,400 patient with psychiatric disorder from the South Carolina Medicaid Database, and examined their course over a 2-year period from 2002-2004 (Abstract NR561). 1057 patients had a diagnosis of bipolar disorder and received mood stabilisers, antipsychotics and antidepressants. The mean age was 42 years; the average number of months on therapy and the average time from diagnosis to starting treatment was 13 months in each case. A large proportion of the patients had no prescription of any medication and among those on therapy, 58% were fully, 20% partially, and 22% non compliant. A significant association was found between compli-

ance rate and start of treatment: patients were more likely to be compliant if treatment with a mood stabiliser or antipsychotic medication was started at the time of diagnosis.

Jane Clatworthy and her colleagues from the University of Brighton, UK, examined the perceptual and practical barriers that hinder bipolar patients in adhering to their medication (Abstract 50). 16 adults on prophylactic treatment for bipolar disorder completed a semi-structured interview with two independent researchers: 81% of the patients reported non-adherence, either currently or in the past, i.e. they took less or more medication than prescribed, and they experimented with combinations and dosages. Non-acceptance of the diagnosis, believing that it is an acute or uncontrollable illness, and great concerns about treatment were associated with intentional non-compliance, whereas forgetting, or being confused, if already taking the drug, was associated with unintentional non-compliance.

The importance of patient perception in adherence was investigated by Richard Horne and his colleagues, also from the University of Brighton,



UK (Abstract 129). A detailed postal questionnaire, including validated measures of beliefs about treatment, adherence to medication and demographic and clinical variables was completed by 223 members of the Manic Depression Fellowship. Non-adherence was associated with higher concerns about treatment and lower perceived personal need for treatment. Based on the questionnaire, the Group of Richard Bowskill from Brighton found that more than 50% of the 223 patients reported not having received enough information on how the medication works and for how long they would have to take it (Abstract 51). More than 60% were dissatisfied about the information given on side effects and this discontentment had a clear negative impact on compliance.

Elderly bipolar patients

Helen Kyomen from the Harvard Medical School in Belmont/USA reminded the audience that bipolar disorder accounts for 5 to 9% of mood disorders that are identified in treatment centres for the elderly (Abstract 11a). These numbers are only a rough estimate, as elderly people tend to avoid mental health care, underreport psychiatric symptoms, and are cared for in nursing homes or other assisted

living facilities. The number of Americans over 65 years with psychiatric illness is increasing and a total of 15 million is projected for 2030 – in 1970 it was 4 million and is currently 7 million. The reasons are the changing demographics and increasing awareness of psychiatric problems in the elderly. This growing number will have an impact on the health care system, especially with regard to increasing limitation of resources.

Aging in bipolar disorder may be associated with a greater risk of hospitalisation and greater use of mental health services, as Sarah Pratt, Concord, USA, outlined (Abstract 11b).

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Overview

Anticonvulsants in Bipolar Disorder

Valproate, lamotrigine and carbamazepine have a valuable place in the management of bipolar disorder – this was confirmed again by the latest literature review about anticonvulsants in bipolar disorder, published by Charles Bowden and Nancy Karren (Australian and New Zealand Journal of Psychiatry 2006).

The first findings to indicate that valproate (Lambert et al., *Ann Med Psychology* 1966) and carbamazepine (Okuma, *Neuropsychobiology* 1969) might be useful in bipolar disorder were published in the mid-60s. All anticonvulsant mood stabilizers, which were first approved for the treatment of epilepsy, are different molecules, and have different pharmacodynamics, and therefore also different profiles in bipolar disorder. The behavioural disturbances characteristic of bipolar disorder comprise not only mania and depression, but also depressive cognition, motor retardation, mental anxiety, somatic distress, hyperactivity, impulsiveness, irritability, manic cognitions of elation and grandiosity, and psychoses. These behavioural targets all respond differently to the different mood stabilizers.

Valproate

Valproate has demonstrated prompt and robust efficacy in most open trials, but more importantly, in randomised trials. Based on two placebo-controlled studies in which valproate was superior to placebo (Bowden et al., *Depression and Anxiety* 1997), it was approved for treatment of mania in 1995. Valproate has a more rapid onset of action than lithium and carbamazepine (Bowden et al., *JAMA* 1994; Vasudev et al., *Psychopharmacol* 2000) and a similar onset to atypical antipsychotics (Keck et al., *J Clin Psychiatry* 1993). Improvement with valproate is seen within the first week of treatment, and even faster if a loading dose or intravenous formulation is used (Hirschfeld et al., *J Clin Psychiatry* 1999; Grunze et al., *J Clin Psychopharmacol* 1999). If patients remain symptomatic under valproate monotherapy, an antipsychotic can be added: an effective and better strategy than starting with two drugs from the beginning (Sachs et al., *Am J Psychiatry* 2002). Controlling the manic symptoms also has a positive impact on depressive symptoms, but valproate has no major clinical benefit in

acute depression (Bowden et al., *Arch General Psychiatry* 2000; Winsberg *J Affect Disord* 2001).

Maintenance therapy with valproate was compared to that with lithium and placebo in a large randomised trial (Bowden et al., *Arch General Psychiatry* 2000): The primary outcome measure – time to any mood episode – showed a trend in favour of valproate, and it was significantly superior to placebo with regard to rates of discontinuation, and efficacy with valproate was similar or significantly better than lithium with regard to intolerance, overall effectiveness, and time to develop depression. More valproate patients than placebo or lithium patients completed the acute phase of this study (41%, 12% and 24%). A further randomised, blinded study showed that valproate and olanzapine have similar efficacy, and that when patients respond early, i.e. show remission within the first 3 weeks, they had a higher chance of completing the study (Tohen et al., *Am J Psychiatry* 2003).

Useful predictors of good and even a better response to monotherapy with

valproate compared to monotherapy with lithium are mixed mania, history of a poor response to lithium, and more than two prior depressive episodes (Bowden, *J Clin Psychiatry* 1995; Freeman et al., *Am J Psychiatry* 1992; Dil-saver et al., *J Psychiatry & Neuroscience* 1993; Swann et al., *Arch General Psychiatry* 1997). Manic patients with prominent irritability respond better to valproate than lithium and carbamazepine (Swann et al., *Neuropsychopharm* 2002; Vasudev et al., *Psychopharm* 2000).

Valproate is generally well tolerated, particularly in lack of emotional impairment, physical dulling or cognitive impairment, but weight gain is more common at serum levels above 100 µg/mL (Bowden et al., *Gen Psychiatry* 2000). Studies have indicated that there is a risk of women developing polycystic ovary syndrome and that avoidance of overweight may protect against this (Rasgon et al., *J Clin Psychiatry* 2000; Bauer et al., *Epilepsy Research* 2000) (see section “new studies” in this newsletter). As valproate acts beneficially

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Conference Report

Brief notes from the APA



Skyline from Toronto

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But there are little data about the psychosocial treatment of bipolar disorder in elderly patients. A current randomised controlled trial is now investigating the improvement of psychological functioning among elderly patients with combined skills training and health care management intervention. Half of 183 mental health centre outpatients of 50 years and older are receiving randomly assigned skills training and assistance with health care from a nurse for 2 years, or no training and assistance. To enhance the outcome (cognition, psychosocial functioning and general health), and hereby to reduce the risk of nursing home placement, the most promising approach is to focus on enhancing social support and functioning, and facilitate health care for co-morbid medical illness.

Juvenile bipolar disorder

The subtype "juvenile bipolar disorder" (JBD) has recently been subject to research. Perugi and co-workers from Pisa, Italy conducted a study in 136 patients with a mean age of 13.5 years to establish whether the most useful subtyping should be based on clinical features (elated vs. irritable) or disease course (episodic vs. chronic) (Abstract 52). They used the structured clinical interview tool, K-SADS-PL. 56.6% of the patients had an episodic and 43.4% a chronic course: Those with the chronic course were significantly younger, had an earlier onset of JBD, and presented with higher comorbidity with disruptive behaviour disorder. 55.1% showed elated mood, which was more frequent in patients

with an episodic course, and 44.9% had an irritable mood and more frequent mood swings in the chronic course. The authors concluded that the distinction between episodic and chronic may be a putative differential feature in JBD.

Bipolar disorder and the legal system

Individuals with bipolar disorder are at an increased risk of criminal arrest, as David Quanbeck, Sacramento/USA, observed (Abstract 45B). This increased risk is mainly caused by the combination of manic symptoms and substance misuse, as these illness factors together impair impulse control and can lead to aggressive behaviour. To decrease the risk of arrest, psychiatrists should screen patients with bipolar disorder for substance misuse.

An epidemiological survey in the USA identified 181 people with a lifetime bipolar disorder with a forensic history (F+) and 1,228 people with a lifetime bipolar disorder without forensic history (F-). The data were presented by Benjamin Goldstein, Toronto, Canada (Abstract 45C). F+ individuals were significantly more likely to have alcohol, drug and antisocial personality disorders and a history of suicide attempts compared to F- individuals. F+ individuals had an earlier onset of bipolar disorder (22.1 vs. 26.4 years). In males, alcohol abuse and antisocial disorder were more common, and in females, a higher prevalence of mixed mania and suicide attempts. As less than half of the male F+ individuals seek health care, the bipolar disorder may often be unrecognised in this population. ■

Interview

Psychiatric concomitant disorders in epilepsy patients

A few timely words on an orphan subject in epileptology.

Epilepsy patients have a high comorbidity with mental and psychiatric disorders, especially depression and anxiety are amongst the most frequent concomitant disorders diagnosed in epilepsy patients. This was a topic that was long ignored and regarded as a taboo by the medical world in this area, but over the past few years, an awareness has grown that mental disturbances occur very much more frequently in epilepsy patients than in the general population and that these can considerably impair the quality of life of those affected. Science and research are very much at the beginning in this area. There are many different reasons why epilepsy patients suffer from concomitant psychiatric disorders. Intensive interdisciplinary collaboration, especially between psychiatrists and neurologists, is necessary if these patients

are to be offered adequate treatment.

An important step in this direction was taken at a satellite symposium organised by Desitin Pharmaceuticals, at the 46th Meeting of the German Chapter of the International League Against Epilepsy (ILEA) entitled 'Epilepsy and Psychiatric Comorbidity'. Experts from the areas of neurology, epileptology and psychiatry met in Strasbourg in May 2006 to discuss this topic. Prof. Bettina Schmitz, senior registrar and head of the Epilepsy Clinic, Department of Neurology at the Charité University Hospital, Campus Virchow Clinic, Berlin, Germany, was interviewed after her lecture at the symposium on 'Epilepsy and Psychiatric Comorbidity - an Overview' by 'Think Bipolar' about concomitant mental disorders in epilepsy patients.

Think Bipolar: Professor Schmitz, you were chair for the satellite symposium organised by Desitin Pharmaceuticals, at the ILEA Meeting this year entitled 'Epilepsy and Psychiatric Comorbidity'. In your opinion, how important is it to open up and intensify the discussion on this subject?

Prof. Schmitz: I think that it is a subject that has been almost completely ignored for a long time by medical specialists, and has even been regarded as a taboo subject. It is only over the past few years that we have begun to realise just how frequently epilepsy patients also suffer from psychiatric disorders and how important it is for those concerned and their wellbeing that these disturbances are properly treated.

Think Bipolar: Your lecture at the symposium organised by Desitin gave the audience a brief overview of the topic 'Epilepsy and Psychiatric Comor-

idity'. How often do epilepsy patients suffer from concomitant psychiatric disorders?

Prof. Schmitz: The prevalence of psychiatric disorders is generally high in epileptic patients, both in children and adult epileptic patients. Mental disturbances occur about five to ten times more frequently in epilepsy patients than the population as a whole.

Think Bipolar: What are the most frequent concomitant psychiatric disorders in epilepsy patients and how can they best be diagnosed?

Prof. Schmitz: Affective disorders, especially depression and anxiety, are particularly common in epilepsy patients. The first thing that has to be borne in mind is that it is important to realise that the patients concerned not only have epileptic seizures, but may also have mental problems. As attending physicians, we have to learn



Professor Bettina Schmitz

how to 'interpret' the signals in the symptoms that patients tell us they have. In order to be able to make a psychopathological diagnosis, we have to have the task of examining the patient for possible mental problems and asking them about them. This all takes time and certainly means that we have

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Overview

Anticonvulsants in Bipolar Disorder

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on serum lipids by lowering LDL-cholesterol, total cholesterol and triglycerides, it counteracts the increases seen under atypical antipsychotics (Geda et al., Acta Neurologica Belgica 2002; Calandre et al., Acta Neurologica Scand 1991; Zajecka et al., J Clin Psychiatry 2002). In patients which can be sufficiently treated with daily doses of valproate at 1000 mg and serum levels below 50 µg/mL, the rate of adverse effects is in the placebo range (Freitag et al., Neurology 2002). On the other hand maintenance studies have indicated that the outcome with serum levels of valproate between 75 and 99 µg/mL is better than higher or lower valproate serum levels and is better than with lithium at any serum level (Keck et al., Int J Psychiatry in Clin Practice 2005).

Lamotrigine

Lamotrigine primarily ameliorates depression in bipolar disorder. Two placebo-controlled trials showed that in bipolar I depressed patients lamo-

trigine is superior to placebo (Calabrese et al., J Clin Psychiatry 1999; Frye et al., J Clin Psychopharmacology 2000). At least two 18-months double-blind, placebo-controlled studies have established the use of lamotrigine in bipolar depression (Bowden et al., Arch Gen Psychiatry 2003; Calabrese et al., J Clin Psychiatry 2003). Whilst a pooled analysis of these two studies showed that lithium was not superior to placebo (Goodwin et al., J Clin Psychiatry 2004). In blinded, placebo-controlled trials, lamotrigine was not effective in controlling acute manic symptoms, including one in which lithium was superior to placebo (Ascher et al., APA 2001).

Carbamazepine

Carbamazepine was approved in the USA for the treatment of mania, based on two parallel-group, placebo-controlled trials (Weisler et al., J Clin Psychiatry 2004 and 2005). The drug showed greater efficacy, but more adverse effects than valproate in a small trial (Vasudev et al., Psychopharmacology 2000) and carbamazepine was

generally inferior to lithium as maintenance therapy (Greil et al., J Affective Disorders 1997 and J Clin psychopharmacology 1998). Side effects of carbamazepine include diplopia, uncoordination, sedation, weight gain, benign rash (in one third of the patients), hypersensitivity syndrome including Stevens-Johnson syndrome (0.1-0.5%) and leucopenia (10.0-20.0%) (Ketter et al., J Clin Psychiatry 2004). Because carbamazepine induces the cytochrome 3A4 system, it increases the metabolism of many drugs and it should generally not be used in combination regimens.

Conclusion of the authors: Valproate is an effective drug for mania as monotherapy and in combination therapy, but has a limited effect on depression. The secondary analysis of the largest randomised maintenance study suggests a trend favouring valproate over lithium/placebo. Lamotrigine is effective in bipolar depression and maintenance therapy, but not in acute mania; carbamazepine brings benefit in mania. ■

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to give more attention to the patient. But I think that this extra effort is worth it for those concerned.

"The prevalence of psychiatric disorders is generally high in epileptic patients, both in children and adult epileptic patients. Mental disturbances occur about five to ten times more frequently in epilepsy patients than the population as a whole."

Think Bipolar: What are the causes of these concomitant psychiatric disorders?

Prof. Schmitz: There are many different causes. First, the epileptic disorder itself, which leads to disorders of cerebral function, changes in transmitters, or metabolic disturbances, which can all be predisposing factors for mental disturbances. But antiepileptic medications can also induce psychiatric disorders, because they can intervene in the brain metabolism, for example, and can affect the state of mind. And the stressful situation of the epileptic as a member of society should also not be forgotten, as this may also lead to psychoreactive disturbances. Many patients suffer from a combination of risk factors.

Think Bipolar: Is there a pathogenetic or aetiological link between epilepsy and depression?

Prof. Schmitz: Depression is the most frequent mental disorder diagnosed in epilepsy patients, and certain types of epilepsy are associated with depression particularly often. In particular, these are epileptic disorders where the epileptogenic focus is in the limbic system. There are therefore evidently certain epilepsy syndromes that can result in disturb-

ances which also affect the emotional balance. An imbalance in this area is therefore possibly the cause for depression in these epilepsy patients. So it is therefore conceivable that there is a pathogenetic relationship between epilepsy and depression in some cases.

Think Bipolar: What may be the further reasons why an epilepsy patient might develop depression?

Prof. Schmitz: Different factors play a role here. On the one hand, there is the organic predisposition that can lead to a depressive disorder. On the other, there is antiepileptic drug therapy which may cause depression, since some antiepileptics have depressive side effects, especially substances that exert their effects via GABAergic mechanisms. But it can also be caused by the course of the epileptic disorder itself, for example, if a patient loses their job because of the epilepsy, and this is compounded by further social restrictions. This may all lead to severe depression. And this is why it is important to look very carefully for the causes in every case, sometimes even using 'detective-like' qualities.

Think Bipolar: What do you think are the reasons why not enough attention is often paid by clinicians to the possibility of depression in epilepsy patients, and is therefore not properly treated?

Prof. Schmitz: One important reason is definitely that epileptic patients often just simply do not admit to being depressed. They often do not say that they have psychiatric problems, because it is unpleasant for them to talk about having a further mental disorder in addition to the epilepsy. Many doctors also assume that it is 'normal' for

an epileptic patient to be depressed. They often do not consider that depression in an epileptic patient is definitely a condition that requires treatment. A further important reason is the reluctance of many neurologists to use antidepressants in epilepsy patients.

Think Bipolar: Is there any scientific evidence that epilepsy patients have a higher suicide risk?

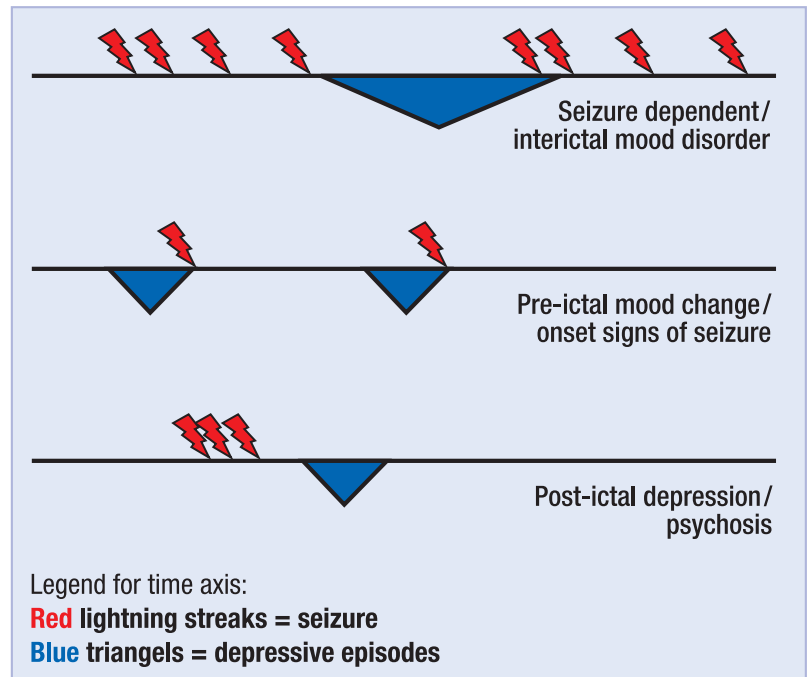
Prof. Schmitz: Suicides account for the high proportion of about 10% of total mortality in epilepsy patients, and occur not only in adults, but also in children. Epilepsy sufferers have a markedly increased risk of committing suicide. In most patients who commit suicide, the event was preceded by a depressive episode – the sort of episode that is usually accessible to treatment – so that the suicide or attempted suicide might well have been avoided.

"Depending on the type of concomitant psychiatric disorder in the respective patient, an antiepileptic medication should be chosen that, as far as possible, will not exacerbate the existing disorder, and, for example, even exert an antidepressant effect."

Think Bipolar: There is a clinical difference between ictal and interictal depression. What is the difference between these two?

Prof. Schmitz: Interictal depression is characterized by the occurrence of mood swings that are unconnected to the frequency of seizures or type of seizures. Ictal, peri-ictal and post-ictal depressions are temporary disorders that occur with a clear relationship to epileptic seizures (see Figure 1). For example, after an epilep-

Figure 1: Forms of affective co-morbidity in epilepsy. Where does the seizure begin, and where does it end? (according to Schmitz)



tic seizure, a patient may drop into a brief, very severe depressed mood that suddenly starts immediately together with the seizure and ends just as abruptly. Especially in these severe depressed phases, the risk of suicide in such patients is particularly high.

Think Bipolar: How can the incidence of concomitant psychiatric disorders in epilepsy patients be reduced?

Prof. Schmitz: Optimal treatment of the epileptic disorder is the primary objective in order to keep the risk of concomitant psychiatric disorders as low as possible. This means diagnosing it as early as possible and choosing the best treatment. It is important to achieve seizure freedom as soon as possible, so that those concerned do not feel medically or socially impaired

by the epilepsy. In addition to this, we have the possibility of exploiting the psychotropic properties of antiepileptics. Depending on the type of concomitant psychiatric disorder in the respective patient, an antiepileptic medication should be chosen that, as far as possible, will not exacerbate the existing disorder, and, for example, even exert an antidepressant effect. Thanks to the wide spectrum of antiepileptic medications available today and to the fact that we now know that antiepileptic agents can also have psychotropic effects, it is possible to select the best treatment regimen from the psychiatric point of view to treat not only the epileptic disorder, but also any concomitant psychiatric disorder. Optimisation of the epileptic regimen can also therefore have a positive effect on psychiatric comorbidity.

Think Bipolar: Which are the most suitable antiepileptics to achieve this?

Prof. Schmitz: I don't think there is any 100% ideal antiepileptic agent equally well-suited to all patients, with which you can also generally avoid psychiatric disorders. This is why it is of the utmost importance to look for the best individual solution for each epileptic patient. There are a number of substances, such as carbamazepine (e.g. T(r)imonil®), valproate (e.g. Orfiril® long) or lamotrigine (e.g. Plexxo®), which have proved very useful in patients with primary psychiatric disorders and act as mood stabilisers, or even have an antidepressant effect. Their positive psychotropic properties have also been demonstrated in epilepsy patients. Other agents, and particularly GABAergic substances, should be used with caution or avoided in epileptic patients with concomitant psychiatric disorders. In aggressive patients, for example, levetiracetam should be used with caution, since aggressive behavioural disturbances have been observed with this substance in some cases. A further example is the antiepileptic phenytoin: it can cause psychoses depending on the dose, or aggravate them. A good knowledge of

Short Product Information Orfiril® long Please note that this information may differ from the local summary of product characteristics (SPC). Active constituent: sodium valproate. Prescription only.

Indications: Treatment of - generalised seizures in the form of absences, myoclonic and tonic-clonic seizures, - partial and secondary generalised seizures, combination treatment of other forms of seizures, - acute mania.

Contraindications: - hypersensitivity to sodium valproate or other constituents of the drug (see side effects), - previous or present liver disease and/or severe dysfunction of the liver or pancreas, - a history of a sibling having died from liver dysfunction during valproic acid treatment. Posology and method of administration. **Oral treatment:** In general, unless otherwise prescribed, the average daily dosage during long-term treatment is as follows: Children 30 mg sodium valproate/kg body weight / Adolescents 25 mg sodium valproate/kg body weight / Adults 20 mg sodium valproate/kg body weight. A 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 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 while monitoring the plasma level closely. **Interactions with other medications and other forms of interaction:** Mefloquine and enzyme-inducing antiepileptics such as phenobarbital, phenytoin and carbamazepine may increase valproic acid excretion. Valproate may rise the phenobarbital concentration and the free (non-protein-bound) phenytoin without increase of total phenytoin concentration. Valproic acid inhibits the metabolism of lamotrigine and felbamate. The plasma 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 ketone bodies, the possibility of false-positive results for tests of ketone-body excretion should be borne in mind in diabetics with suspected ketoacidosis. **Pregnancy and lactation:** Sodium valproate crosses the placental barrier and concentrations in foetal plasma are higher to those in the mother. There is an increased risk of malformations. Valproic acid passes into breast milk. As a rule it is not necessary to avoid or stop breast-feeding. **Effects on ability to drive and use machines:** At the start of treatment with sodium valproate, at higher dosages or with concomitant ingestion of other centrally acting drugs, reaction time may be altered to an extent that affects the ability to drive or to operate machinery. This is especially the case when taken in combination with alcohol. **Undesirable effects:** Occasionally, dose-related increases or decreases in weight, increased or reduced appetite, drowsiness, transient hair loss, tremor, thrombocytopenia, leucopenia, paraesthesia or amenorrhoea have been observed. Rarely, hypersalivation, diarrhoea, peripheral oedema, bleeding, headaches, spasticity, ataxia, irritability, hyperactivity, confusion, stupor and minor gastrointestinal disturbances, especially at the start of therapy, have been reported. Tinnitus, hallucinations and enuresis in children have also been observed. Encephalopathy of unknown pathogenesis has been observed in rare cases, that developed shortly after use of medication containing valproic acid and was reversible after withdrawal of the medication. Rarely, dose-independent severe (and even fatal) liver damage has been observed. In isolated cases, lymphocytopenia, neutropenia or anaemia, reduced concentrations of fibrinogen and/or Factor VIII, inhibition of platelet aggregation, skin reactions (erythema multiforme), lupus erythematosus, disorders of high cortical functions, Fanconi's syndrome, increased levels of testosterone and cystically enlarged ovaries have been reported. A single case of vasculitis was observed. There have been individual reports of pancreatic damage, partly with fatal outcome. **Special precautions for storage:** Keep dry. Do not use after the expiry date. Orfiril® long 150 (sustained release minitabets), Orfiril® long 300 (sustained release minitabets), Orfiril® long 500 (sustained release minitabets), Orfiril® long 1000 (sustained release minitabets), Orfiril® syrup (solution), Orfiril® 300 retard (enteric-coated sustained release tablets), Orfiril® 150/300/600 (enteric-coated tablets). **DESITIN ARZNEIMITTEL GMBH** · Weg beim Jäger 214 · D-22335 Hamburg, Germany Fax +49-40-59101-433 · www.desitin.de

* Hetzow et al., Drug Res. 47 (II), Nr. 12 (1997). ** Fraunberger et al., Akt. Neurologie 2006; 195-199; Cramer et al., Epilepsy & Behaviour 3 (2002) 338-342.

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Interview Psychiatric comorbidities in epileptic patients

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the psychotropic properties of certain antiepileptics is therefore necessary if we wish to offer patients optimised therapeutic regimens.

Think Bipolar: Do you think it is important to intensify the scientific and interdisciplinary debate on the subject of 'Concomitant psychiatric disorders in epilepsy sufferers' in the future?

Prof. Schmitz: I think it is very important indeed. Physicians and scientists have only just begun to recognise how frequently concomitant psychiatric disorders occur in epilepsy patients and that a considerable range of disorders is seen. Unfortunately, there have so far been almost no scientific studies on the use of psychotropic agents or antiepileptics for the treatment of concomitant psychiatric disorders in epilepsy patients. There have also been only very few well-founded investigations into the best approaches to treatment in such cases. As far as I am concerned, interdisciplinary collaboration, particularly between psychiatrists and neurologists, must certainly continue for the benefit of patients.

Think Bipolar: What recommendations do you have for colleagues in office practice with regard to 'epilepsy and concomitant psychiatric disorders'? What can they do to be prepared for such cases.

Prof. Schmitz: In my opinion, we also have to make sure that the subject of concomitant psychiatric disorders in epilepsy patients are no longer taboo in office practice. Not only inspecting the seizure calendar, but also probing more deeply into the patient's psychiatric wellbeing is an essential factor in the patient's quality of life. Attending physicians should free themselves from concerns they have in this

"There are a number of substances, such as carbamazepine (e.g. Trimonil®), valproate (e.g. Orfiril® long) or lamotrigine (e.g. Plexxo®), which have proved very useful in patients with primary psychiatric disorders and act as mood stabilisers, or even have an antidepressant effect."

area about giving treatment. Many colleagues in office practice have absolutely no problem combining three different antiepileptics, but when it comes to titrating up an additional antidepressant or an antipsychotic, they start to worry about possible side effects and interactions, and treatment which is urgently necessary is not given. I think that these concerns are exaggerated. Concomitant psychiatric disorders in epilepsy patients must be seen for what they are, properly diagnosed and properly treated.

Think Bipolar: Thank you Professor Schmitz. ■

New Studies Screening for bipolar disorder in women with polycystic ovary syndrome: A pilot study

Klipstein K and Goldberg J,
J Affective Disorders 2006;
91: 205-209

Design: Screening pilot study

Setting: Mount Sinai Medical Center, New York/USA, and The Zucker Hillside Hospital, Glen Oaks/USA

Objective: Investigate the hypothesis that there is an intrinsic association between polycystic ovary disorder syndrome (PCOS) and bipolar disorder independent of pharmacotherapy

Patients: 78 women with PCOS were screened for bipolar disorder using the Mood Disorder Questionnaire (MDQ)

Results: 28% of women had either a previous bipolar diagnosis or met MDQ thresholds, and 97% had no valproate exposure before PCOS diagnosis

Conclusions: The observed higher rate of bipolar disorder in women with PCOS independent of VPA may be linked to the shared hypothalamic-pituitary-gonadal axis abnormality

Polycystic Ovary Syndrome (PCOS) is considered to be the most common endocrine disorder among women of reproductive age (Franks, *NEJM* 333 1995). There are conflicting results and discussions about the cause of PCOS. For example: One study found a higher rate of menstrual disturbances in more women taking valproate as antiepileptic treatment compared to women taking carbamazepine; the authors concluded that PCOS may be caused by valproate, but is reversible if the antiepileptic treatment is changed (Isojärvi et al., *NEJM* 329 1993; Isojärvi et al., *Ann Neurol* 1996). This launched a debate as to whether valproate alone contributes to the pathogenesis of PCOS, whether the risk is comparable in women with epilepsy, bipolar disorder or migraine, and whether non-pharmacological risks for PCOS such as epilepsy and obesity contribute independently to PCOS. Three subsequent studies did not replicate the findings of Isojärvi (Murialdo et al., *J Clin Invest* 1997; Murialdo et al., *Clin Neuropharmacol* 1998; Bauer et al., *Epilepsy Res* 2000). Two subsequent studies, albeit with small sample sizes, found higher risks for the development of PCOS in women with bipolar disorder taking valproate (O'Donovan et al., *J Clin Psychiatry* 2002; McIntyre et al., *Bipolar Dis* 2003). Rasgon and his working group (*J Clin Psychiatry* 2000) found no anatomic or hormonal indications for PCOS in 22 bipolar women, but did document an increased prevalence of menstrual disturbances. Other studies, however, found an association between depression and PCOS markers such as obesity, insulin resistance and hyperandrogenism (Rasgon et al., *J Affect Disord* 2003; Weiner et al., *Psychosom Med* 2004).

These findings all raise the question of whether there is a metabolic link between PCOS and affective illness. Klipstein and Goldberg therefore asked

women from the non-profit-making PCOS Association to take part in a study to investigate whether there is an intrinsic endocrinopathy for PCOS associated with bipolar disorder. 78 out of 195 participants at a conference identified themselves as officially diagnosed with PCOS by a gynaecologist. The study assessments comprised the

MDQ and a questionnaire concerning medical and family history, including height and weight, menstrual and reproductive history, medication, and past psychiatric diagnoses and treatment.

54 women with PCOS were positive and 21 negative for bipolar disorder. The two groups were comparable for age, BMI, race and bipolar family history; the age at PCOS diagnosis was younger in bipolar women, but the difference was not statistically significant. Lifetime exposure to valproate was low (4%); none of the 78 women were taking valproate at the time of the study, and 2 women had

been taking valproate before PCOS diagnosis.

Despite the limitations of this pilot study, Klipstein and Goldberg suggest that the findings revealed a higher rate of bipolar disorder in women with PCOS than in the general population and that PCOS and bipolar disorder potentially share a hypothalamic-pituitary-gonadal-axis defect. According to the authors this possible relationship between PCOS and bipolar disease independent of valproate use warrants further clarification in well-designed prospective studies. ■

New Studies Impact of lamotrigine and lithium on weight in obese and non-obese patients with bipolar I disorder

**Bowden et al., Am J Psychiatry 2006;
163: 1199-1201**

Design: Post hoc analysis of data from two double-blind, placebo-controlled, 18-months studies

Objective: Assessment of weight changes in a large cohort of patients with bipolar I disorder who were treated randomly with lamotrigine, lithium or placebo as maintenance monotherapy

Patients: 155 obese patients and 399 non-obese patients from two double-blind, placebo-controlled, 18-months studies

Results: At week 52 mean changes in weight gain among obese patients were -4,2, +6,1 and -0,6 kg and in non-obese patients -0,5, +1,1 and +0,7 with lamotrigine, lithium, and placebo respectively

Conclusions: One possible explanation could be, that patients with bipolar I disorder who are susceptible to obesity in general, are also susceptible to lithium-induced weight gain.

Compared to the normal population, patients with bipolar disorder are nearly twice as likely to be obese. A clinically significant body weight gain – defined as $\geq 5\%$ change from baseline or 5 kg – has been reported in 1/4 to 1/3 of patients in studies with lithium, anticonvulsants, and atypical antipsychotics. To assess the weight gain of long-term-treatment with lamotrigine, lithium and placebo in patients with bipolar I disorder, data from two 18-months studies, which compared the efficacy and safety of these drugs, were analysed in a post hoc analysis.

A total of 155 obese patients and 399 non-obese patients received lamotrigine, lithium or placebo. The mean total dose of lamotrigine was 248,6 mg/day in the obese and 245,3 mg/day in the non-obese study population, the corresponding doses for lithium were 838,8 mg/day and 844,2 mg/day respectively. In the obese patients the maintenance therapy with lithium was

associated with a marked weight gain (+6,1 kg), whereas maintenance therapy with lamotrigine was associated with a weight loss (-4,1 kg). Obese patients taking lamotrigine had a significant ($p < 0,05$) decrease in body weight compared with placebo at week 20, 36, and 44, and compared to lithium at week 12, 20, 28, 36, 44 and 52. A significant increase in weight has been observed for those patients taking lithium compared with placebo at week 28, 36, 44 and 52. There was no significant differences in mean weight change among the groups of the non-obese patients at any time during the studies.

The authors mentioned that these results should be interpreted in the context of a post hoc analysis. They explained the unexpected finding that only obese patients had a marked weight with lithium, with could a higher susceptibility of these patients to obesity in general and weight gain with lithium in particular. ■

Literature Review

Long-term prophylaxis in bipolar disorder

Taylor M.J., & Goodwin G.M.,
CNS Drugs 2006; **20 (4)**

Prophylaxis with medication has largely been neglected in the past. Now, however, we are seeing more and more evidence from randomised trials that both newer and longer established drugs are effective prophylactic agents. The compounds differ as to whether they are better at preventing manic or depressive episodes; the understanding of these differences may enable tailored therapy for each patient. In this article, Taylor and Goodwin review the evidence relating to a range of different drugs in the prevention of recurrent manic or depressive episodes, and they summarise issues of clinical management in line with different guidelines.

A prophylactic medication should be considered for patients with bipolar I disorder who have had at least one episode of mania. Based on efficacy, the adverse effect profile and the pat-

tern of the illness, both the physician and the patient should choose together the medication that should be given for long-term prophylaxis. Clinical monitoring is necessary, such as regular determination of the body weight, because there is emerging evidence that bipolar patients may have a higher risk of metabolic syndrome. Regular differential blood counts, renal and liver function tests, and determination of blood glucose and lipids are also necessary, depending on the drug.

Lithium has long been used in bipolar disorder and remains the benchmark for the other drugs. Poor compliers with treatment should not be treated with lithium due to the high risk of recurrence. Like lithium, valproate prevents manic episodes, and patients receiving valproate are less likely to stop the medication, as compared to lithium and placebo. Lamotrigine is more effective in preventing depressive than manic episodes. In studies, olanzapine has been as effective as lithium and valproate and, like lithium, olanzapine should be tapered off over 2-4 weeks. When long-term mono-

therapy fails, combination therapies are now more often used, and more clinical findings with combinations from trials are now available or are expected soon.

As an adjunct to medication, psychological intervention can improve the outcome of prophylaxis. Discontinuation of prophylaxis remains a problem, as even patients who suffer no manic or depressive episodes over a long period are still at risk of relapse. In elderly patients, treatment can be complicated due to comorbidities and drug interactions with comedication. And the long-term use in pregnant women requires very careful consideration of the risk-benefit situation.

Conclusions of the authors: Long-term treatment with medication for prophylaxis should be considered in all patients with bipolar I disorder. Clinical care of this complex mental illness can be enhanced by educating the patients about the disorder, using cognitive therapies to improve compliance, and recognising and managing prodromal symptoms. ■