Arch. Psychiat. Nervenkr. 229, 1–16 (1980)

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Effect of Sodium Valproate on Mania

The GABA-Hypothesis of Affective Disorders

H. M. Emrich[1*], D. v. Zerssen[1], W. Kissling[1], H.-J. Möller[1], and A. Windorfer[2]

[1] Max-Planck-Institut für Psychiatrie, Munich, Federal Republic of Germany
[2] Kinderklinik und Poliklinik der Technischen Universität, Munich, Federal Republic of Germany

Summary. A possible antimanic property of the GABA-ergic anticonvulsant valproate was examined by use of a double-blind placebo-controlled ABA design in 5 acutely ill manic patients. In 4 cases a marked improvement was observed after valproate medication whereas one patient showed no response. Seven further patients with frequently recurrent episodes of a manic or maniform schizoaffective psychosis, irresponsive to lithium prophylaxis, were chronically treated with valproate in combination with low doses of lithium (one case only with valproate). Over an observation period of 1½–3 years none of the patients exhibited a relapse. It is proposed that, in general, GABA-ergic anticonvulsants possess antimanic properties and that the specific antimanic effect of lithium is due to a GABA-ergic mode of action. The possible role of GABA-systems in affective disorders and in organic types of psychoses (e.g., porphyria-psychosis, delirium tremens) is discussed on the basis of pharmacopsychiatric considerations.

Key words: Manic psychoses – Valproate – GABA – Lithium.

Zusammenfassung. Unter Verwendung eines doppel-blinden ABA-Designs mit Placebo-Kontrolle wurde bei 5 Patienten mit akuter Manie eine mögliche antimanische Wirkung des GABA-ergen Anticonvulsivums Valproat untersucht. Bei 4 Patienten wurde eine deutliche Besserung beobachtet, während ein Patient auf Valproat nicht reagierte. Bei 7 weiteren Patienten mit häufig wiederkehrenden Phasen einer manischen oder maniformen schizoaffektiven Psychose, die auf die Lithium-Prophylaxe nicht ansprachen, wurde eine Dauerbehandlung mit Valproat in Kombination mit kleinen Lithium-Dosen durchgeführt. (In einem Fall wurde nur Valproat, ohne Lithium, gegeben.) Im Verlauf einer Beobachtungsphase von 1½–3 Jahren wurde bei keinem dieser

* Supported by the Heisenberg-grant of the Deutsche Forschungsgemeinschaft
Offprint requests to: Prof. Dr. H. M. Emrich, Max-Planck-Institut für Psychiatrie, Kraepelinstr. 10, D-8000 München 40, Federal Republic of Germany

0003-9373/80/0229/0001/$03.20

Patienten ein Rückfall beobachtet. Es wird die Hypothese vorgeschlagen, daß grundsätzlich GABA-erge Anticonvulsiva antimanische Eigenschaften aufweisen und daß auch der spezifische antimanische Effekt von Lithium auf einer GABA-ergen Wirkungskomponente beruht. Eine mögliche pathophysiologische Bedeutung zentraler GABA-Systeme bei affektiven und organischen Psychosen (z.B. Porphyrie, Delirium tremens) wird auf der Basis pharmakopsychiatrischer Überlegungen diskutiert.

Schlüsselwörter: Manische Psychosen – Valproat – GABA – Lithium.

Introduction

The weak anticonvulsant valproate[1] has been widely used in the past, frequently in combination with other antiepileptic medication, in treatment of various types of epilepsy (grand mal, mixed grand mal and petit mal, drug-refactory temporal lobe epilepsy, and myoclonic epilepsy). In particular, in cases that proved irresponsive to other types of anticonvulsants valproate has been applied (overview: Pinder et al. 1977). The observation that patients with epileptic psychoses responded to valproate treatment, not only as concerning their epilepsy but also with respect to their psychotic symptomatology, is of interest from the psychiatrical point of view (Köhler 1975). Thus a possible beneficial influence of valproate upon patients displaying an endogenous type of psychosis may be hypothesized. Moreover it is not only the clinical picture which is suggestive of a possible efficacy of valproate in the therapy of psychiatric disorders.

Both pharmacological and biochemical data has accumulated concerning the mode of action of valproate and pointing to a relationship of valproate to GABA-ergic systems. In addition to the data of Harvey et al. (1975) and of Anlezark et al. (1976), evidential of an inhibitory effect of valproate upon the degradative enzymes involved in the GABA shunt, several authors have demonstrated that valproate raises the brain levels of GABA and lowers those of cGMP in rats and other animals (cf. Pinder et al. 1977). Recently, Bernasconi and Martin (1979) showed a valproate-induced dose-dependent decrease of GABA turnover in vivo in different regions of the mouse brain, suggestive of an indirect GABA-ergic effect of this drug.

A substantial body of evidence suggestive that GABA may play a crucial role in regulatory, predominantly inhibitory processes within the CNS, in particular in the basal ganglia, hypothalamus and midbrain has been generated in recent years (overview: Krogsgaard-Larsen et al. 1979). J. Stevens et al. (1974), for example, upon injection of bicuculline, a GABA antagonist, into the mesencephalic ventral tegmental area of cats observed an arousal, searching behavior and other effects upon motor activity. Furthermore, Kelly et al. (1977) demonstrated that microinjections of bicucculine into the anterolateral hypothalamus in rats result in an enhancement of feeding and locomotor activity. The emergence of evidence suggestive that GABA may function as a presynaptic modulator of dopamine neurons (Tapia 1974; Wu and Roberts 1974) has led to the hypothesis (Roberts 1972; Van Kammen 1977) that a defect in GABA systems might be a causative

1 Sodium valproate: Ergenyl®, Depakine®, Orfiril®; valproic acid: Convulex®

factor in the pathogenesis of schizophrenia. In a single-blind study Frederiksen (1975) administered para-chlor-phenyl GABA (baclofen) to chronic schizophrenic patients and detected an amelioration of psychotic symptoms in several cases within a few days. However, Beckmann et al. (1977), using baclofen in 21 schizophrenic patients, proved unable to reproduce these results and discussed several reasons for this failure. Besides the possibility that baclofen only poorly penetrates the blood-brain barrier (Faigle and Keberle 1972), there are some indications that baclofen may not act via GABA-ergic receptors (Curtis et al. 1974; Davies and Watkins 1974). Interestingly, some preliminary results are available pointing to a possible curative action of valproate in schizophrenic patients, as observed in a single-blind pilot study by Gündürewa et al. (1980). In this context the results obtained recently by Beckmann and Haas (1980) as to the effect of high-dosage treatment of schizophrenic patients with diazepam—which also exhibits GABA-ergic properties (Costa et al. 1975)—should be considered.

However, our special interest in the possible therapeutic value of valproate in the treatment of manic patients has its basis in two additional observations. Firstly the finding that the antimanic efficacy of propranolol is apparently not confined to the β-blocking l-stereoisomer but is also (although to a smaller extent) possessed by d-propranolol, which is largely devoid of β-blocking activity (Emrich et al. 1979; Möller et al. 1979). These data are in line with pharmacological results obtained in an animal model of mania (reserpine-pargyline-treatment, Delini-Stula and Meier 1976; Vassout and Delini-Stula 1977). The results of certain animal experiments (Delini-Stula, personal communication) are indicative that an indirect GABA-ergic effect of propranolol may be involved in its antiexcitatory action in this animal model of manic behavior. This view is further supported by the findings of Bernasconi (personal communication) that the turnover of GABA is reduced by propranolol to the same extent irrespective of whether the d- or the l-isomer is applied.

The second reason which prompted the investigation as to a possible antimanic property of valproate lies in the clinical findings of Lambert et al. (1975) demonstrating the therapeutic efficacy of the valproate derivative dipropylacetamide[2] in manic depressive psychoses. This anticonvulsant is metabolized rapidly to valproate; thus, a similar pharmacological and therapeutic profile of action may be postulated. The, as yet, published studies of Lambert et al. (1966, 1968, 1971, 1975) involve only open trials without the use of rating scales or other types of standardized evaluative techniques; thus, the reliability of these data, although encouraging, cannot easily be assessed. One specific point mentioned by these authors was the impression that patients displaying recurrent phases of affective disorders and not responding properly to lithium therapy, showed a marked improvement if a combined prophylactic treatment of lithium and dipropylacetamide was undertaken (Lambert et al. 1975). This observation is of especial interest in view of the volume of reports claiming a nephrotoxic effect of chronic treatment with lithium (Johnson 1980). As a result of new therapeutic guidelines for lithium prophylaxis, involving the use of lower blood levels (0.6–1.0 mval/l; Cooper et al. 1979), a higher percentage of lithium non-responders in the prophylactic treatment of patients with affective disorders is to be expected. Therefore, a considerable

2 Depamide®

interest in a therapeutic 'adjuvance' in prophylactic treatment with lithium or a substitution of lithium treatment by another treatment appears justified.

Dipropylacetamide is not the only antiepileptic drug considered in the literature as a possible antimanic agent: diphenylhydantoin (DPH), shown in the crayfish-stretch-receptor to act via a postsynaptic site localized very close to the GABA-activated chloride channel (Deisz and Lux 1977), has also been applied clinically in psychotic patients (Kubanek and Rowell 1946). The authors treated 35 patients suffering from schizophrenia and 9 from mania with DPH. Of the schizophrenic patients 8 showed a great (23%) and 2 a slight improvement whilst in the group of manic patients 5 revealed a great (55%) and 2 others a slight improvement. This data indicates that DPH may be a more suitable therapy in manic psychoses than in schizophrenia. Therefore, the hypothesis that a defect in the GABA-systems may be involved in the pathogenesis of schizophrenia (Roberts 1972) should at least be extended to the situation of manic psychoses, as has been discussed by van Kammen (1977). A modification of the hypothesis in order to account for the possibility that mania results from a dysfunction, and depression from a hyperactivity, of one of the GABA systems, would be required.

A further antiepileptic drug previously used in the pharmacotherapy of manic psychoses is carbamazepine (Tegretol[3]). For this substance prophylactic as well as acute antimanic effects have been observed in 63 patients (Okuma et al. 1973, 1979). Although the mechanism of action of carbamazepine has not, as yet, been established, from the fact that, in addition to DPH (Deisz and Lux 1977), the anticonvulsant barbiturates (Nicoll 1978) and diazepam (Costa et al. 1975) exhibit a GABA-ergic mode of action, one may hypothesize that carbamazepine might also possess GABA-ergic properties. This view has recently been substantiated by in vivo measurements of GABA turnover after carbamazepine treatment (Bernasconi and Martin 1979).

The presently-discussed therapeutic trial with valproate involves the performance of two types of studies: one using a double-blind placebo-controlled ABA-design in inpatients suffering from an acute manic episode of their affective psychosis and the other using an open trial with a prophylactic long-term treatment of lithium non-responders. These patients received low doses of lithium (blood levels 0.5–0.8 mval/l) in combination with doses of valproate normally used in anticonvulsive treatment (blood levels 50–120 µg/ml). Both studies remain, as yet, incompleted. However, a publication of the preliminary findings appears to be justified in view of the promising nature of the data and their clinical and therapeutic relevance.

Methods

Acute Treatments. Five inpatients[4] displaying maniform psychoses (ICD 296.3, 295.7) were treated with valproate as part of a double-blind placebo-controlled ABA-design. Before commencement of the trial, both the patients themselves and their close relatives gave their

3 Tegretal®

4 One patient was treated in the Bezirkskrankenhaus Haar. We are greatly indebted to director Dr. Dr. Ch. Schulz and Dr. R. Oechsner for their very valuable cooperation

informed consent. 300 mg tablets of valproate were provided 3 times per day (at 7:45, 12:15 and 18:15) up to a dosage in one case of 3.8 g/d. Psychopathological evaluation was performed by a physician using the Inpatient Multidimensional Psychiatric Scale (IMPS, Lorr et al. 1962). Five of the twelve IMPS-factors (EXC, HOS, GRN, MTR, CNP) were summed to form a score reflecting the patient's manic symptomatology (cf. v. Zerssen and Cording 1978). In three patients the mania rating scale MS-M (Murphy et al. 1974) was also used. In all patients an extensive physical and neurological examination was performed prior to initiation of the trial. The laboratory tests undertaken prior to beginning valproate medication included an X-ray examination of the chest, ECG, EEG and routine chemical measurements. Thrombocyte-count and bleeding time, in particular, were controlled both before and during valproate medication. Valproate serum concentration (venous puncture at 7:15, 13 h after last medication) was measured by one of us (A.W.) by use of gas-chromatography (Löscher and Essenwein 1978; detection limit: 2 µg/ml) in a double-blind design.

Chronic Prophylactic Treatments. Prophylactic long-term medication with valproate was performed in seven lithium non-responders (ICD 296.3 (5), 295.7 (2)) in six of them in combination with low doses of lithium (serum levels 0.4–0.8 mval/l) and in one case in the complete absence of lithium treatment owing to the presence of severe lithium side effects.

The clinical course of these outpatients was assessed by a physician (open study) by use of the VBS (= *V*erlaufs-*B*eurteilungs-*S*kala, i.e. course-assessment-scale), a self-constructed scale (Emrich et al. 1977) with 8 degrees of intensity, adapted here to reflect the global impression of 'manic behavior' and 'depression'.

Case Reports

Case 1. Miss VL, a 21-year-old waitress suffering from her first manic episode in the course of a schizoaffective psychosis (ICD 295.7). Prominent symptoms upon admission included euphoria mixed with dysphoria, flight of ideas, expansiveness, overactivity of speech-production and restlessness. During treatment with valproate (dosage up to 1800 mg/d) the manic symptomatology disappeared within three days. After discontinuation of this medication (second placebo phase) there was only a very slight reappearance of the manic symptoms (Fig. 1) and the patient could be released from hospital within two weeks.

Case 2. Mr. RO, a 23-year-old former broker suffering from his second manic phase of a bipolar manic depressive psychosis (ICD 296.3). He had been hospitalized three years ago during his first manic episode owing to his severe aggression and grandiosity. In the meantime the patient has suffered from depression. On admission his psychopathology was characterized by excitation and elation, flight of ideas, grandiosity, distancelessness and aggressive behavior. During treatment with valproate (dosage up to 3850 mg/d) manic symptomatology was reduced by about 60% but reappeared after discontinuation of this therapy (Fig. 1). After treatment with neuroleptic drugs the manic symptoms once more receded. However, the patient then complained about troublesome side effects such as his 'heavy legs and lead in his bones', 'severe motor retardation combined with distressing internal excitation'.

Case 3. Miss RA, a 31-year-old cosmetician suffering from a manic episode of a bipolar manic depressive psychosis (ICD 296.3). She had already experienced three depressive phases of relatively long duration. On admission, her psychopathological symptomatology constituted a psychomotor hyperactivity, logorrhoic speech, aggressive behavior and loss of social distance. Noisy fits of crying alternated with apparently unmotivated laughing. Flight of ideas and grandiosity completed the picture. During valproate medication in a dosage up to 2700 mg/d manic symptoms almost completely disappeared but gained pretreatment intensity during the second placebo phase (Fig. 2).

Case 4. Miss MO, a 18-year-old scholar suffering from a bipolar manic depressive psychosis (ICD 296.3). She had already experienced several depressive and manic episodes of relatively short duration and had been hospitalized twice prior to admission to our clinic. Her peculiar

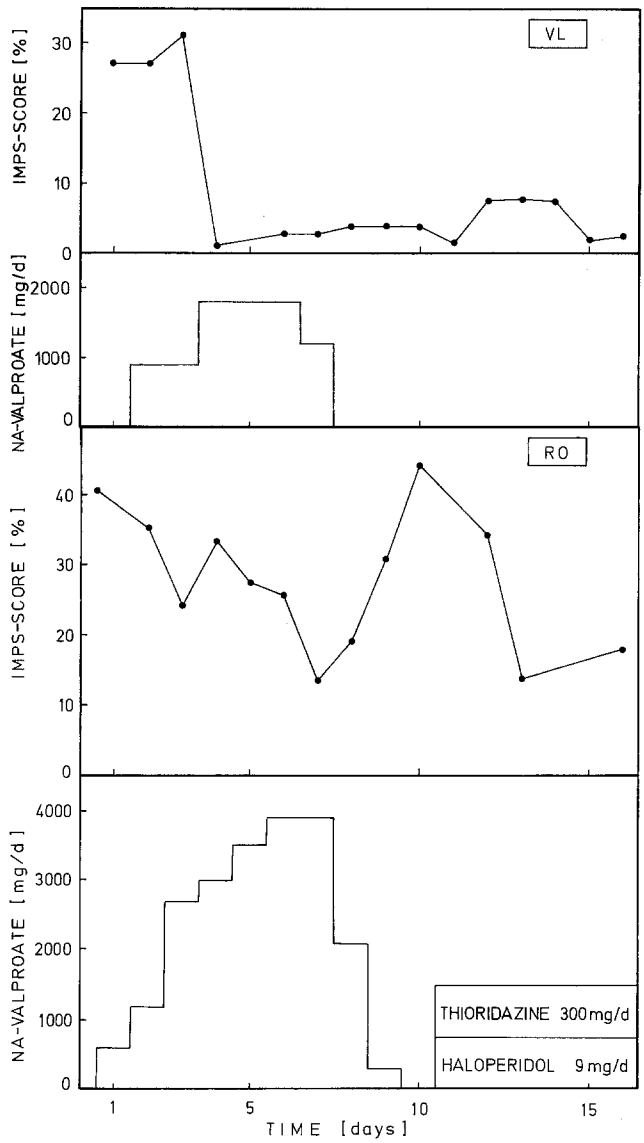

Fig. 1. Time-course of psychopathological data (IMPS-scores EXC, HOS, GRN, MTR, CNP) and of valproate dosage in two patients with manifform psychoses (cases 1 and 2)

psychopathological features upon admission were grandiosity, motor hyperactivity with intense gesticulation, logorrhea, flight of ideas and euphoria. During valproate medication with daily doses of up to 1800 mg/d the manic symptoms ceased and although reappearing during the second placebo period, not to the extent of the pretreatment level (Fig. 2).

Case 5. Mrs. FI, a 53-year-old former photolaboratory assistant suffering for eleven years from a bipolar manic depressive psychosis (ICD 296.3). The course of her illness had begun with three depressive phases and continued with a regular alternation of manic and depressive episodes. Prophylactic treatment with lithium over a period of two years proved ineffective and the existence of pronounced side effects led to its discontinuation. On admission she showed extreme excitation, motor hyperactivity, flight of ideas, logorrhoic speech production and aggressive behavior. During two treatment periods with valproate (dosage up to 3000 mg/d) there was

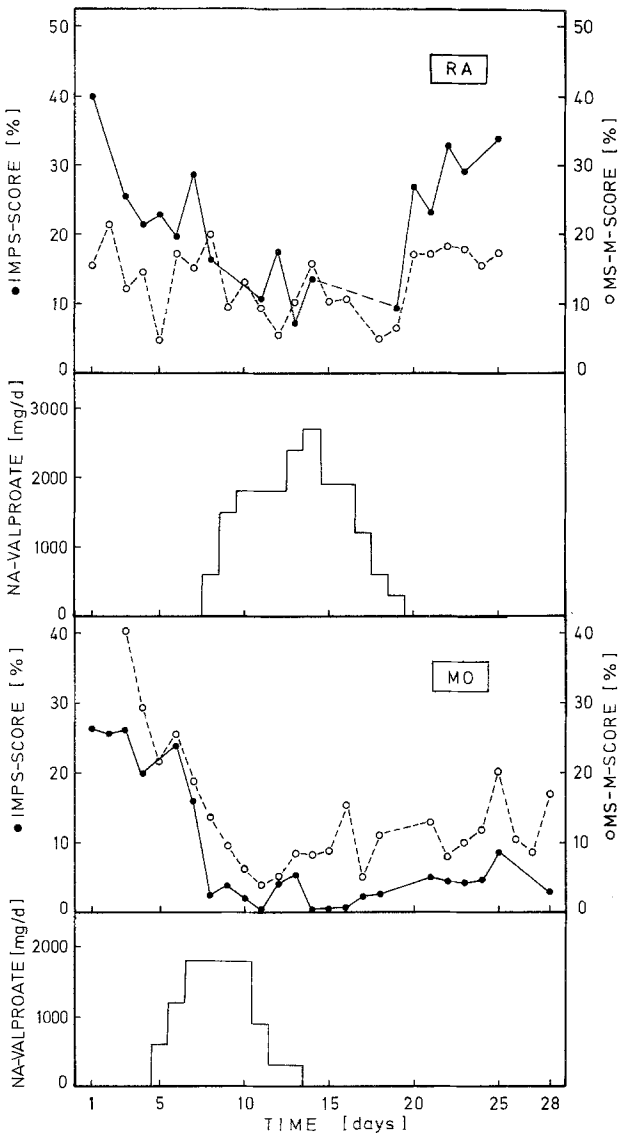

Fig. 2. Time-course of psychopathological data (IMPS-scores EXC, HOS, GRN, MTR, CNP; MS-M-scores = mania-scale by Murphy) and of valproate dosage in two patients with maniform psychoses (cases 3 and 4)

practically no change in the clinical picture (Fig. 3). However, the patient also showed no improvement upon neuroleptic treatment. The manic symptomatology lasted six weeks and was then replaced by a subdepressive state which responded to amitriptyline within 2 weeks.

Results

The course of the psychopathological data, obtained during the five acute trials, is represented in Figs. 1–3. In two patients (cases 2 and 3, Figs. 1 and 2) a remarkable improvement was obtained which disappeared during the second placebo phase.

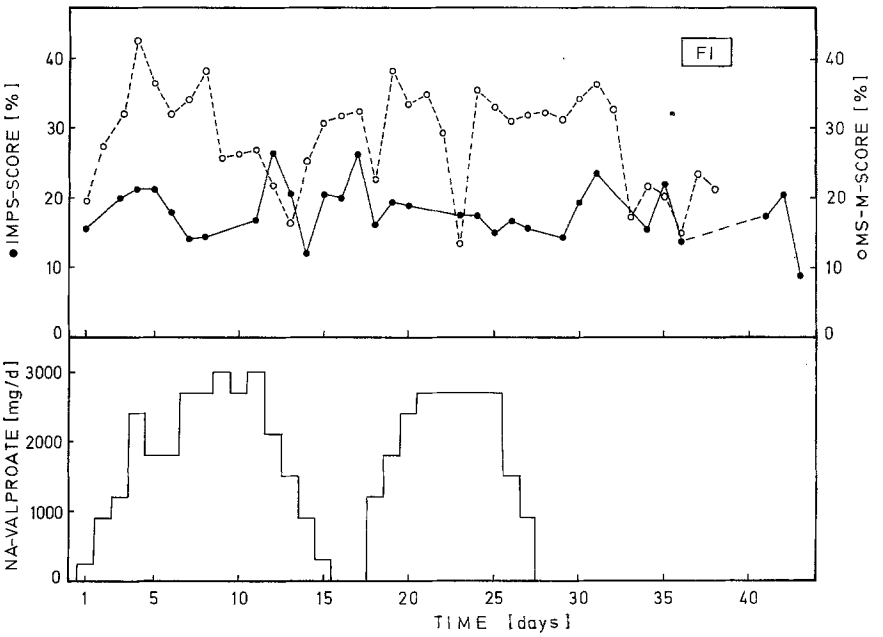

Fig. 3. Time-course of psychopathological data (IMPS-scores EXC, HOS, GRN, MTR, CNP; MS-M-scores = mania-scale by Murphy) and of valproate dosage in a patient with maniform psychosis (case 5)

Two patients (cases 1 and 4, Figs. 1 and 2) showed also an immediate response. However, in the second placebo phase the manic symptomatology reappeared to only a small extent. One patient (case 5, Fig. 3) showed no response to valproate, but was similarly unresponsive to conventional neuroleptic therapy.

Dose-Response Relation. A dose-response relationship in the conventional pharmacological sense cannot be performed in the course of a clinical investigation, owing to the necessity for the performance of several trials each using only one dosage level—this impossible for both clinical and ethical reasons. Therefore, an evaluation of the efficacy of the drug is achieved by relating the data of the daily psychopathological ratings to the oral dose per day (cf. Emrich et al. 1979). The results of this procedure are represented in Fig. 4. Here the mean psychopathological ratings during the placebo phase (dosage 0) are normalized to 100% to yield inter-individual comparability. From the present data it can be ascertained that a 30% reduction in manic symptomatology is induced by a dosage of 900 mg in case 4, of 950 mg in case 3, of 1600 mg in case 1, of 2000 mg in case 2, whereas in case 5 the therapy appears ineffective. Spearman's rank-correlation coefficients are: $r = -0.84$ (case 2); $r = -0.72$ (case 3); $r = -0.24$ (case 4[5]); $r = -0.13$ (case 1[5]); $r = 0.04$ (case 5).

5 The small correlation coefficients in cases no. 1 and 4 are an expression of the fact that in the second placebo phase the manic symptomatology reappeared only to a small extent. A calculation of Spearman's rank correlation coefficients after elimination of the second placebo phase gives higher values: $r = -0.75$ (case 1) and $r = -0.70$ (case 4)

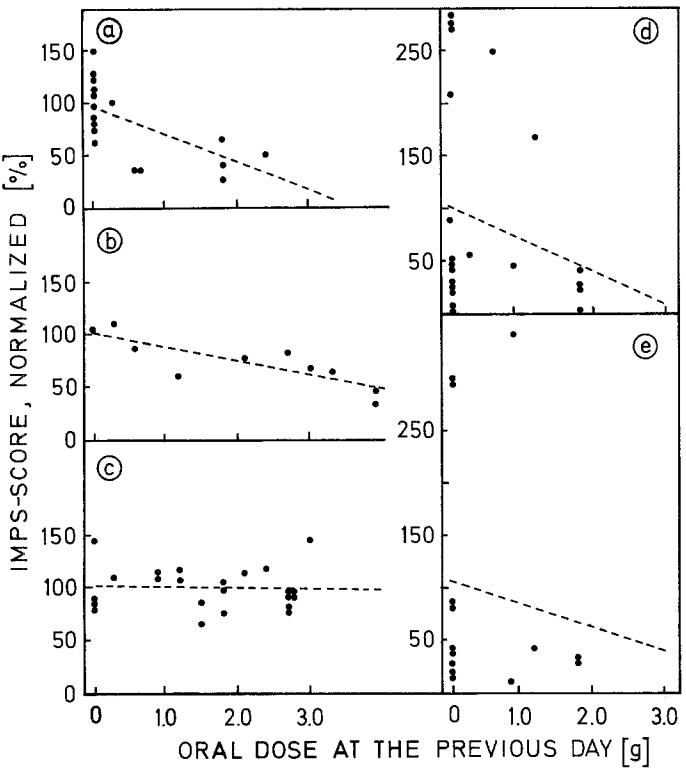

Fig. 4. Psychopathological data (IMPS-scores EXC, HOS, GRN, MTR, CNP; mean values at dosage = 0 (placebo phases) normalized to 100%) as a function of the oral dose of valproate received on the previous day. **a:** case 3; **b:** case 2; **c:** case 5; **d:** case 1; **e:** case 4

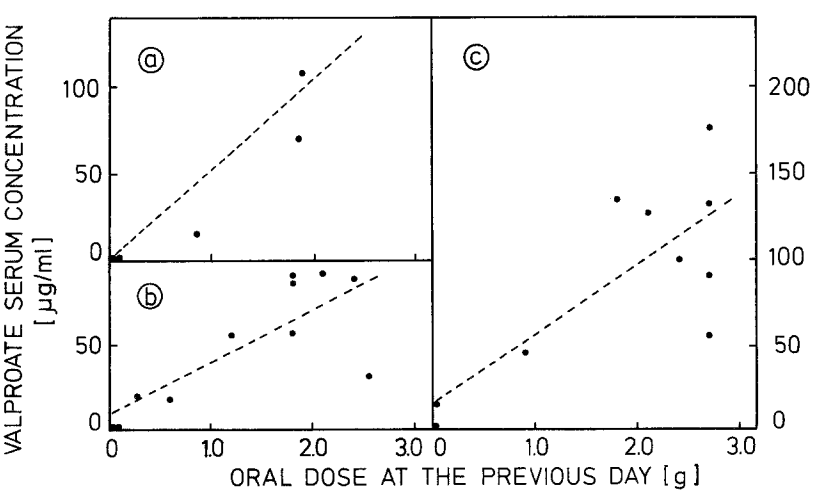

Fig. 5. Valproate serum concentrations (7:15 a.m.) as a function of the oral dose given on the previous day in three patients of the study. **a:** case 1; **b:** case 3; **c:** case 5

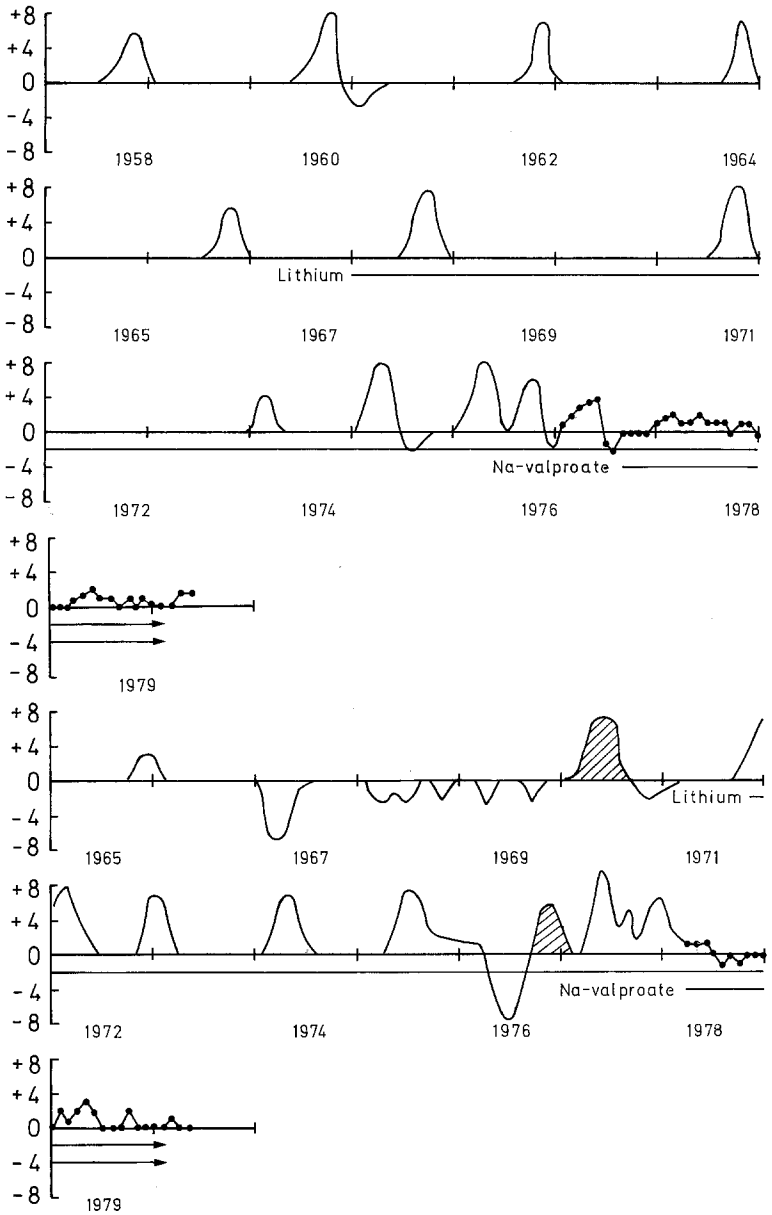

Fig. 6. Time-course of the affective state of two patients under prophylactic long-term medication with valproate in combination with low doses of lithium, as represented by use of the VBS. *Upper part:* patient S.W., *lower part:* patient S.A. Cross-hatched areas represent admixture of schizophrenic symptoms

Serum Concentration. Serum levels of valproate were measured during the different treatment periods (valproate-/placebo-phase) in three of our acute trials. Fig. 5 shows the serum levels at 7:15, 13 h after the last medication, as a function of the oral dose of the previous day. A serum concentration of 50–100 µg/ml was

obtained in all cases after administration of a dosage of 2.0 g/d. Spearman's rank-correlation coefficients are: $r = 0.93$ in patient no. 1, $r = 0.79$ in patient no. 3 and $r = 0.77$ in patient no. 5.

Side Effects. The presence of abdominal pain was reported during the initial phase of valproate medication in one case. No other adverse reactions or symptoms were observed. Laboratory data appeared normal after valproate treatment.

Prophylactic Treatment. Five of the seven patients included in this study have been treated at present over a period of more than $1\frac{1}{2}$ years, whereas two patients (S.W., S.A.) have been treated for 2 and 3 years, respectively. The clinical course of these two patients is shown in Fig. 6. In none of these patients was it necessary to withdraw the drug or to reduce dosage owing to side effects of the medication.

A careful anamnestic examination of the patients and a comparison with the different hospital reports allowed for the retrospective documentation of the course of the disease by use of an eight degrees rating scale (VBS) for mania (upwards in Fig. 6) and for depression (downwards in Fig. 6). Further evaluation was performed by rating the state of the patient monthly in the same fashion (dots in Fig. 6). Case S.W., a 46-year-old actor suffers from a bipolar affective psychosis (ICD 296.3) with preponderance of manic phases. He has already experienced twelve manic episodes all of which necessitated hospitalization. At the beginning of 1968, lithium therapy was started which apparently, for a period of several years, decreased the frequency of manic phases. However, since 1974, within four years, five manic phases occurred and severely disturbed his professional life, which would have resulted in the loss of all his engagements. It was then that the combined therapy with lithium and valproate was begun. This treatment appears to be still effective.

The other patient (case S.A.), a 32-year-old actor, suffers from a schizoaffective psychosis (ICD 295.7). The episodes with prominent schizophrenic symtoms are represented by cross-hatched areas in Fig. 6. Lithium therapy was started at the end of 1971 and was apparently ineffective. During his illness the patient has been hospitalized eleven times. He was severely ill for practically all of 1976/77 and was treated four times as an inpatient with neuroleptic therapy. In the beginning of 1978 he insisted on being treated in the same way, as his friend, case S.W. Since this time he has suffered from one subdepressive and a hypomanic episode, the intensity of which, however, was low. Subjectively, he has experienced the therapy as a great advance in his treatment.

The other five patients have not, as yet, relapsed. The dosage for chronic treatment ranges from 800–1800 mg/d (serum levels: 48–102 µg/ml). In one case some hair-loss occurred and in another there were slight abdominal cramps. No other adverse reactions or side effects have been observed, particularly no pathological liver tests.

Discussion

The introduction of the long-term administration of lithium in the treatment of affective disorders represented tremendous progress, since it constituted the first

type of effective prophylactic medication in pharmacopsychiatry. Nonetheless, lithium prophylaxis is complicated by a large number of uncomfortable side effects (tremor, struma, diabetes insipidus, weight gain, etc.), recently added to by the finding of non-reversible toxic effects on the kidney (cf. Cooper et al. 1979). Furthermore, in addition to the low safety margin of lithium there exists a sizable percentage of lithium non-responders and one anticipates that the lower lithium blood levels which must be recommended in view of effects on kidney function will increase the size of this group. Therefore—besides the inherent interest in the pathomechanistic basis of new attempts in the prophylaxis of affective disorders—the aim of a development of a complementary treatment is of importance for therapeutic reasons.

Treatment of manic syndromes with propranolol (Rackensperger et al. 1976; v. Zerssen 1976; Emrich et al. 1979; Möller et al. 1979) appears to be more specific than the use of the sedating neuroleptic therapy, at least with respect to the affective component of the spectrum of symptomatology including, e.g., grandious delusions, flight of ideas with loosening of associations, etc. However, the dosages necessary for an antimanic action of propranolol are too high to justify its use as a routine treatment. Anticonvulsants apparently represent a group of drugs it may be profitable to introduce into the routine therapy of affective disorders, as has been shown in the present study for valproate and earlier for carbamazepine (Okuma et al. 1973, 1979; Bunney pers. comm.) and DPH (Kubanek and Rowell 1946). The therapeutic efficacy of these treatments presumably should be attributed to a direct or indirect GABA-mimetic effect of these substances, an assumption which has been experimentally supported in the cases of DPH (Deisz and Lux 1977), valproate and carbamazepine (Bernasconi and Martin 1979).

The present study suggests that valproate—at least as an 'adjuvans'—can be used therapeutically in combination with low doses of lithium salts in prophylaxis of affective disorders. As to whether valproate can be used, alone, is, as yet, undetermined and should be the subject of future studies.

The pharmacological and biochemical basis underlying the hypothesis of a possible antimanic action of valproate and of other GABA-ergic substances has recently been added to by the studies of Mandel and his group of the molecular basis of certain models of aggressive behavior (Mandel et al. 1979; cf. also Delini-Stula and Vassout 1978). These authors showed that the GABA-contents of the olfactory bulbs were lower in killer—compared with normal rats and that an experimental increase in these GABA concentrations (by diaminobutyric acid or muscimol) inhibited killing behavior, whereas application of a GABA antagonist (picrotoxine) or an inhibitor of glutamate decarboxylase (allylglycine) induced killing behavior. It was further demonstrated that intraperitoneal injections of valproate strongly inhibited spontaneous mouse killing behavior. Since the manic syndrome is not simply confined to the presence of euphoric and elated behavior, but frequently contains elements of dysphoria and aggression, a possible antimanic therapeutic value of GABA-mimetic substances—and especially of valproate—is also suggested by these experiments.

The results obtained in the present investigation are in line with the previous findings of Lambert et al. (1966, 1968, 1971, 1975) as to the therapeutic and

prophylactic properties of dipropylacetamide. This substance is rapidly metabolized to valproic acid and, for this reason, presumably, exerts similar effects.

The finding that in lithium non-responders an apparently effective prophylaxis can be attained by use of a combination of lithium and valproate raises the question as to a possible synergistic mode of action of these two substances. It may be hypothesized that the efficacy of lithium in manic depressive disorders is due to an activation of GABA-systems. The findings that chronic lithium administration activates GABA-systems in the corpus striatum and hypothalamus (Bernasconi, personal communication; Maggi and Enna 1980) are supportative of this contention.

Lithium exerts a great variety of neurobiological effects (cf. Johnson 1980), such that it is extremely difficult to determine which particular action is responsible for its therapeutic potency in manic depression. Aldenhoff and Lux (1979) observed an increase in levels of intracellular calcium in helix pomatia neurones upon lithium application. The possible relevance of these findings to GABA-systems remains in need of evaluation.

The investigation into the possible antimanic properties of propranolol (cf. v. Zerssen 1976) has its historical origin in the discovery by Atsmon and Blum (1970) that high dosage treatment with propranolol is effective in porphyria. This observation, subsequently replicated in our institute (Schwarz and Mertin 1973) suggested the performance of studies concerning its possible antipsychotic effects in schizophrenic patients (Atsmon et al. 1972). Our group was unable, however, to establish the existence of such an effect (Rackensperger et al. 1974), whereas in schizoaffective patients the manic component of the psychopathology could be improved by application of propranolol, this being the starting point for an investigation of its efficacy in manic patients (cf. v. Zerssen 1976). However, since treatment with d-propranolol is also successful in mania (Emrich et al. 1979; Möller et al. 1979)—this action being possibly due to an indirect GABA-ergic mode of action (Bernasconi, personal communication)—the original finding that propranolol is effective in treatment of porphyria may be seen in another light:

Brennan and Cantrill (1979) recently demonstrated that Δ-aminolaevulinic acid, a substance, the levels of which are elevated in the plasma of patients suffering from porphyria, is an inhibitor of potassium-induced GABA release in rat brain synaptosomes. It is speculated (Brennan 1980) that some of the clinical features of porphyria (e.g., epileptic seizures) may be due to a Δ-aminolaevulinic acid-induced central deficiency in GABA. This hypothesis coincides with our concept of an indirect GABA-ergic action of high doses of propranolol (Emrich et al. 1979; Bernasconi, personal communication) and it may be concluded that valproate should also be an effective therapy in porphyria.

Valproate, furthermore, has recently been shown to be efficacious in the therapy of delirium tremens (Brassuer 1978; Hillbom 1975) and one is also tempted to speculate as to its mode of action in this respect. Since ethanol has been demonstrated to exert indirect GABA-ergic effects (Supavilai and Karobath 1980) one may speculate that the symptomatology—e.g., the seizures of ethanol-withdrawal—can be conceived of as—at least partially—the manifestation of a

state of GABA-deficiency. Thus, the potency of valproate could be regarded in terms of a compensation for this withdrawal-induced GABA-deficiency.

In general, one might speculate that in organic types of psychoses, particularly in those which are mainly characterized by excitation, aggression and epileptic seizures, a central defect in the functioning of GABA may be involved and that substances which act directly or indirectly in a GABA-ergic fashion might represent valuable therapeutic agents in these psychotic states.

The presently made observation of a high correlation between oral dose and valproate serum concentration is in line with pharmacokinetic observations of Klotz (1977), who in a group of 13 patients observed a significant correlation ($r = 0.88$).

In our study the subjective and medical side effects of valproate were practically negligible. On the other hand there are several recent reports concerning hepatotoxic effects of valproate (e.g., Willmore et al. 1978; Gerber et al. 1979; Suchy et al. 1979). Thus, a generalized use of valproate in pharmacopsychiatry cannot be justified: the indication must be restricted to patients displaying severe bipolar affective disorders and/or schizoaffective psychoses or patients with unipolar mania—not responding adequatly to lithium therapy. Liver function must be carefully and routinely controlled. On the other hand, if these precautions are adhered to rigorously, this treatment may be strikingly beneficial to our patients and should serve as a stimulus for further research and progress in the pharmacotherapy of affective disorders with valproate or similar substances.

Acknowledgements. For the kind supply of valproate thankful appreciation is given to Dr. F. Hahn, Labaz GmbH, Düsseldorf. Furthermore, we wish to thank Miss A. Wendl and the nurses of our wards for excellent technical assistance.

References

Aldenhoff JB, Lux HD (1979) The influence of lithiumchlorid on ionic conductance of a bursting pacemaker neuron of helix pomatia. Pflügers Arch ges Physiol 379:R117

Anlezark G, Horton RW, Meldrum BS, Sawaya MCB (1976) Anticonvulsant action of ethanolamine-O-sulphate and di-n-propylacetate and the metabolism of γ-aminobutyric acid (GABA) in mice with audiogenic seizures. Biochem. Pharmacol. 25:414–417

Atsmon A, Blum J (1970) Treatment of acute porphyria variegata with propranolol. Lancet I, 196–197

Atsmon A, Blum J, Steiner M, Latz A, Wijsenbeek H (1972) Further studies with propranolol in psychotic patients. Psychopharmacologia 27:249–254

Beckmann H, Frische M, Rüther E, Zimmer R (1977) Baclofen (para-chlorphenyl-GABA) in schizophrenia. Pharmakopsychiat 10:26–31

Beckmann H, Haas S (1980, in press) High dose diazepam in schizophrenia. Psychopharmacology

Bernasconi R, Martin P (1979) Effects of antiepileptic drugs on the GABA turnover rate. Arch Pharmacol 307:251

Brassuer R (1978) Depakine bei der Behandlung des chronischen Alkoholismus. Therapiewoche 28:9981–9984

Brennan MJW (1980, in press) GABA autoreceptors: structure-activity relationship for agonists. In: Di Chiara G (ed) GABA and benzodiazepines receptors and glutamate as a neurotransmitter. Raven Press, New York

Brennan MJW, Cantrill RC (1979) The effect of delta-aminolaevulinic acid on the uptake and efflux of [^{3}H]GABA in rat brain synaptosomes. J Neurochem 32:1781–1786
Cooper TB, Gershon S, Kline NS, Schou M (eds) (1979) Lithium. Controversis and unresolved issues. Excerpta Medica, Amsterdam Oxford Princeton
Costa E, Guidotti A, Mao CC, Suria A (1975) New concepts on the mechanism of action of benzodiazepines. Life Sci 17:167–186
Curtis DR, Game CJA, Johnston GAR, McCulloch RM (1974) Central effects of beta (p-chlorophenyl) aminobutyric acid. Brain Res 70:493–499
Davies J, Watkins JC (1974) The action of beta-phenyl-GABA derivatives on neurones of the cat cerebral cortex. Brain Res 70:501–505
Deisz RA, Lux HD (1977) Diphenylhydantoin prolongs postsynaptic inhibition and iontophoretic GABA action in the crayfish stretch receptor. Neurosci Lett 5:199–203
Delini-Stula A, Meier M (1976) Inhibitory effects of propranolol and oxprenolol on excitation induced by a MAO inhibitor and reserpine in the mouse. Neuropharmacology 15:383–388
Delini-Stula A, Vassout A (1978) Modulatory effects of baclofen muscimol and GABA on interspecific aggressive behaviour in the rat. Neuropharmacology 17:1063–1065
Emrich HM, Cording C, Pirée S, Kölling A, v Zerssen D, Herz A (1977) Indication of an antipsychotic action of the opiate antagonist naloxone. Pharmakopsychiat 10:265–270
Emrich HM, v Zerssen D, Möller, H-J, Kissling W, Cording C, Schietsch HJ, Riedel E (1979) Action of propranolol in mania: comparison of effects of the d- and the l-stereoisomer. Pharmakopsychiat 12:295–304
Faigle JW, Keberle H (1972) Metabolismus und Pharmakokinetik von Lioresal. In: Birkmayer W (Hrsg) Aspekte der Muskelspastik. Huber, Bern Stuttgart Wien, S 94–100
Frederiksen PK (1975) Baclofen in the treatment of schizophrenia. Lancet I, 702
Gerber N, Dickinson RG, Harland RC, Lynn RK, Houghton D, Antonias JI, Schimschock JC (1979) Reye-like syndrome associated with valproic acid therapy. J Pediatr 95:142–144
Gündürewa M, Beckmann H, Zimmer R, Rüther E (1980, in press) Wirkung von Valproinsäure auf schizophrene Symptome. Arzneim-Forsch/Drug Res
Harvey PKP, Brandford HF, Davison AN (1975) The inhibitory effect of sodium n-dipropylacetate on the degradative enzymes of the GABA shunt. FEBS Letters 52:251–254
Hillbom ME (1975) The prevention of ethanol withdrawal in rats by dipropylacetat. Neuropharmacology 14:755–761
Johnson FN (ed) (1980) Handbook of lithium therapy. MTP Press, Lancaster
Kammen DP van (1977) γ-Aminobutyric acid (Gaba) and the dopamine hypothesis of schizophrenia. Am J Psychiatr 134:138–143
Kelly J, Alheid GF, Newberg A, Grossmann SP (1977) GABA stimulation and blockade in the hypothalamus and midbrain: effects on feeding and locomotor activity. Pharmacol Biochem Behav 7:537–541
Klotz U (1977) Pharmacokinetic studies with valproic acid in man. Arzneim-Forsch/Drug Res 27:1085–1088
Köhler G-K (1975) Epileptische Psychosen — Klassifikationsversuche und EEG-Verlaufsbeobachtungen. Fortschr Neurol Psychiat 3:99
Krogsgaard-Larsen P, Scheel-Krüger J, Kofod H (eds) (1979) GABA-neurotransmitters. Munksgaard, Copenhagen
Kubanek JL, Rowell RC (1946) The use of dilantin in the treatment of psychotic patients unresponsive to other treatment. Dis Nerv Syst 7:1–4
Lambert P-A, Borselli S, Midenet J, Baudrand C, Marcou G, Bouchardy M (1968) L'action favorable du Dépamide sur l'évolution à long terme des psychoses maniaco-depressives. Compte rendu du Congrès de Psychiatrie et de Neurologie de langue française, 66 session, Clermont-Ferrand, 16–21 septembre 1968, pp 489–493
Lambert P-A, Borselli S, Marcou G, Bouchardy M, Cabrol C (1971) Action thymo-régulatrice à long terme du Dépamide dans la psychose maniaco-dépressive. Ann Med Psychol (Paris) 2:442–447
Lambert P-A, Carraz G, Borselli S, Carrel S (1966) Action neuro-psychotrope d'un nouvel antiépileptique: le Dépamide. Ann Med Psychol (Paris) 1:707–710
Lambert P-A, Carraz G, Borselli S, Bouchardy M (1975) Le dipropylacétamide dans le traitement de la psychose maniaco-dépressive. L'Encéphale I:25–31

Lorr M, Klett CJ, McNair DM, Lasky JJ (1962) Inpatient multidimensional psychiatric scale. Consulting Psychologists Press, Palo Alto/California

Löscher W, Esenwein H (1978) Gaschromatographischer Nachweis von Valproat. Arzneim-Forsch/Drug Res 28:782–785

Maggi A, Enna SJ (1980) Regional alterations in rat brain neurotransmitter systems following chronic lithium treatment. J Neurochem 34:888–892

Mandel P, Mack G, Kempf E (1979) Molecular basis of some models of aggressive behavior. In: Sandler M (ed) Psychopharmacology of aggression. Raven Press, New York, pp 95–110

Möller H-J, Zerssen D v, Emrich HM, Kissling W, Cording C, Schietsch HJ, Riedel E (1979) Action of d-propranolol in manic psychoses. Arch Psychiat Nervenkr 227:301–317

Murphy DL, Beigel A, Weinbartner H, Bunney WE (1974) The quantitation of manic behavior. In: Pichot P (ed) Psychological measurements in psychopharmacology. Karger, Basel, pp 203–220

Nicoll R (1978) Selective actions of barbiturates on synaptic transmission. In: Lipton MA, DiMascio A, Killam KF (eds) Psychopharmacology: A generation of progress. Raven Press, New York, pp 1337–1348

Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, Mori A, Watanabe M (1979) Comparison of the antimanic efficacy of carbamazepine and chlorpromazine: a double-blind controlled study. Psychopharmacology 66:211–217

Okuma T, Kishimoto A, Inone K (1973) Antimanic and prophylactic effects of carbamazepine (Tegretol) on manic depressive psychoses. A preliminary report. Folia Psychiat Neurol Jpn 27:283–297

Pinder RM, Brogden RN, Speight TM, Avery GS (1977) Sodium valproate: a review of its pharmacological properties and therapeutic efficacy in epilepsy. Drugs 13:81–123

Rackensperger W, Fritsch W, Schwarz D, Stutte KH, Zerssen D v (1976) Wirkung des Beta-Rezeptoren-Blockers Propranolol auf Manien. Arch Psychiat Nervenkr 222:223–243

Rackensperger W, Gaupp R, Mattke DJ, Schwarz D, Stutte KH (1974) Behandlung von akuten schizophrenen Psychosen mit Beta-Rezeptoren-Blockern. Arch Psychiat Nervenkr 219: 29–36

Roberts E (1972) An hypothesis suggesting that there is a defect in the GABA system in schizophrenia. Neurosci Res Prog Bull 10:468–482

Schwarz D, Mertin J (1973) Die Anwendung von Propranolol bei der akuten intermittierenden Porphyrie. Nervenarzt 44:648–651

Stevens J, Wilson K, Foote W (1974) GABA blockade, dopamide and schizophrenia: experimental studies in the cat. Psychopharmacologia (Berl) 39:105–119

Suchy FJ, Balistreri WF, Buchino JJ, Sondheimer JM, Bates SR, Kearns GL, Stull JD, Bove KE (1979) Acute hepatic failure associated with the use of sodium valproate. N Engl J Med 300: 962–966

Supavilai P, Karobath M (1980) Ethanol and other CNS depressants decrease GABA-synthesis in mouse cerebral cortex and cerebellum in vivo. Life Sci 27:1035–1040

Tapia R (1974) The role of γ-aminobutyric acid metabolism in the regulation of central excitability. In: Myers RD, Drucker-Colin RR (eds) Neurohumoral coding of brain function. Plenum Press, New York London, pp 3–26

Vassout A, Delini-Stula A (1977) Effects de β-bloquers (propranolol et oxprénolol) et du diazépam sur différents modéles d'agressivité chez le rat. J Pharmacol (Paris) 8:5–14

Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ (1978) Effect of valproic acid on hepatic function. Neurology 28:961–964

Wu J-Y, Roberts E (1974) Properties of brain L-glutamate decarboxylase: inhibition studies. J Neurochem 23:759–767

Zerssen D v (1976) Beta-adrenergic blocking agents in the treatment of psychoses. A report on 17 cases. In: Carlsson C, Engel J, Hansson L (eds) Neuro-psychiatric effects of adrenergic beta-receptor blocking agents. Urban & Schwarzenberg, München Berlin Wien, pp 105–114

Zerssen D v, Cording C (1978) The measurement of change in endogenous affective disorders. Arch Psychiat Nervenkr 226:95–112

Received August 6, 1980