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Lamotrigine has no antiparkinsonian activity in rat models of Parkinson's disease

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Abstract

In rodent models of Parkinson's disease such as reserpinized or 6-hydroxydopamine substantia nigra lesioned rats, blockade of glutamate receptors of the NMDA (*N*-methyl-D-aspartate) or the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor subtypes and concomitant treatment with L-DOPA (L-3,4-dihydroxyphenylalanine) or direct dopamine agonists restores locomotor activity and induces rotations. An alternative approach to interfere with glutamatergic transmission would involve the inhibition of glutamate release resulting in functional glutamate antagonism. The novel antiepileptic drug lamotrigine blocks the veratridine-evoked release of the excitatory transmitters L-glutamate and L-aspartate. Due to its presumed antiglutamatergic action it has been suggested that lamotrigine may be useful in the treatment of Parkinson's disease. In a preliminary open-label study in patients with Parkinson's disease some favourable effects were reported. The present study was undertaken to systematically investigate the effects of lamotrigine in rat models of Parkinson's disease. However, lamotrigine failed to exert antiparkinsonian activity in reserpinized rats when administered alone or in combination with the dopamine receptor agonist apomorphine. In rats bearing 6-hydroxydopamine lesions of the substantia nigra lamotrigine did not induce rotations when given alone and did not modify rotations induced by apomorphine or the preferential dopamine D_2 receptor agonist lisuride. On the basis of these negative results it is predicted that lamotrigine will not have significant favourable effects on akinesia and rigidity in Parkinson's disease patients.

Keywords: Parkinson's disease; Animal model; Lamotrigine

1. Introduction

Degeneration of dopaminergic nigrostriatal neurons with depletion of striatal dopamine is the primary histopathological finding in Parkinson's disease. Replacement therapy with the dopamine precursor L-DOPA (L-3,4-dihydroxyphenylalanine) remains the most effective treatment available. Limiting factors of L-DOPA therapy are loss of efficacy and complications such as motor fluctuations, dyskinesia, confusional states and hallucinations. Therefore, alternative therapeutic strategies that reduce the requirement of dopaminergic stimulation would be useful in the management of Parkinson's disease. Advances in our understanding of the anatomy, physiology and pharmacology of basal ganglia organization over the past decade revealed a functional relationship between excitatory glutamatergic and dopaminergic transmitter systems which could serve as a target for pharmacological interventions in Parkinson's disease or schizophrenia (Albin et al., 1989; Klockgether and Turski, 1989; Kim et al., 1980). Excitatory amino acids such as L-glutamate or L-aspartate activate ionophore-coupled receptors, which are subdivided pharmacologically into NMDA

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(*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and kainate subtypes. Cortical excitatory glutamatergic pathways innervate the caudate nucleus, putamen and the subthalamic nucleus of the basal ganglia (Carpenter, 1981). Dopaminergic projections arising from the substantia nigra pars compacta terminate in the caudate nucleus and putamen. Studies in primates with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesions of the basal ganglia indicate that degeneration of nigral dopamine neurons results in glutamatergic overactivity in the caudate nucleus and putamen and disinhibition of the subthalamic nucleus. Akinesia and rigidity are thought to be the consequence of overactivity of excitatory glutamatergic projections from the subthalamic nucleus to the internal segment of the pallidum and the substantia nigra pars reticulata, resulting in increased inhibitory output of the basal ganglia to the thalamocortical system (Bergman et al., 1990).

Experimental evidence indicates that inhibition of glutamatergic systems could be beneficial in Parkinson's disease. Blockade of NMDA receptors by the non-competitive antagonist dizocilpine (MK-801), the competitive antagonist CPP (3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) or the AMPA receptor antagonist NBQX (6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3(1*H*,4*H*)-dione) antagonizes dopamine receptor antagonist induced catalepsy in rats, restores locomotor activity and reduces muscular rigidity in catecholamine-depleted mice, rats and primates. This effect is enhanced by concomitant treatment with L-DOPA (Schmidt and Bubser, 1989; Carlsson and Carlsson, 1989; Klockgether and Turski, 1990; Löschmann et al., 1991).

An alternative approach to interfere with glutamatergic transmission would involve the inhibition of glutamate release resulting in functional glutamate antagonism. The phenyltriazine derivative lamotrigine possesses anticonvulsant activity in a variety of animal models of epilepsy including maximal electroshock test and pentylenetetrazol induced seizures (Miller et al., 1986). It was introduced as an antiepileptic drug for patients with refractory partial seizures and generalised tonic clonic seizures (Goa et al., 1993; Löscher and Schmidt, 1993). The mechanism of action may be related to the blockade of voltage-sensitive Na^+ channels and subsequent inhibition of transmitter release (Leach et al., 1986; Lang et al., 1993). In vitro studies indicate that lamotrigine has no effect on basal neurotransmitter release but blocks veratridine-evoked release of excitatory transmitters such as L-glutamate and L-aspartate and in higher concentrations the release of the inhibitory transmitter γ-aminobutyric acid (GABA) as well (Leach et al., 1986). Based on its presumed antiglutamatergic mechanism of action, it has been suggested that lamotrigine may be useful to prevent excitotoxic cell death in ischemia and in neurodegenerative conditions such as Parkinson's disease or motoneuron disease (Brodie, 1992). In fact, high oral doses of lamotrigine provided some protection to hippocampal CA 1 neurons against irreversible damage in the gerbil model of global ischemia, when administered before or immediately after the insult (Leach et al., 1991). Intrastriatal injection of kainate causes neurotoxic cell damage by increasing glutamate release. Pretreatment with lamotrigine resulted in a dose-related neuroprotection of marker enzymes for cholinergic and GABAergic systems (McGeer and Zhu, 1990). Competitive and non-competitive NMDA receptor antagonists protect against MPTP- and MPP^+ (1-methyl-4-phenylpyridinium ion)-induced neurodegeneration in primates and rodents (Lange et al., 1993; Zuddas et al., 1992; Turski et al., 1991). Similarily, lamotrigine protects against MPTP-induced dopamine depletion in C57 black mice, suggesting that it may have antiglutamatergic activity (Jones-Humble et al., 1993).

These considerations suggest that lamotrigine may be useful in the management of Parkinson's disease due to its presumed antiglutamatergic action. In fact, a preliminary open-label study in patients with Parkinson's disease reported some favourable effects (Zipp et al., 1993). The present study was therefore undertaken to systematically investigate the effects of lamotrigine in rat models of Parkinson's disease.

2. Materials and methods

Male Wistar rats (Interfauna, Tuttlingen, Germany) weighing 100–200 g were housed in groups of 10 under standard conditions at a temperature of 22 ± 1°C and a 12 h light-dark cycle (light on from 6.00–18.00 h). They had free access to food and water. Experiments were conducted between 9.00 and 17.00 h.

For measurement of locomotor activity animals were placed singly, without prior acclimatisation, onto the floor of circular cages (30 cm diamater) equipped with a second inner cylinder (10 cm diameter) forming a circular runway (10 cm wide). Horizontal movements were registered automatically by six infrared sensitive photocells per cylinder (Elektro-und Elektronik Anlagen, Berlin). The number of interruptions, as a measure of locomotion (count), was accumulated in 10 min intervals and stored for individual sensors in an IBM AT computer system for subsequent analysis. The system allowed testing of eight animals in parallel. Experimental groups consisted of 7–12 animals and each animal was tested once only.

Rotations were measured in male Wistar rats (Interfauna, Tuttlingen, Germany), weighing 400–590 g, aged 10 months and housed in groups of 4 under standard

conditions as described above. For stereotaxic lesions of the substantia nigra rats were pretreated with pargyline (25 mg/kg s.c.). Thirty minutes later 6-hydroxydopamine hydrochloride (Sigma, USA), 16 μg dissolved in 4 μl physiological saline containing 0.02% ascorbic acid, was injected into the left substantia nigra under pentobarbital anesthesia (50 mg/kg i.p.). The stereotaxic coordinates were: AP 1.9; L 1.8; AP −2.1 according to a stereotaxic atlas (König and Klippel, 1963). Experiments were performed 2–6 months after the lesion. Ipsiversive and contraversive rotations were registered by means of an automatic device consisting of 6 Perspex bowls (40 cm diameter) and electro-mechanical transducer systems. The latter registered a count each time the animal moved through 36 degrees in clockwise or counterclockwise direction. In addition full 360 degree rotations were registered for each direction. Animals were placed into the bowls and connected to the transducers following injection of test compounds. Counts and full circle rotations were accumulated in 10-min intervals and recorded for 60 or 120 min. Only rotations were analyzed since the number of rotation counts and full rotations show a robust correlation in animals exposed to apomorphine or amphetamine, respectively. Animals showing more than 30 contraversive rotations in 30 min when exposed to a standard dose of apomorphine (0.1 mg/kg s.c.) and more than 60 ipsiversive rotations in 60 min following treatment with amphetamine (1.56 mg/kg i.p.) at 1 and 2 weeks after the lesion were included in experimental groups. The majority of animals showed more than 100 rotations in 30 min when exposed to apomorphine under these conditions. To control for recovery from the lesion all animals were tested every 6 weeks using a lower dose of apomorphine (0.05 mg/kg s.c.). Animals showing fewer than 60 rotations in 30 min were excluded from subsequent pharmacological studies. Rats were allocated to treatment groups of 6–8 animals in a quasi-random fashion with the restriction that no animal received active or non-active treatment more than twice consecutively. A wash-out period of 2 weeks was allowed between experiments.

The means ± S.E.M. were calculated for accumulated locomotor or rotation counts of the different treatment groups. Statistical differences were calculated for locomotor counts or rotations accumulated over 60 or 120 min by one-way analysis of variance (ANOVA) followed by post-hoc comparisons using the Tukey test (SYSTAT, USA).

The following compounds were used: reserpine (Sigma), α-methyl-*p*-tyrosine (Sigma), apomorphine hydrochloride (Sandoz), lisuride hydrogenmaleate (Schering), lamotrigine (3,5-diamino-6-(2,3-dichlorphenyl)-1,2,4-triazine, Wellcome). All drugs except reserpine and apomorphine were suspended in physiological saline containing 10% (v/w) polyethoxylated castor oil (Cremophor, BASF, Germany). Reserpine was dissolved in a minimum quantity of glacial acetic acid and diluted to volume with distilled water. Apomorphine was dissolved in physiological saline containing 0.01% ascorbic acid. All solutions were prepared immediately before intraperitoneal (i.p.) administration and injected in a volume of 5 ml/kg body weight; dosages refer to the free form (acid, base). To deplete monoaminergic transmitters animals were injected with reserpine (5 mg/kg i.p.) and were returned to their home cages. 21.5 h later animals were treated with α-methyl-*p*-tyrosine (250 mg/kg i.p.) and after 3.5 h with drugs or vehicle.

All experiments were carried out in accordance with the recommendations of the Declaration of Helsinki and the animal welfare guidelines and laws of the Federal Republic of Germany.

3. Results

In the first experiment the effects of lamotrigine in doses ranging from 0.1–25 mg/kg i.p. upon locomotor activity were studied in otherwise drug-naive rats. The highest dose tested (25 mg/kg i.p.) induced a significant inhibition of locomotor activity whereas all other doses were ineffective (Fig. 1A). In animals pretreated with reserpine (5 mg/kg i.p.) and α-methyl-*p*-tyrosine (250 mg/kg i.p.) to deplete monoaminergic stores, lamotrigine did not modify locomotor activity within the same range of doses (Fig. 1B). Finally, lamotrigine (0.39–25 mg/kg i.p.) in combination with apomorphine (0.1 mg/kg s.c.) was administered to monoamine-depleted rats. The locomotor stimulation induced by apomorphine was not significantly influenced by lamotrigine (Fig. 1C).

In a similar series of experiments, rats bearing 6-hydroxy dopamine lesions of the substantia nigra were treated with vehicle or lamotrigine (3.13–50 mg/kg i.p.). Within this range of doses, lamotrigine did not modify spontaneous contraversive or ipsiversive rotations in the 120-min observation period (Fig. 2A). When combined with a threshold dose of apomorphine (0.1 mg/kg s.c.), lamotrigine (0.78–6.25 mg/kg i.p.) had no effect upon apomorphine-induced contralateral rotations (Fig. 2B). In a further experiment the dopamine D_2 receptor agonist lisuride (0.01 mg/kg i.p.) was tested alone or in combination with lamotrigine (0.025–1.56 mg/kg i.p.). Although the results were more variable and the rotation counts tended to be lower following combined treatment, this effect did not reach the level of statistical significance (Fig. 2C).

In none of the experiments were side effects observed except for mild sedation in doses of 25 or 50 mg/kg i.p. of lamotrigine.

4. Discussion

We have shown earlier that combined treatment of monoamine-depleted rats with L-DOPA and the com-

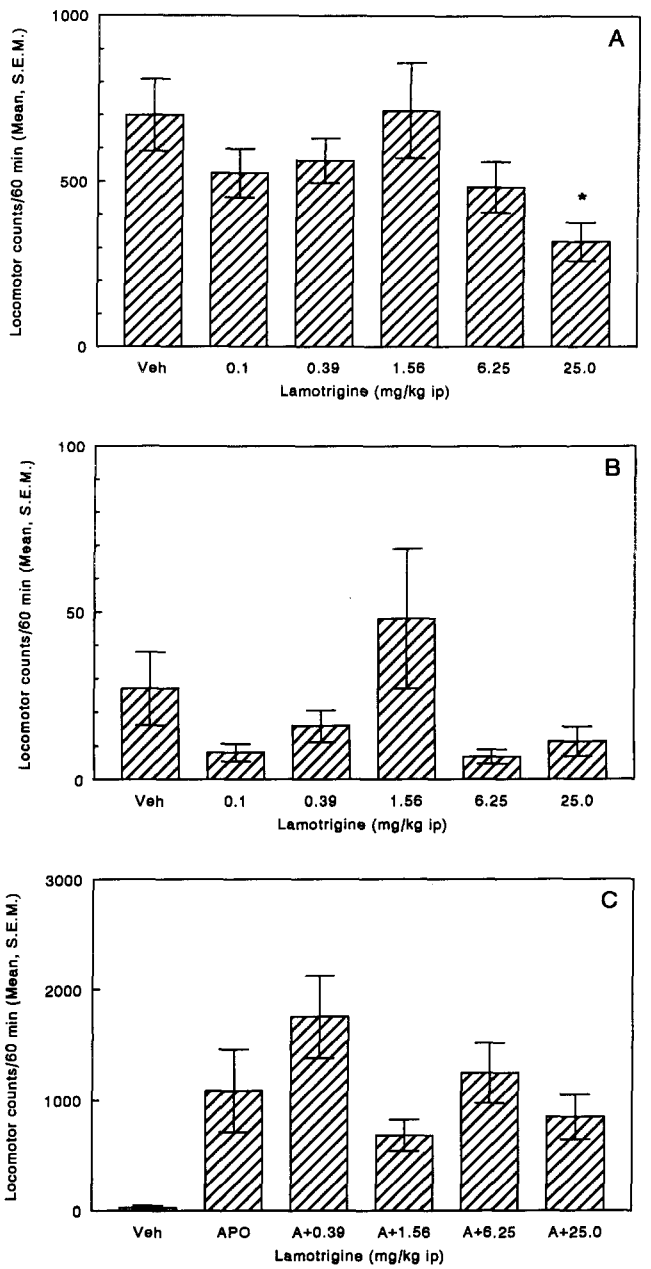

Fig. 1. Effects of lamotrigine on locomotor activity of male Wistar rats. A: Groups of 12 animals were treated with lamotrigine (0.1–25 mg/kg i.p.) or vehicle. The highest dose tested caused a significant inhibition of locomotor activity ($P < 0.05$, ANOVA followed by a Tukey test). B: Groups of 11 animals were treated with reserpine (5 mg/kg i.p.) and α-methyl-*p*-tyrosine (250 mg/kg i.p.) at 24 and 3.5 h prior to the administration of vehicle or lamotrigine (0.1–25 mg/kg i.p.), respectively. C: Groups of 7 animals were treated with reserpine (5 mg/kg i.p.) and α-methyl-*p*-tyrosine (250 mg/kg i.p.) 24 and 3.5 h prior to the administration of vehicle or apomorphine (APO 0.1 mg/kg s.c.) alone or in combination with lamotrigine (0.39–25 mg/kg i.p.), respectively.

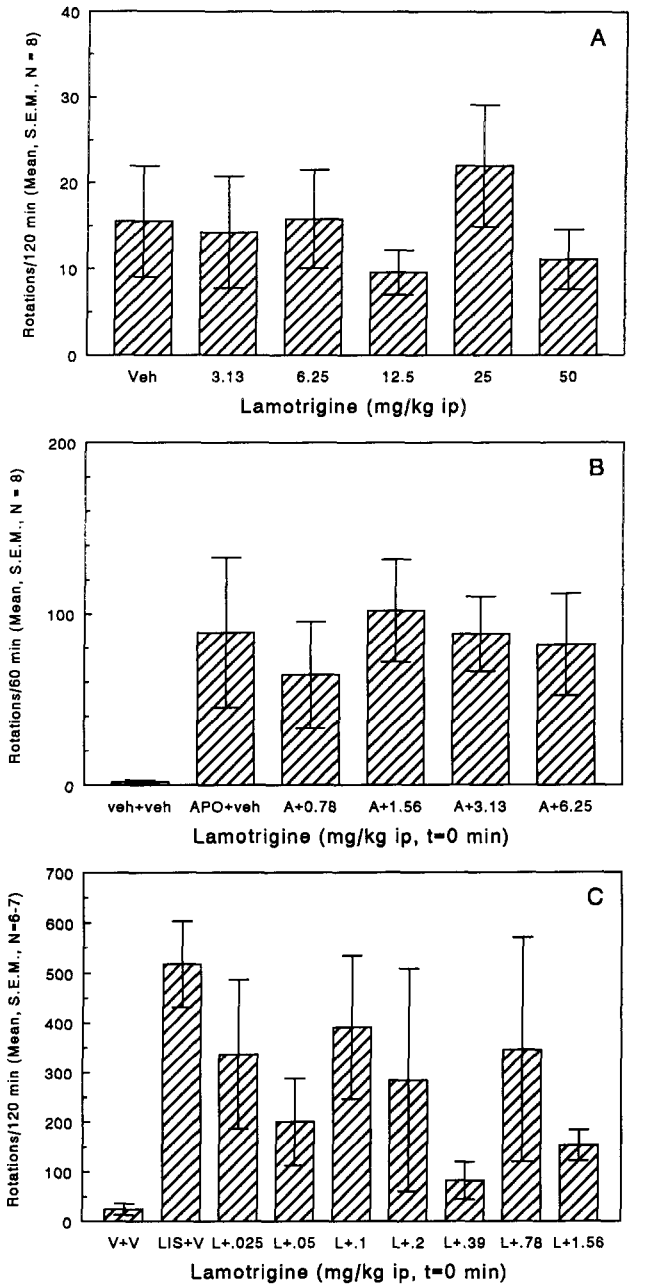

Fig. 2. Contralateral rotations in 6-hydroxydopamine substantia nigra lesioned rats. Because ipsiversive rotations were not altered by drug treatments, these data are not presented for clarity. A: Groups of 8 animals were treated with lamotrigine (3.13–50 mg/kg i.p.) or vehicle. B: Groups of 8 animals were treated with vehicle or apomophine (APO, 0.1 mg/kg s.c.) alone and in combination with lamotrigine (0.78–6.25 mg/kg i.p.). C: Groups of 6–7 animals were treated with vehicle or lisuride (LIS 0.01 mg/kg i.p.) alone and in combination with lamotrigine (0.025–1.56 mg/kg i.p.).

petitive NMDA receptor antagonist CPP and the AMPA receptor antagonist NBQX restores locomotor activity in a synergistic manner (Klockgether et al., 1991). Similar effects of CPP and NBQX were obtained in 6-hydroxydopamine-lesioned rats following

combined treatment with L-DOPA and benserazide or direct dopamine agonists such as apomorphine or lisuride (Löschmann et al., 1991, 1992). In line with these findings both antagonists were also active in common marmosets rendered parkinsonian by systemic treatment with MPTP, again in combintion with L-DOPA and benserazide (Löschmann et al., 1991). Further evidence for the assumption that glutamate receptor blockade could be a valuable target for the symptomatic treatment of Parkinson's disease comes from the observation that aminoadamantane derivatives such as amantadine or memantine act as non-competitive NMDA receptor antagonists (Kornhuber et al., 1991).

The novel antiepileptic drug lamotrigine is presumed to exert its effects by inhibition of glutamate release. The present series of experiments was designed to test the hypothesis that lamotrigine could exert effects similar to those elicited by competitive NMDA receptor receptor blockade in experimental models of Parkinson's disease. However, our negative results indicate that lamotrigine lacks antiparkinsonian activity. In none of the models was induction of locomotor activity or rotations observed. The range of doses tested was within the limits (2–20 mg/kg) sufficient to observe anticonvulsant activity of the compound, depending on the seizure type and species used (Goa et al., 1993). To exclude further that pharmacokinetic effects, i.e. slow absorption of lamotrigine and the short-lasting effect of apomorphine, could account for the absence of effects, we also combined lamotrigine with the preferential dopamine D_2 receptor agonist lisuride, which induces longer-lasting rotations in rats. In earlier studies using glutamate receptor antagonists in this type of experiment we often obtained non-linear dose-response relationships with great efficacy at very low doses. Therefore, lower doses of lamotrigine were tested, but again no additive effects were seen.

Richter et al. (1994) have recently reported on the effects of lamotrigine in a mutant hamster model of generalised dystonia. In this model lamotrigine, like the sodium channel inhibitors phenytoin and carbamazepine, exerts prodystonic effects, whereas NMDA and AMPA receptor antagonists have antidystonic effects.

Several hypotheses could explain the absence of antiparkinsonian or antidystonic effects of lamotrigine. Following systemic administration lamotrigine could interfere with all glutamatergic synapses within the central nervous system. Therefore, not only the overactive pathways driving the output nuclei of the motor loop, i.e. the substantia nigra reticulata and the internal pallidum, would be inhibited but also the underactive thalamo-cortical pathways, leading to an overall reduction of glutamatergic drive rather than region-specific effects. This would result in the observed absence of cooperative effects of systemic treatment with the dopamine receptor agonists apomorphine and lisuride. Another explanation could be related to the fact that lamotrigine is not a selective inhibitor of glutamate release but also interferes with the release of other amino acids such as GABA. In vitro, lamotrigine blocks evoked transmitter release with some specificity for excitatory amino acids with an ED_{50} of 21 μM whereas the ED_{50} for inhibition of GABA release is 44 μM in a rat cortical slice preparation (Leach et al., 1986). In acute dialysis experiments lamotrigine dose dependently reduced veratridine-but not K^+-evoked aspartate, glutamate and GABA release in the hippocampus to the same extent (Ahmad et al., 1995). In rats treated chronically with lamotrigine, basal glutamate release was not altered in hippocamal dialysates, whereas a significant reduction of veratridine evoked glutamate release was obtained throughout the study (Leach, personal communication). Veratridine-evoked transmitter release may mimic the massive release of transmitters that occurs in epileptic seizures or during ischemia. It is not known, however, whether lamotrigine inhibits glutamate release in animals with derangements of transmitter function due to impaired dopaminergic transmission in vivo.

The present results show that in the rodent models employed here lamotrigine does not exert pharmacological actions that are comparable to those of NMDA or AMPA receptor antagonists. The findings suggest that lamotrigine either does not affect glutamate release under these conditions or blocks transmitter release in an unspecific way, probably affecting GABA release as well. Since the striato-pallidal GABAergic pathway and the GABAergic projections from the substantia nigra pars reticulata and the internal pallidum to the thalamus are overactive in Parkinson's disease, this effect would not necessarily be counterproductive. However, if in parallel the GABAergic pathways from the external pallidum to the subthalamic nucleus and the internal pallidum are underactive, the net result again could be a non-specific reduction in all systems involved.

In summary, lamotrigine did not have antiparkinsonian actions in acute animal models of Parkinson's disease. On the basis of these negative results we predict that lamotrigine will not have significant favourable effects on akinesia and rigidity in Parkinson's disease patients. This conclusion is in apparent contradiction to the beneficial effects of lamotrigine seen in patients with Parkinson's disease in a small open-label study (Zipp et al., 1993). However, these results were not confirmed in a subsequent double-blind, placebo-controlled study: lamotrigine did not significantly improve motor functions in parkinsonian patients when added on to a standard therapy with L-DOPA and selegeline (Zipp, personal communication).

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