Drugs 42 (5): 721-729, 1991
0012-6667/91/0011-0721/$04.50/0

DRU1

Do Calcium Antagonists Have a Place in the Treatment of Mood Disorders?

Cyril Höschl
Department of Psychiatry, 3rd School of Medicine, Charles University, Prague, and Psychiatric Center, Prague, Czechoslovakia

Calcium antagonists (also called calcium channel blockers due to their mechanism of action) are a chemically heterogeneous group of compounds (fig. 1, table I). They have been used primarily in the treatment of cardiac tachyarrhythmias, angina and hypertension. Fleckenstein (1971) was the first to suggest that they antagonise calcium in a dose-proportional manner. Intracellular signal pathways were subsequently described, and central binding sites for calcium antagonists were identified as pharmacologically relevant receptors (Snyder & Reynolds 1985). The bulk of the evidence suggests that at least 3 classes of receptors for calcium antagonists exist: one for nitrendipine-like drugs (DHP-receptors, as nitrendipine is a dihydropyridine), one for verapamil-like drugs, and possibly one for diltiazem. All of these receptors influence each other and are associated with the voltage-dependent calcium channels. A peptide endogenous ligand for DHP-receptors was discovered recently (Callewaert et al. 1989). Receptors for calcium antagonists largely employ phosphoinositides as second messengers.

1. Effects of Calcium Antagonists and Their Action in Neuropsychiatric Disorders

There are several reasons for studying the effects of calcium antagonists in neuropsychiatric disorders: calcium cellular homeostasis plays a key role both in neural metabolism and in signal processing (for review, see Abdel-Latif 1986). In neurons at rest, the intracellular concentration of free calcium ions at about 0.1 μmol/L is more than 4 orders of magnitude lower than the extracellular free calcium concentration. This gradient seems to be essential for maintaining cell integrity. The intracellular free calcium ions are kept below critical levels by active transport out of the cell or into intracellular storage sites, by inactivation of calcium influx channels, and by complexing of calcium ions with intracellular calcium-binding proteins such as calmodulin. There are 2 main types of Ca^{++} influx channels: voltage-sensitive (potential-operated) and receptor-operated (for example, nicotinic or excitatory amino acid *N*-methyl-*D*-aspartate). Calcium antagonists influence intracellular calcium homeostasis by blocking calcium influx through potential-operated, slow calcium channels (Miller 1987). Consequently, they inhibit potential-dependent processes such as smooth muscle contraction (and therefore vasconstriction), synthesis and release of neurotransmitters (Turner & Goldin 1985), neural signal propagation, and even hormone secretion. High concentrations of calcium antagonists can act as competitive antagonists on α-adrenergic receptors (Triggle 1982). Verapamil and several other calcium channel-associated drugs enhance the decline of dopamine present in intraneural vesicles (Bagchi 1990). By preventing a critical increase of intracellular calcium, calcium ant-

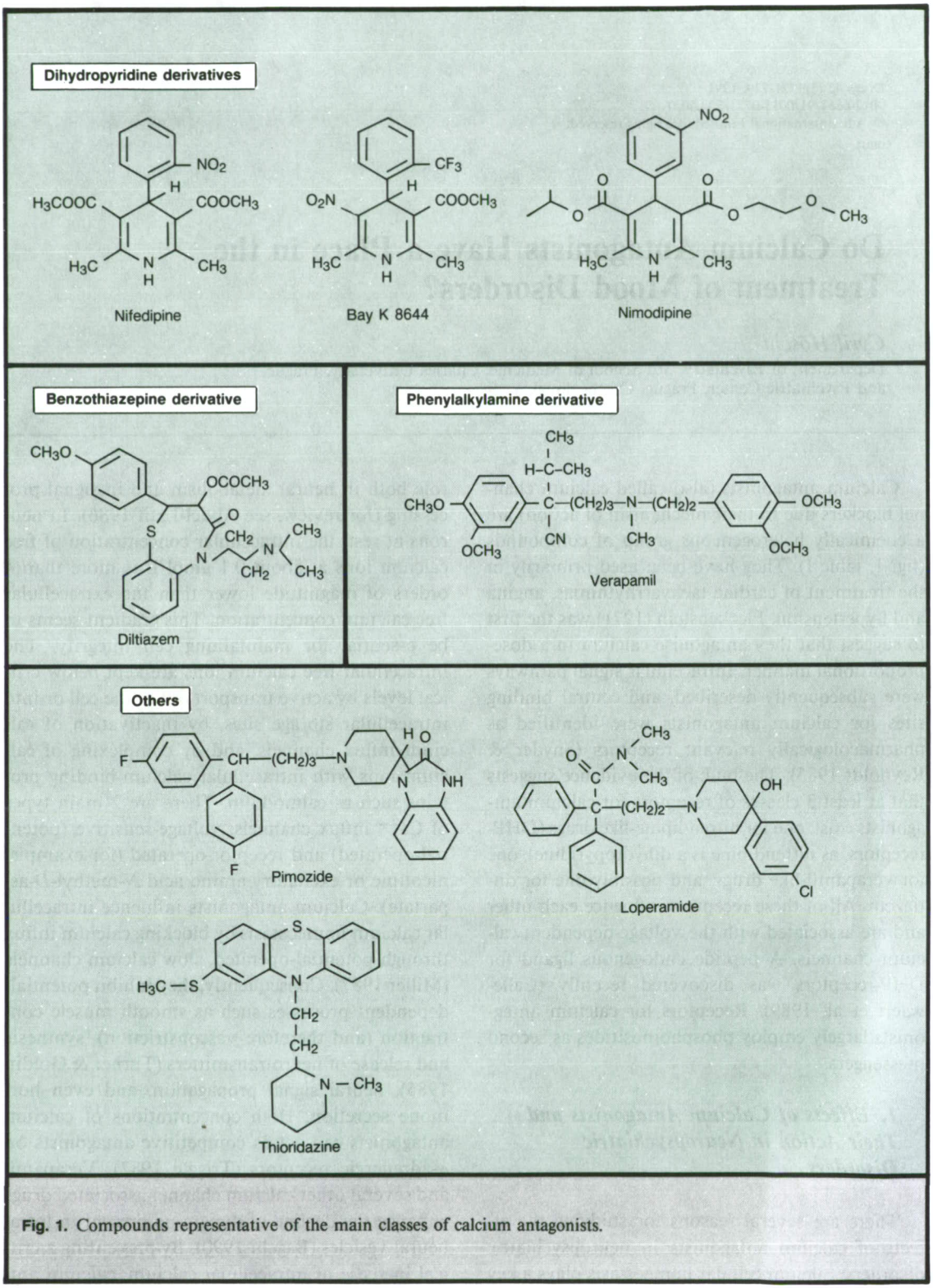

Fig. 1. Compounds representative of the main classes of calcium antagonists.

agonists protect the cell from the damage caused by a huge calcium influx during hypoxia (Higushi & Takenaka 1978).

The mode of action of calcium antagonists suggests their potential clinical use: in arrhythmias (inhibiting the pacemaker), in hypertension and migraine (vasodilation), in ischaemia (cell protection), in functional diarrhoea (smooth muscle relaxation) and in neuropschyiatric illnesses, e.g. affective disorders, where calcium intracellular concentration may be elevated in mania and strikingly so in a particular subgroup of depression cases (Dubovsky & Franks 1983). Calcium antagonists may also have a protective function in the brain. It has been suggested that new nootropic drugs could be designed based on their calcium antagonist activity. Flunarizine is a calcium antagonist, though its mode of action differs from that of other calcium antagonists mentioned above. Differences in their chemical structure, pharmacodynamics (different affinity to various populations of receptors) and pharmaockinetics lead to diversity in the therapeutic actions of these drugs. For example, although calcium antagonists are all to some extent efficacious in the treatment of hypertension, diltiazem and verapamil are superior in the regulation of the heart rhythm. Nimodipine, in contrast to nifedipine, which is in the same class, acts more selectively on cerebral vessels.

2. CSF Distribution of Calcium Antagonists

The crucial question for psychoactive drugs is their availability in the brain, which does not always correlate with their lipophilia. For example, gastrointestinal absorption of verapamil is considered both rapid and complete (90%), but its availability is low and highly variable (Doran et al. 1985; Dunn & Groth 1985; Keefe et al. 1981; McGowan et al. 1983; McTavish & Sorkin 1989; Narang et al. 1988). In contrast to healthy subjects, Narang et al. (1988) reported less variable absorption in schizophrenic patients. Steady-state CSF and plasma concentrations of verapamil, norverapamil and D-620 were measured in 7 patients with schizophrenia after 3 to 5 weeks of dosing. Simultaneous sampling of CSF and plasma just before the dose during the week 4 of the trial showed that verapamil, norverapamil and D-620 partition in the CSF reflected 7, 5 and 12%, respectively, of the cor-

Table I. Main classes of calcium antagonists

Class	Drugs	Comment
Dihydropyridines	Nifedipine, nitrendipine, nimodipine, nicardipine, riodipine, nisoldipine, niludipine, felodipine, isradipine, darodipine, amlodipine	
Diphenylalkylamines	Verapamil, tiapamil, anipamil[a], gallopamil (methoxy verapamil), desmethoxy verapamil	
Benzothiazepines	Diltiazem	
Others	Pimozide	Neuroleptic (diphenylbutylpiperidine)
	Cinnarizine	Nootropic, vasodilator
	Flunarizine	-
	Lidoflasine	Coronary vasodilator
	Loperamide	Opiate agonist
	Thioridazine	Neuroleptic (phenothiazine)

a First introduced long-acting calcium antagonist.

responding levels in plasma. There was a high correlation between plasma and CSF levels of verapamil (r = 0.85) and norverapamil (r = 0.74). The mean unbound fraction of verapamil was significantly lower in schizophrenic patients than in healthy subjects. This might be explained by an increase in the systemic pool concentration of albumin or α_1-acid glycoprotein in the patients.

Circumstantial evidence for the distribution of calcium antagonists in the brain is given also by EEG changes after oral or intravenous administration. Gilmore et al. (1985) found shortened latencies of peaks III and V during intravenous infusions of verapamil in multiple sclerosis patients with abnormally prolonged brainstem auditory-evoked potentials. However, our group did not observe any marked EEG changes in healthy volunteers after oral verapamil administration (David et al., unpublished study).

The administration of calcium antagonists is safe and well tolerated. Nausea, vertigo, headache, dry mouth, sweating and obstipation are the main adverse effects observed if high doses are used. Other observed adverse effects are not significantly more frequent than for placebo (for nimodipine see Dycka et al. 1984). Calcium antagonists are contraindicated in recent heart stroke and in atrioventricular block. Exceptionally we have observed extrapyramidal side effects, similar to neuroleptic-induced Parkinsonism, after verapamil administration. Marti Massó et al. (1987) reported an aggravation of Parkinson's disease by cinnarizine, and quote in their discussion Pileblad and Carlsson's (1986) finding of reduced release and synthesis of striatal dopamine in mice administered nimodipine, perhaps through calcium-dependent activation of tyroxine hydroxylase.

Adverse interactions between verapamil and lithium were observed, including higher lithium toxicity in combination with verapamil (Dubovsky et al. 1987; Price & Giannini 1986b, 1987). Verapamil may also potentiate carbamazepine neurotoxicity (MacPhee et al. 1986). Flunarizine has been suspected to cause Parkinsonism, tardive dyskinesia, akathisia and depression (Chouza et al. 1986; Nappi 1986).

3. Rationale for the Administration of Calcium Antagonists in Neuropsychiatric Disorders

Various drugs with calcium antagonist effects also possess psychotropic properties: calcitonin (Carman & Wyatt 1979), neuroleptics, lithium (Cade 1949; Schou 1968) and verapamil (Dose & Emrich 1986; Dubovsky et al. 1982, 1986; Giannini et al. 1984; Höschl et al. 1986). All have antimanic effects. Unlike most neuroleptics, phenylbutylpiperidines have a favourable effect on negative symptoms of schizophrenia, e.g. social withdrawal. They differ from other neuroleptics by blocking a calcium channel, but they also display the anticalmodulin and antidopaminergic activity common to neuroleptics (see Snyder & Reynolds 1985). Thus 'neuroleptic-like' features of some calcium antagonists could explain the beneficial effect of verapamil and diltiazem on tardive dyskinesia (Barrows & Childs 1986; Buck & Havey 1988; Reiter et al. 1989; Ross et al. 1987). Conversely, 'calcium (calmodulin)-antagonistic' features of neuroleptics may account for some of their peripheral side effects, such as the loss of ejaculation after thioridazine (Snyder & Reynolds 1985). We can hypothesise that calcium antagonists, either endogenous (calcitonin) or exogenous (neuroleptics, lithium, carbamazepine, verapamil), may influence the psychopathology of affective disorders. In its short history, the use of verapamil in psychiatry strongly resembles that of lithium salts: both lithium and verapamil were first used in internal medicine; both were shown to ameliorate agitation and mania (Cade 1949; Dubovsky et al. 1982); neither lithium nor verapamil has sedative, hypnotic, or cataleptic effects; both block potential-dependent calcium channels; and both have some effects on the endocrine system, i.e. they antagonise vasopressin and thyroid functions, interfere with insulin, etc. (Meltzer 1986). These facts led Dubovsky's and my groups independently to introduce calcium antagonists in psychiatry 10 years ago (Dubovsky et al. 1982; Höschl et al. 1982).

Besides cardiovascular diseases, verapamil has been used in the treatment of mania (Barton & Gi-

tlin 1987; Brotman et al. 1986; Dose & Emrich 1986; Dubovsky et al. 1982, 1985, 1986; Giannini et al. 1984, 1985, 1989; Höschl et al. 1986; Höschl & Kožený 1989; Patterson 1987), depression (Höschl 1982, 1983; Höschl et al. 1986; Höschl & Kožený 1989; Kennedy et al. 1986; Pollack & Rosenbaum 1987), maintenance treatment of manic depressive illness (Giannini et al. 1987; Gitlin & Weiss 1984; Höschl et al. 1990), schizophrenia (Grebb et al. 1986; Pickar et al. 1987; Price et al. 1985a, 1986a,b; Price & Giannini 1986b; Reiter et al. 1989), premenstrual syndrome (Deicken 1988; Price et al. 1985b; Price & Giannini 1986a), stuttering (Brady et al. 1989), migraine (Markley et al. 1984), intoxication with phencyclidine (McCann et al. 1986; Montgomery & Mueller 1985; Price et al. 1986), diarrhoea (see Snyder & Reynolds 1985), asthma (Russi et al. 1983), and Tourette's syndrome (Walsh et al. 1986). Its use has also been suggested in pain, because of its analgesia-potentiating activity in mice (Del Pozo et al. 1987), and in other neurological conditions. Nimodipine has been used first in migraine (Gelmers 1983) and brain ischaemia, both in humans and animals (Dýcka et al. 1984; Gelmers 1987; Pickard et al. 1987), flunarizine in organic brain syndrome (Heinze et al. 1986), migraine (Louis & Spierings 1982; Olesen 1986), and epilepsy (Bussche et al. 1985). Diltiazem (Caillard 1985; Ross et al. 1987), nifedipine (Goldstein 1984) and other calcium antagonists have occasionally been used in similar conditions (Caillard & Massé 1982; Goldstein 1985).

3.1 Verapamil

Verapamil has been the most widely studied calcium-channel blocker in psychiatry. To date, reports on other calcium antagonists in mood disorders are fairly scarce.

Table II evaluates the results of studies on verapamil in mood disorders. Most of the studies are handicapped by the use of concomitant medication, such as neuroleptics, lithium salts, antidepressants and anxiolytics. Since there is also a lack of large double-blind, well-controlled trials, it is very difficult to make any definitive conclusions as to efficacy of verapamil (and therefore of other calcium antagonists) in the mood disorders, although work on verapamil in mood disorders has been recently reviewed (Verapamil in mood disorders: theory and practice. 143rd meeting of the American Psychiatric Association, May 12-17, New York 1990). Giannini (1990) suggested that verapamil was as effective as lithium and superior to both clonidine and valproic acid in the treatment of moderately severe mania. In treating severely manic symptoms, however, it was less effective than clonidine, lithium or carbamazepine. According to Giannini (1990), verapamil's proposed specificity may be a function of its actions on calmodulin. Optimum dosage effects were seen at 80mg orally 3 or 4 times daily (Giannini 1990). Berlant (1990) pointed out that there may exist a subgroup of bipolar depressed patients who do respond to verapamil. He stressed the bipolar-unipolar distinction as being a very important point to consider when designing further clinical trials. The bipolar-unipolar distinction is very important from a biological point of view, as these 2 subgroups of depression may have different hereditary backgrounds different reactivity to various antidepressants, different epidemiology and different prognosis. No study has yet tested the specific antidepressant activity of verapamil. Höschl recommended verapamil for the treatment of manic symptoms (Höschl & Kožený 1989), since its efficacy has been shown to be comparable with lithium salts: 47 manic inpatients gave informed consent and participated in a study lasting 35 days. Six women and 6 men were treated immediately after admission with oral verapamil doses ranging from 120 to 480 mg/day. 23 women and 1 man were treated with neuroleptics, and 8 women and 3 men received a combination of neuroleptics and lithium carbonate. All patients were somatically healthy. One patient in the verapamil group did not finish the study because ECT became necessary. One patient from the neuroleptic group was discharged from hospital. The results indicated that the effect of verapamil seemed to be at least as pronounced as that of standard treatments in reducing manic symptoms.

Table II. Some published reports examining the use of verapamil in the treatment of mood disorders

Type of trial	No. of pts	Dose (mg/day)	Effect	Reference
Mania				
Case report	1	160	Noticeable	Dubovsky et al. (1982)
Open	8	< 240	Worsening (2) None (6)	Barton & Gitlin (1987)
Double-blind crossover	20	< 320	Superior to clonidine	Giannini et al. (1985)
Case reports	2	480 320	None Improved, but died from MI in combination with lithium	Dubovsky et al. (1987)
Case reports	6	< 320	Very good	Brotman et al. (1986)
Double-blind crossover	12	320	Equal to lithium	Giannini et al. (1984)
Open	6	< 480	Good	Höschl et al. (1986)
Double-blind	9	< 480	Fair (7) None (1) Drop-out (1)	Dose & Emrich (1986)
Double-blind, controlled case reports	2	< 480	Good	Dubovsky & Franks (1983)
Crossover, blind?	10	320	Equal to lithium, superior to valproic acid	Giannini et al. (1989)
Double-blind controlled	12	< 480	Equal to lithium	Höschl & Kožený (1989)
Pharmacogenic mania				
Case report	1	400	Fair to good	Dubovsky et al. (1985)
Open	2	< 320	Very good	Barton & Gitlin (1987)
Depression				
Double-blind, placebo-controlled case report	1	320	Good	Höschl (1983)
Case report	1	320	Good	Pollack & Rosenbaum (1987)
Open	23	< 400	Good (9) Slight (6) None (3) Worsening (2) Dropouts (3)	Höschl et al. (1986)
Double-blind controlled	26		Equal to placebo	Höschl & Kožený (1989)
Remission (prophylaxis)				
Open	4	< 320	Mild (2) None (2)	Barton & Gitlin (1987)
Open, controlled	11	< 240	Significantly better than antidepressants, slightly worse than lithium	Höschl et al. (1990)
Premenstrual syndrome				
Case report	1	< 320	Improved	Deicken (1988)
Case report	1	150	Improved	Price & Giannini (1986)

As with lithium, verapamil's efficacy in depression remains questionable. Höschl and Kožený (1989) divided 64 depressed inpatients randomly into 4 subgroups according to their treatment regimen: 31 were treated with verapamil, 21 with amitriptyline and 12 with placebo only. In addition, a fourth group, consisting of 32 patients freely treated according to the judgement of the ward physician ('state adjustment treatment', SAT), was rated and matched to the experimental population. 52 patients suffered from recurrent major depression according to DSM-III, 12 from bipolar depression, the rest from other types of depression. Assessment was performed using a blind, independent rater. The patients' psychopathology was assessed 3 times a week using the HRSD, 3 times during the course of the study using the ZUNG scale, and daily using both the general clinical impression and 100mm analogue self-rating scale. There was no significant difference among the initial total scores of these assessment scales. When displaying the cumulative proportion of improved patients, as defined by the total score of HRSD = 10, by the end of the study 89% patients improved on amitriptyline, 76 to 80% on SAT, 50 to 57% on verapamil and 40% on placebo.

We also evaluated the most important results for the homogeneous subgroup of patients of the same sex and diagnosis, i.e. for women with a diagnosis of major depression. Both the results and the courses of psychopathology were similar to what has been shown above. However, the difference between verapamil and placebo on one hand, and amitriptyline and SAT on the other, was even more pronounced. The proportion of improved patients increased constantly throughout the study for those on amitriptyline and on SAT, finally reaching 91 and 86%, respectively, in contrast to verapamil or placebo groups, which remained constant or even decreased to levels of 31 and 38%, respectively, from the second week of treatment to the end of the study.

Nevertheless, at least 50% of the depressed patients improved on verapamil. Even if we take into account the influence of spontaneous improvement and placebo effect (40% improved on placebo), we can assume there is a small proportion of depressed patients who do respond to verapamil. Comparing the data of the entire group and subgroup of females with major depression, we can hypothesise that responders were usually not patients with major depression. However, the sample of patients was too small to compare the effect of verapamil in unipolar *vs* bipolar patients. In summary, the anticipated antidepressant action of verapamil was not confirmed in our study. However, verapamil does have considerable antimanic efficacy, comparable to traditional treatments (Höschl 1990), similar results of which have been reported by Dubovsky (1990).

4. Recommendations

Among calcium antagonists, the most widely studied drug in the treatment of mood disorders has been verapamil, although nifedipine, nimodipine, diltiazem and flunarizine are also of interest. [For example, when administered to 7 manic patients, diltiazem led in 7 to 14 days to considerable improvement in 5 of them, slight improvement in 1 and worsening in 1 (Caillard 1985)].

Verapamil is contraindicated in patients with recent heart stroke or AV blocks. Care is recommended when it is administered in combination with lithium, cyclosporin or carbamazepine. Headache, obstipation and nausea are frequent but benign side effects of calcium antagonists. Extrapyramidal signs occur occasionally. In general, verapamil is well tolerated and comfortable for patients. The recommended dosage ranges from 160 to 320 mg/day, and exceptionally more (480 mg/day). Both before and during treatment with verapamil, blood pressure and heart rate should be checked daily, and ECG at 1-week intervals to assess tolerance. Routine biochemical screening (liver tests) is also advised before treatment.

Verapamil is the drug of second choice in mania. Its effect is comparable to that of lithium but its mode of action, adverse effects and contraindications are different. Verapamil is not sufficient for monotherapy in acute agitation or aggressive states, where neuroleptics are necessary at the beginning.

In clinical practice, it is possible to start maintenance prophylaxis of manic-depressive illness with verapamil, in spite of the fact that its efficacy has not been convincingly proven. We use it in cases of resistance or contraindication to lithium, if there are no other alternatives.

In other indications, including depression and premenstrual syndrome, verapamil and other calcium antagonists should be given only as an experimental medication at present.

Further studies of various types of calcium antagonists are necessary, particularly the more lipophilic drugs. Their role in protecting central nervous tissue against hypoxia and ischaemia also requires investigation.

As the mechanism of psychotropic action of the calcium antagonists is still unclear, it would be interesting to study compounds and derivatives which have no calcium blocking activity, and see whether they retain their psychotropic activity. This could suggest yet another mechanism of central action of these drugs.

References

Abdel-Latif AA. Calcium-mobilizing receptors, poly-phosphoino-sitides, and the generation of second messengers. Pharmacological Review 38: 227-272, 1986

Bagchi SP. Antidopaminergic action of verapamil and several other drugs: inactivation of vesicular dopamine. Life Sciences 46: 857, 1990

Barrows M, Childs A. An anti-tardive dyskinesia effect of verapamil. Correspondence. American Journal of Psychiatry 143: 1485, 1986

Barton BM, Gitlin MJ. Verapamil in treatment-resistant mania. Journal of Clinical Psychopharmacology 7: 101-103, 1987

Berlant JL. Verapamil in bipolar and unipolar depression. Abstract 35B. CME Syllabus & Proceedings Summary, American Psychiatric Association 143rd Annual Meeting, p. 177, New York, May 12-17, 1990

Brady JP, Price TRP, McAllister TW, Dietrich K. A trial of verapamil in the treatment of stuttering in adults. Biological Psychiatry 25: 626-630, 1989

Brotman AV, Farhadi AM, Gelenberg AJ. Verapamil treatment of acute mania. Journal of Clinical Psychiatry 47: 136-138, 1986

Buck OD, Havey P. Treatment of tardive dyskinesia with verapamil. Journal of Clinical Psychopharmacology 8: 303-304, 1988

Bussche GV, De Beukelaar F, Wauquier A. Calcium entry-blockade and epilepsy. In Godfraind et al. (Eds) Calcium entry blockers and tissue protection, pp. 229-236, Raven Press, New York, 1985

Cade JFJ. Lithium salts in the treatment of psychotic excitement. Medical Journal of Australia 36: 349-352, 1949

Caillard V. Treatment of mania using a calcium antagonist. Preliminary trial. Neuropsychobiology 14: 23-26, 1985

Caillard V, Massé traitement de la manie par un inhibiteur calcique: étude préliminaire. Encéphale 8: 587-594, 1982

Callewaert G, Hanbauer I, Morad M. Modulation of calcium channels in cardiac and neural cells by an endogenous peptide. Science 243: 663-666, 1989

Carman JS, Wyatt RJ. Use of calcitonin in psychotic agitation or mania. Archives of General Psychiatry 36: 72-75, 1979

Chouza C, Caamano JL, Aljanati R, Scaramelli A, De Medina O, et al. Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. Lancet 1: 1303-1304, 1986

Deicken RF. Verapamil treatment of premenstrual syndrome. Biological Psychiatry 24: 689-692, 1988

Del Pozo E, Caro G, Baeyens JM. Analgesic effects of several calcium channel blockers in mice. European Pharmacology 90: 155-160, 1987

Doran AR, Narang PK, Meigs CV, Wolkowitz OM, Roy A, et al. Verapamil concentrations in cerebrospinal fluid after oral administration. New England Journal of Medicine 312: 1261-1262, 1985

Dose M, Emrich HM. Antimanic properties of verapamil. In Shagass C et al. (Eds) Biological psychiatry 1985, pp. 320-322, Elsevier, New York, 1986

Dubovsky SL. Intracellular calcium in affective disorders: evidence in favour of deranged dynamics. In Shagass C et al. (Eds) Biological psychiatry 1985, pp. 317-319, Elsevier, New York, 1986

Dubovsky SL. Intracellular calcium and ion disturbances in affective disorders. Abstract 35D. CME Syllabus & Proceedings Summary, American Psychiatric Association, 143rd Annual Meeting, pp. 177-178, New York, May 12-17, 1990

Dubovsky SL, Franks RD. Intracellular calcium ions in affective disorders: a review and a hypothesis. Biological Psychiatry 18: 781-797, 1983

Dubovsky SL, Franks RD, Allen S. Verapamil: a new antimanic drug with potential interactions with lithium. Journal of Clinical Psychiatry 48: 371-372, 1987

Dubovsky SL, Franks RD, Allen S, Murphy J. Calcium antagonists in mania: A double-blind study of verapamil. Psychiatry Research 18: 309-320, 1986

Dubovsky SL, Franks RD, Lifschitz ML, Coen P. Effectiveness of verapamil in the treatment of a manic patient. American Journal of Psychiatry 139: 502-504, 1982

Dubovsky SL, Franks RD, Schrier D. Phenelzine-induced hypomania: effect of verapamil. Biological Psychiatry 20: 1009-1014, 1985

Dunn JM, Groth PE. Verapamil – a once-daily dosage: pharmacokinetic and pharmacodynamic observation. Research 38: 572-578, 1985

Dycka J, Aufdembrinke B, Rode CP. Efficacy and tolerance of nimodipine in comparison to placebo in 1165 patients with cerebral dysfunction. In Betz E, et al. (Eds) Nimodipine: pharmacological and clinical properties. Proceedings of the 1st International Nimotop^{R} Symposium, pp. 319-328, Munich, February 9-11, 1984

Fleckenstein A. Specific inhibitors and promotors of calcium action in the excitation-contraction coupling of heart muscle and their role in prevention or production of myocardial lesions. In Harris P & Opie L (Eds) Calcium and the heart, pp. 135-188, Academic Press, London, 1971

Gelmers HJ. Nimodipine, a new calcium antagonist in the prophylactic treatment of migraine. Headache 23: 106-109, 1983

Gelmers HJ. Nimodipine in ischemic stroke. Clinical Neuropharmacology 10: 412-422, 1987

Giannini AJ. Verapamil specificity in mania. Abstract 35A. CME Syllabus & Proceedings Summary, American Psychiatric Association 143rd Annual Meeting, p. 177, New York, May 12-17, 1990

Giannini AJ, Houser WL, Loiselle RH, Price WA. Antimanic effects of verapamil. American Journal of Psychiatry 139: 502-504, 1984

Giannini AJ, Loiselle RH, Price WA, Giannini MC. Comparison of antimanic efficacy of clonidine and verapamil. Journal of Clinical Pharmacology 25: 307-308, 1985

Giannini AJ, Sullivan BS, Folts DJ. Comparison of lithium carbonate, valproic acid and verapamil in the treatment of manic symptoms. Abstract 1. Journal of Clinical Pharmacology (Suppl. 29): 832, 1989

Giannini AJ, Taraszewski RS, Loiselle RH. Verapamil and lithium in maintenance therapy of manic patients. Journal of Clinical Pharmacology 27: 980, 1987

Gilmore RL, Kasarskis EJ, McAllister RG. Verapamil induced changes in central conduction in patients with multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry 48: 1140-1146, 1985

Gitlin MJ, Weiss J. Verapamil as maintenance treatment of bipolar illness: a case report. Journal of Clinical Psychopharmacology 4: 341-343, 1984

Goldstein JA. Nifedipine treatment of Tourette's syndrome. Correspondence. Journal of Clinical Psychiatry 45: 360, 1984

Goldstein JA. Calcium channel blockers in the treatment of panic disorder. Journal of Clinical Psychiatry 46: 546, 1985

Grebb JA, Shelton RC, Taylor EH, Bigelow LB. A negative, double-

blind, placebo-controlled, clinical trial of verapamil in chronic schizophrenia. Biological Psychiatry 21: 691-694, 1986
Heinze B, Karrass W, Peters T. Pharmacopsychological effects of flunarizine in geriatric patients with light brainorganic psychosyndrome. European Neurology 25 (Suppl. 1): 115-121, 1986
Higuishi M, Takenaka F. Effects of verapamil on the transmural energy metabolism in the isoproterenol-induced myokardial lesion. Japanese Heart Journal 19: 913-917, 1978
Höschl C. Verapamil for depression? Correspondence. American Journal of Psychiatry 140: 1100, 1983
Höschl C, Blahoš J, Kabeš J. The use of calcium channel blockers in psychiatry. In Shagass C, et al. (Eds) Biological psychiatry 1985, pp. 329-331, Elsevier, New York, 1986
Höschl C, Blahoš J, Taussigová D, Břicháček V, Lukešová J. Má verapamil vliv na psychiku? (in Czech). Československá Psychiatrie 78: 388-391, 1982
Höschl C, Kožený J. Verapamil in affective disorders: a double-blind, controlled study. Biological Psychiatry 25: 128-140, 1989
Höschl C, Kožený J. Verapamil in affective disorders. Abstract 35C. CME Syllabus & Proceedings Summary, American Psychiatric Association 143rd Annual Meeting, p. 177, New York, May 12-17, 1990
Höschl C, Vacková J, Janda B. Mood stabilizing effect of verapamil. Abstract P-11-4-15. 17th C.I.N.P. Congress, p. 95, Kyoto, September 10-14, 1990
Keefe DL, Yee Y-G, Kates RE. Verapamil protein binding in patients and in normal subjects. Clinical Pharmacology and Therapeutics 29: 21-26, 1981
Kennedy S, Ozersky S, Robillard M. Refractory bipolar illness may not respond to verapamil. Correspondence. Journal of Psychopharmacology 6: 316-317, 1986
Louis P, Spierings ELH. Comparison of flunarizine (Sibelium^{R}) and pizotifen (Sandomigran^{R}) in migraine treatment: a double-blind study. Cephalalgia 2: 197-203, 1982
MacPhee GJA, Thompson GG, McInnes GT, Brodie MJ. Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. Lancet 1: 700-703, 1986
Markley HG, Cheronis JCD, Piepho RW. Verapamil in prophylactic therapy of migraine. Neurology 34: 973-976, 1984
Martí Massó JF, Obeso JA, Carrera N, Martinez-Lage JM. Aggravation of Parkinson's disease by cinnarizine. Journal of Neurology, Neurosurgery, and Psychiatry 50: 804-805, 1987
McCann DJ, Smith CM, Winter JC. A caution against use of verapamil in the treatment of phencyclidine intoxication. Correspondence. American Journal of Psychiatry 143: 679, 1986
McGowan FX, Reiter MJ, Pritchett ELC, Shand DG. Verapamil plasma binding: relationship to alpha$_1$-acid glykoprotein and drug efficacy. Clinical Pharmacology and Therapeutics 33: 485-490, 1983
McTavish D, Sorkin EM. Verapamil: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs 38: 19-76, 1989
Meltzer HL. Lithium mechanisms in bipolar illness and altered intracellular calcium functions. Biological Psychiatry 21: 492-510, 1986
Miller RJ. Multiple calcium channels and neuronal function. Science 235: 46-52, 1987
Montgomery PT, Mueller ME. Treatment of PCP intoxication with verapamil. Correspondence. American Journal of Psychiatry 142: 882, 1985
Nappi G. Chronic flunarizine treatment in migraine sufferers and the occurrence of depressive phenomena. Giornale di Neuropsicofarmacologia 8: 5, 1986
Narang PK, Blumhardt CL, Doran AR, Pickar D. Steady-state cerebrospinal fluid transfer of verapamil and metabolites in patients with schizophrenia. Clinical Pharmacology and Therapeutics 44: 550-557, 1988
Olesen J. Role of calcium entry blockers in the prophylaxis of migraine. European Neurology 25 (Suppl. 1): 72-79, 1986
Patterson JF. Treatment of acute mania with verapamil. Correspondence. Journal of Clinical Psychopharmacology 7: 206-207, 1987
Pickar D, Wolkowitz OM, Doran AR, Labarca R, Roy A, et al. Clinical and biochemical effects of verapamil administration to schizophrenic patients. Archives of General Psychiatry 44: 113-118, 1987
Pickard JD, Walker V, Vile J, Perry S, Smythe PJ, et al. Oral nimodipine reduces prostaglandin and tromboxane production by arteries chronically exposed to a periarterial haematoma and the antifybrinolytic agent tranexamic acid. Journal of Neurology, Neurosurgery and Psychiatry 50: 727-731, 1987
Pileblad E, Carlsson A. *In vivo* effects of the Ca^{++} antagonist nimodipine on dopamine metabolism in mouses brain. Journal of Neural Transmission 66: 171-187, 1986
Pollack MH, Rosenbaum JF. Verapamil in the treatment of recurrent unipolar depression. Biological Psychiatry 22: 779-782, 1987
Price WA, Giannini AJ. Verapamil in acute psychosis. Psychosomatics 27: 797, 1986
Price WA, Giannini AJ. Use of verapamil in premenstrual tension syndrome. Journal of Clinical Psychiatry 47: 213, 1986a
Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. Journal of Clinical Pharmacology 26: 717-719, 1986b
Price WA, Giannini AJ. Lithium-verapamil: further considerations. Correspondence. Journal of Clinical Psychiatry 48: 124, 1987
Price WA, Giannini AJ, DiMarzio L. Effectiveness of verapamil in the treatment of premenstrual tension syndrome. Journal of Clinical Pharmacology 25: 455, 1985b
Price WA, Giannini AJ, Krishen A. Management of acute PCP intoxication with verapamil. Clinical Toxicology 24: 85-87, 1986
Price WA, Giannini AJ, Loiselle RH. Verapamil in the treatment of schizophrenia. Abstract. Journal of Clinical Pharmacology 25: 461, 1985a
Price WA, Giannini AJ, Loiselle RH. Treatment of the negative symptoms with verapamil. Abstract. Journal of Clinical Pharmacology 26: 548, 1986a
Price WA, Giannini AT, Pascarzi G. Verapamil as an adjunct in the treatment of chronic schizophrenia. Journal of Clinical Pharmacology 26: 546, 1986b
Reiter S, Adler L, Angrist B, Peselow E, Rotrosen J. Effects of verapamil on tardive dyskinesia and psychoses in schizophrenia patients. Journal of Clinical Psychiatry 50: 26-27, 1989
Ross J, Mackenzie T, Hanson D, et al. Diltiazem for tardive dyskinesia. Correspondence. Lancet 1: 268, 1987
Russi EW, Marchette B, Yerger L, Abraham WM, Ahmed T. Modification of allergic bronchoconstriction by a calcium antagonist: mode of action. American Review of Respiratory Diseases 127: 675-679, 1983
Schou M. Lithium in psychiatric therapy and prophylaxis. Journal of Psychiatric Research 6: 67-95, 1968
Snyder SH, Reynolds IJ. Calcium-antagonist drugs: receptor interactions that clarify therapeutic effects. New England Journal of Medicine 313: 995-1002, 1985
Solomon L, Williamson P. Verapamil in bipolar illness. Canadian Journal of Psychiatry 31: 442-444, 1986
Triggle DJ. Biochemical pharmacology of calcium blockers. In Flaim SF & Zelis R (Eds) Calcium blockers, pp. 137-152, Urban and Schwarzenberg, Baltimore, 1982
Turner TJ, Goldin SM. Calcium channels in rat synaptosomes: Identification and pharmacological characterization: high affinity blockade by organic Ca^{2+} channel blockers. Journal of Neuroscience 5: 841-849, 1985
Walsh TL, Lavenstein B, et al. Calcium antagonists in the treatment of Tourette's disorder. American Journal of Psychiatry 143: 1467-1468, 1986

Correspondence and reprints: Professor *Cyril Höschl*, 3rd School of Medicine, Charles University, Šrobárova 48, 100 42 Praha 10, Czechoslovakia.