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The Correct Treatment of mixed states

Recognising complex forms of bipolar disorder

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5th annual meeting of the German Association for Bipolar Disorders, Bonn 1-3 September 2005.

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The Correct Treatment of mixed states

Recognising complex forms of bipolar disorder

Defining bipolar disorders as consisting of alternating episodes of manic-euphoric and depressive-dysphoric states, with or without intervening intervals of euthymia, does not adequately describe the complexities of the psychopathology and the course that this condition normally follows. Affective mixed states with de-synchronisation of mood, thought and motor action are at least as frequent. The diagnosis is additionally complicated by psychiatric co-morbidity and/or substance abuse. From a differential therapeutic point of view it must be taken into consideration that, among the established mood stabilisers, the response achieved by lithium is generally limited to euphoric mania, while valproic acid offers better chances of success in the considerably higher manifestations of bipolar disorders.

Controlled release valproate now available in Germany without restrictions

Internationally, the anticonvulsant valproic acid is a long-established treatment option for patients with bipolar disorders. Its advantages, among others, are a rapid onset of action, a broad therapeutic range, and the low risk of interactions with any other form of comedication. The guidelines issued by the German Association of Psychiatry (the Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde or DGPPN) also approve the use of this mood stabiliser for all forms of mania. It also advocates valproic acid as the treatment of choice, in preference to lithium, for intervention in dysphoric as well as in psychotic mania, in affective mixed states as well as "rapid cycling" (fluctuating rapidly from one mood state to another or "having mood swings"). The use of this standard form of therapy has only been possible "off label" in Germany to date. The administrative barriers to its use have now been removed, however. The marketing authorisation for controlled release valproate (valproic acid) in the form of controlled release mini tablets (Orfiril® long).

Although scientific interest in the group of bipolar disorders has not only increased, resulting in a number of new initiatives designed to help the medical fraternity to improve its diagnostic ability when faced with a patient who exhibits a wide range of extreme moods, many patients are still falling through the diagnostic net.

For neither the "International Classification of Psychiatric Disorders" (ICD 10), whose use is obligatory in Germany, nor the "Statistical Manual of Psychic Disorders" (DSM IV), which is commonly used in the USA, adequately take account of the wide range of the psychopathology found in the disorder. The subdivision of bipolar disorders into "Type I" (alternating episodes of mania and depression) "Type II" (alternating episodes of depression and hypomania) and cyclothymia (alternating phases of dysthymia and hypomania) does not adequately describe the abundance of the affective nuances of the patient's "highs" and "lows". It is particularly difficult to diagnose those patients who present with a manic - depressive mixed state as suffering from bipolar disease. This is particularly worrying since this is not an unusual combination of symptoms, but rather is characteristic of more than 50% of all bipolar episodes. [1]

About half of all episodes are manic-depressive mixed states

The fact that both affective poles of the disorder may be present in an individual patient at the same time is not a new discovery but

	Mood	Psychomotor ability	Formal reasoning
(pure) mania	↑	↑	↑
Inhibited mania	↑	↓	↑
Deflated mania	↑	↑	↓
Manic stupor	↑	↓	↓
Depressive-anxious mania	↓	↑	↑
Aroused depression	↓	↑	↓
Depression accompanied by flight of ideas	↓	↓	↑
(pure) depression	↓	↓	↓

Table 1: Symptom forms of manic-depressive mixed states *(according to Kraeplin [2])*

was already described in antiquity as Prof. Dietrich van Calker, Freiburg, reminded us in his historical survey at the annual meeting of the German Association for Bipolar Disorders *(Deutsche Gesellschaft für bipolare Störungen or DGBS)*. In about 100 A. D. Aretaeus of Cappodocia recognised that mania and melancholia were different symptoms of one single disease of the brain. Today medical opinion is largely based on the work of Wilhelm Weygandt and Emil Kraepelin who at the beginning of the twentieth century founded, after careful clinical observations and theoretical considerations the concept of manic-depressive mixed states [2].

Symptom polymorphism and symptom instability

In accordance with the model suggested by Kraepelin in which symptoms are subdivided to three major groups, each with an "energised" or "activated" as well as a "depressed" form, there are two "pure" forms and six "mixed" affective states *(Table 1)*. According to Dr Stephanie Krüger, Dresden, this means that in everyday clinical practice an affective mixed state is more than just a sequence of depressive and manic symptoms. It is more useful to think in terms of a "de-synchronisation of elementary functions, such as formal reasoning, mood and psychomotor skills". Krüger cites, in addition to symptomatic polymorphism, symptomatic lability as being another essential criterion of the condition.

Intra-episodic switching of mood could even take place within hours, according to Krüger, and this is often therefore (mis-)interpreted as ultra-ultra rapid cycling. There were no indications that patients with affective mixed states ran a higher risk of developing rapid cycling (by definition, this is a bipolar disorder with at least four periods of exacerbated symptoms in one year). On the other hand, patients who exhibited a rapid change from one phase to another more often have episodes involving manic-depressive mixed states. Both phenomena have in common that there is a potential for inducing an episode by antidepressant therapy, there is a higher prevalence of the condition amongst women and there is frequently a concomitant disorder of the thyroid gland.

In general, patients suffering from an affective mixed state have a significantly poorer prognosis than patients suffering from bipolar disease who have episodes of "pure" mania or "pure" depression;

- the symptoms are usually more severe, or often display psychotic features, making a hospital in-patient stay necessary.
- Recidivist or incomplete remissions are more common.
- There is a greater risk of suicide.
- The percentage of patients with a psychiatric co-morbidity, such as, and especially, substance abuse, catatonia and anxiety states is greater.

Better changes of success with valproic acid therapy than with lithium

The complex nature of the clinical picture of patients with an affective mixed state bipolar disorder explains the high risk of a misdiagnosis and therefore of an inadequate treatment program for someone suffering from this disorder. Even with the lege artis interventions using mood stabilisers, however, the chances of successful treatment outcomes are low. The reason for the low treatment success rate is the generally limited response rate displayed by patients because of

the varied nature of the psychopathology. It is also determined, however, by the higher degree of subjective sensitivity to the undesirable side effects of the medication and the patient's lower level of willingness for compliance. In all, there is little data available on the pharmacological treatment of affective mixed states, as Krüger regrets. This is because in many cases studies have failed to differentiate between mixed states and other forms of mania or because patients were precluded from taking part in the study because of their "atypical " symptoms or because they were unable to sign the necessary declaration of informed consent to treatment.
However, it is possible to draw some conclusions from the results of the few double-blind and open studies as well as from the numerous reports arising from clinical practice about the established mood stabilisers. Lithium cannot be recommended as the treatment of choice. The domain of the so-called gold standard is euphoric mania.

The inadequate effect of lithium on all patients whose symptoms do not conform to the pattern of the supposedly "classical" clinical picture of bipolar disorder is well documented, i.e. in manic-depressive mixed states or psychotic manias, or where there is rapid cycling and psychiatric co-morbidity. A general deficit, according to Professor Jörg Walden, Münster, is the limited ability to control the treatment afforded by lithium's narrow therapeutic window and the associated risks for accidental intoxication. Because of the necessity to increase a patient's lithium doses gradually, the period before serum levels rose from latent to the full therapeutic levels was often unacceptably long, especially in the acute manic phase of the condition.

The list of predictors for a good response to valproic acid, however, reads like a mirror image of those for lithium (Table 2). In the USA valproic acid has long since replaced lithium as the treatment of choice for bipolar disorders. Significant new knowledge was gained over the course of a multicentre study designed to provide a double-blind comparison of valproate and Lithium against a placebo, which was conducted in the USA in the early nineties. In this group of patients suffering from acute mania the difference in the response rates in
– the reduction in the MRS sores (Mania Rating Scale scores)
– between the two active substances (48% vs. 49%)
was not great but was statistically significantly higher ($p<0.05$) than in the control group (25%) [3].

In a later sub-analysis it was demonstrated that patients with affective mixed states responded significantly better to valproate (valproic acid), whereas amongst those patients who took lithium there was even a slight worsening of symptoms *(Fig. 1)* [4].

Rapid onset of effect with a loading dose

Walden described one of the advantages of controlled release valproate for the acute therapy of manias as being the rapid onset of the anti-manic effect. By using an initial loading dose (the recommended loading dose is 20mg valproic acid per kg bodyweight per day), it was possible to achieve, even on the first day, effective blood plasma levels (of over 50 Ìg/ml) without having to accept any reduction in the drug's tolerability *(Fig. 2)* [5]. If the use of conventional neuroleptics is necessary as part of the acute management of highly manic patients, then this is usu-

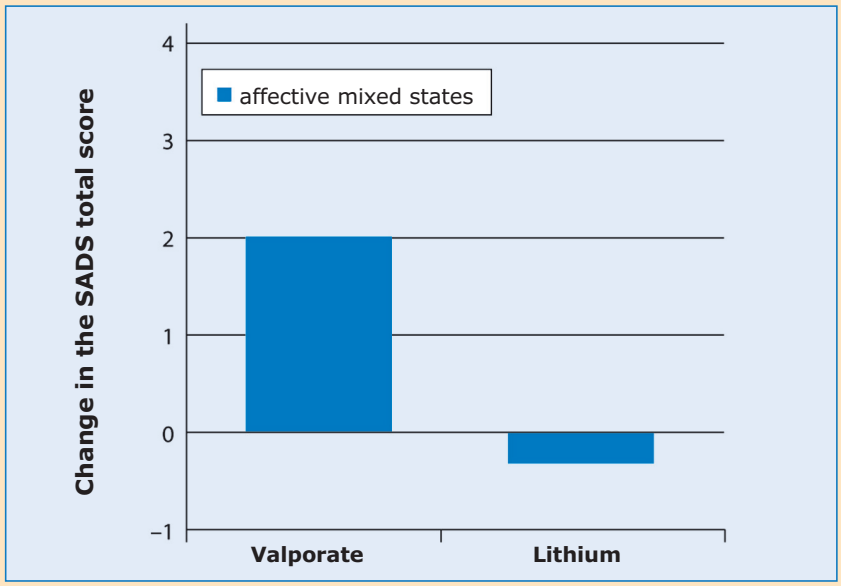

Fig. 1: Acute effectiveness of valproate (valproic acid) in affective mixed states – changes in the SADS total score (Schedule for Affective Disorders and Schizophrenia) compared to placebo *(according to Swann et al. [4])*

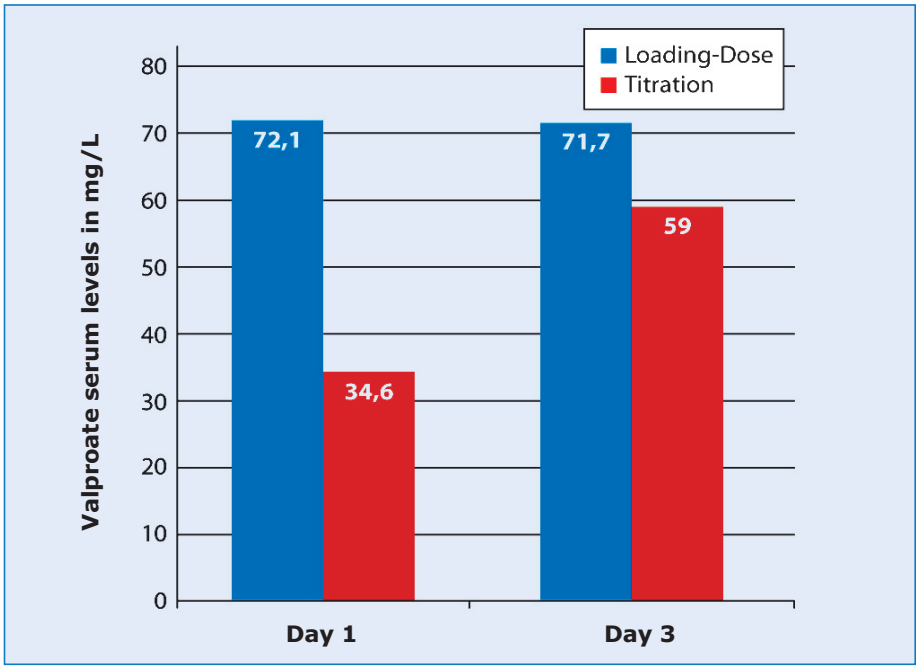

Fig. 2: Valproate serum levels after "Loading-Dose" or "Titration" *(according Lubka et al. [5])*

ally accompanied by a high level of motor extra-pyramidal disorders. It is possible that the use of valproic acid in combination with these neuroleptic drugs might improve the benefit/risk profile of this type of therapy. This conclusion may be drawn from the results of the "European Valproate Mania Study" [6]. There was on average not only a statistically significant reduction in the YMRS scores (Young Mania Rating Scale) when using neuroleptics in combination with valproate when compared with a combination with a placebo *(Fig. 3)* but also lower neuroleptic doses (p = 0.0007) were required to achieve the desired effect and co-medication with a benzodiazepine was less frequently required (p = 0.0304).

Compliance-friendly handling for long-term prophylaxis

At least as important for the patient's quality of life and his/her psycho-social integration as the rapid and complete recovery from an acute bipolar episode is the degree of permanent protection from renewed exacerbations of the disease. For this reason, a lifelong basic course of mood-stabilising medication is usually required. Valproate has also proved its effectiveness under controlled conditions in providing this prophylaxis to reduce recidivism, without the need for any co-medication [7] as well as in combination with other mood stabilisers [8].

The prophylaxis to reduce recidivism is often unsuccessful because of poor compliance on the part of the patients suffering from bipolar disorders. In only 60% of cases was it possible to assume that medication was being taken in full compliance with the directions contained in the prescription, as Dr Heinz Grunze, Munich, says, quoting the results of a Spanish study [9].

The reasons for this state of affairs were, on the one hand, a false assessment by the patient of his/her own illness as well as irrational fears about dependency on or the loss of control involved in taking the medication and, on the other, the often very complicated instructions for taking the medication. With the prescription of controlled release valproate in the authorised pharmaceutical form as controlled release mini tablets *(Orfiril® long)* the patient's concerns have been met to a great extent. Many people who need this therapy will find it a great relief that they only need to think about taking their medication once a day. That a single dose of a drug can have as marked an anti-manic effect or is able to reach similarly adequate blood plasma levels as rapidly as drugs taken in two daily doses was demonstrated during the course of a study conducted at the university psychiatric clinics in Freiburg and Munich (Fig. 4) [10].

Affective mixed states, dysphoric mania [4]
Rapid cycling [11]
Psychotic manias [12]
Co-morbidity with substance abuse [13]
Co-morbidity with other psychiatric diagnoses (esp. anxiety states) [14]

Table 2: Predictors for a better response to valproate (valproic acid), compared with lithium

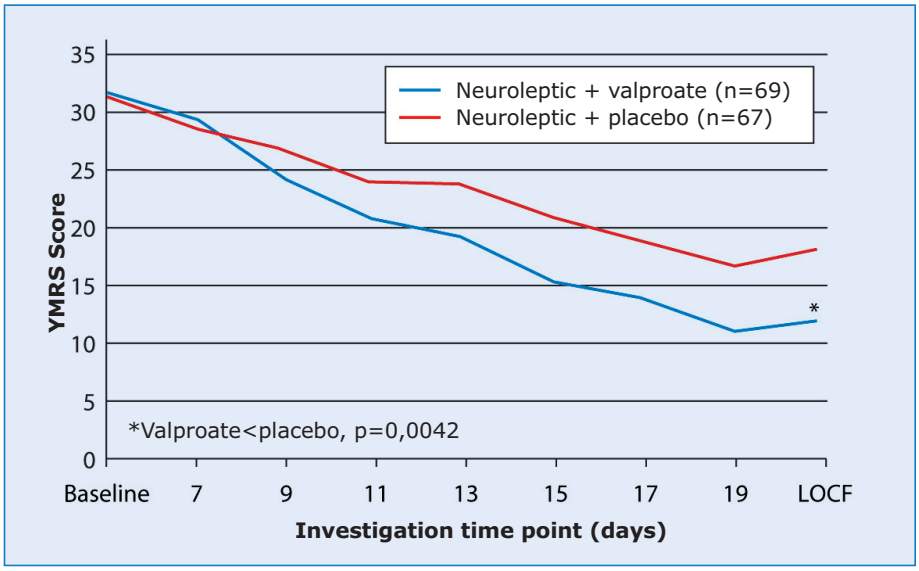

Fig. 3: Change in the YMRS score (Young Mania Rating Scale) during treatment with conventional neuroleptics in combination with valproate or a placebo *(according to Müller-Oerlinghausenet al. [6])* LOCF (Last observation carried forward) analysis

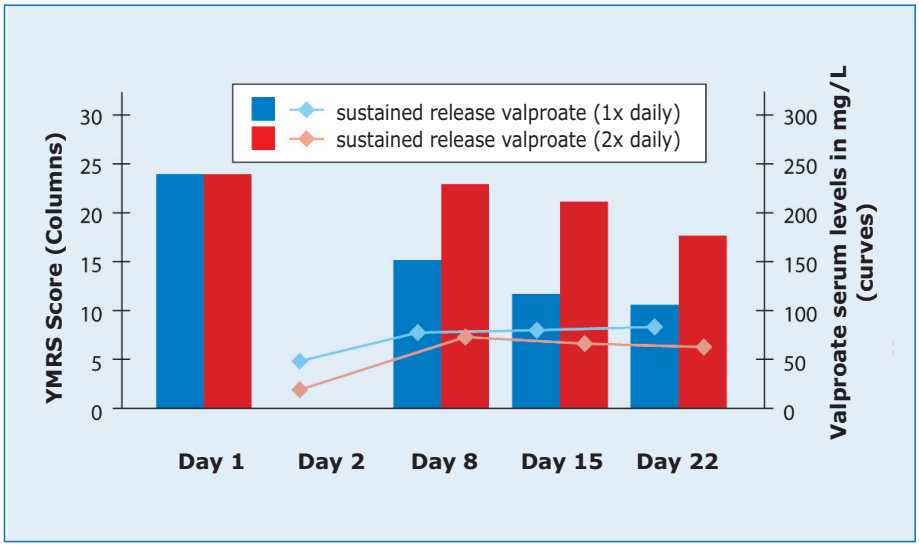

Fig. 4: Rapid anti-manic action (Young Mania Rating Scale) and rapid attainment of therapeutic level of controlled release valproate in single or twice- daily doses of sustained release mini tablets (Orfiril® long) *(according to Grunze et al. [10])*

The sustained release mini tablets are available as capsules (150mg and 300mg) or sachets (500mg and 1,000 mg), each form in packets of 50 (N1), 100 (N2) and 200 (N3). According to personal preference, a capsule may either be swallowed whole on an empty stomach or before/with/following a meal or else, as is the case with the sachets, the contents may taken on a spoon and mixed with soft food or may be poured into a carbonated "fizzy" drink. Because controlled release mini tablets are so small in size (about 2 mm in diameter) they are very quickly absorbed via the stomach and into the small intestine. From here the active ingredient is released continuously. The reasonable daily costs of the drug is an additional reason to make the long-term use of controlled release valproate attractive as a bipolar basic therapy.

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