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(71) Applicant *(for all designated States except US)*: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.** [HU/HU]; Gyömröi út 19-21, H-1103 Budapest (HU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KOCSIS, Pál** [HU/HU]; Mézeskalács tér 5., H-1155 Budapest (HU). **TARNAWA, István** [HU/HU]; Kerékgyártó u. 45/C, H-1147 Budapest (HU). **THÁN, Márta** [HU/HU]; Nagy Lajos Király útja 42/44, F-1148 Budapest (HU). **TIHANYI, Károly** [HU/HU]; Postamester u. 37, H-1171 Budapest (HU). **NÉMETH, György** [HU/HU]; Nagyerdei krt. 60., H-4032 Debrecen (HU).

(74) Common Representative: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.**; Gyömröi út 19-21, H-1103 Budapest (HU).

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(54) **Title:** NOVEL PHARMACEUTICAL COMPOSITIONS WITH INCREASED ACTIVITY

(57) **Abstract:** The invention relates to novel pharmaceutical combinations with improved sodium channel blocking effect. Further, the invention relates to the use of said pharmaceutical combinations in neurodegenerative disorders, chronic pain, in disturbances of the motor system, in epilepsy, as well as in other therapeutic fields where the use of sodium channel blockers is acceptable.

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Novel pharmaceutical compositions with increased activity

The invention relates to novel pharmaceutical combinations of voltage-gated sodium channel blockers and monoamine oxidase B (MAO-B) inhibitors with increased effect. Furthermore, the invention relates to the use of pharmaceutical combinations in Alzheimer diseases, Parkinson diseases and other neurodegenerative diseases, chronic pain, in disturbances of the motor system, in epilepsy, as well as in other therapeutic fields where the use of sodium channel blockers is acceptable.

It is known that voltage-sensitive sodium channels play a crucial role in the generation and conduction of action potentials, thus in the regulation of excitability of the nerve cells. Sodium channels form pores in the nerve cell membrane and in response to membrane depolarization channels open for a short time and let sodium ions flow into the cell causing electric alterations. In certain diseases of the nervous system a change in the channel function can be observed resulting generally in abnormal increase of excitability of the nerve cells. Several pharmaceuticals are on the market or under development that have a beneficial effect on such diseases by blocking the voltage-dependent sodium channels.

Sodium channel blockers, such as lidocaine, are traditionally used as local anaesthetics. Some structurally similar substances (e.g. mexiletine) are used as antiarrhythmic agents. Currently some novel molecules are under development among which crobenetine proved to be effective even at very low doses (Carter, A.J. et al. Potent blockade of sodium channels and protection of brain tissue from ischemia by BIII 890 CL. Proc. Natl. Acad. Sci. USA 97: 4944-4949; 2000). The latter compound seems to be also useful against neuropathic pain. (Laird, J.M.A. et al. Analgesic activity of a novel use-dependent sodium channel blocker, crobenetine, in mono-arthritic rats. Br. J. Pharmacol. 134: 1742-1748; 2001). Several other sodium channel blockers are effective against chronic pain (Hunter, J.C., Loughhead, D. Voltage-gated sodium channel blockers for the treatment of chronic pain. Curr. Opin. CPNS Invest. Drugs 1: 72-81; 1999). Riluzole, used for the treatment of neurodegenerative diseases, has the same mechanism of action (Hurko, O., Walsh, F.S. Novel drug development for amyotrophic lateral sclerosis. J. Neurol. Sci. 180: 21-28; 2000). Recently it has been found that sodium channel blockers can be useful in the treatment of diseases accompanied by painful muscle spasms hindering patients in normal motion (Kocsis, P. *et al.* Mydeton: a centrally acting muscle relaxant drug of Gedeon Richter Ltd. Acta Pharm Hung 72: 49-61;

2002). Further possible fields of application are cerebral ischemia, hereditary channel diseases, tinnitus, migraine and drug abuse (Clare, J.J., *et al.* Voltage-gated sodium channels as therapeutic targets. Drug Discov. Today 5: 506-520; 2000). Several antiepileptics (phenytoin, carbamazepine) have been used for a long time. Sodium channel inhibitory activity was recognized as the major component of their mechanism of action. (Willow, M. *et al.* Voltage clamp analysis of the inhibitory actions of diphenylhydantoin and carbamazepine on voltage-sensitive sodium channels in neuroblastoma cells. Mol. Pharmacol. 27: 549-558, 1985). Lamotrigine was developed with the knowledge of this mechanism of action (Leach, M.J., *et al.* Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II Neurochemical studies on the mechanism of action. Epilepsia 27: 490-497, 1986; Clare, J.J. *et al.* Voltage-gated sodium channels as therapeutic targets. Drug Discov. Today 5: 506-520; 2000).

The MAO-B inhibitor deprenyl (selegiline) can be applied successfully in some neurodegenerative diseases (Parkinson diseases; Youdim M.B., Finberg J.P. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine oxidase B inhibitors. Clin. Pharmacol. Ther. 56: 725-733, 1994). In animal experiments, it was demonstrated that deprenyl prevents NMDA induced striatal cell death, and is also effective against other neurotoxins (Magyar K. Effect of selegiline against selective neurotoxins. Vopr. Med. Khim. 43: 504-514, 1997). The metabolites of deprenyl also have role in this process. In addition to its MAO-B inhibitory action deprenyl has some other therapeutically advantageous effects (Magyar K., Szende B., Lengyel J., Tarczali J., Szatmary I. The neuroprotective and neuronal rescue effects of (-)-deprenyl. J. Neural. Transm. Suppl. 52: 109-123, 1998). It is known, that deprenyl increases NGF level, which contributes to its neuroprotective effect. Rasagiline, the new MAO-B inhibitor neuroprotective compound is described by the European patent EP 436492. Many papers refer to the MAO-B independent neuroprotective effect of deprenyl and rasagiline which involves the gliceraldehid-3-phosphate way (Tatton W., Chalmers-Redman R., Tatton N. Neuroprotection by deprenyl and other propargylamines: glyceraldehyde-3-phosphate dehydrogenase rather than monoamine oxidase B. J. Neural. Transm. 110(5):509-15, 2003) or direct activation of PKC (Am O.B., Amit T., Youdim M.B. Contrasting neuroprotective and neurotoxic actions of respective metabolites of anti-Parkinson drugs rasagiline and selegiline. Neurosci. Lett. 355(3):169-72, 2004). Deprenyl was also found to be effective against ischemic motoneuronal death.

Sodium channel blockers, however, possess several side effects a part of which is a consequence of the sodium channel blocking effect itself; e.g. cardiovascular (e.g. bradycardia, hypotonia) or CNS (e.g. ataxia, sedation) side effects.

Other side effects are unrelated to sodium channels and are associated with their chemical structure, e.g. higher doses of lamotrigine may induce gastrointestinal disorders, damage of the liver or skin complaints, etc. The risk of such side effects can be decreased if the efficacy of drug is increased and effective dose of the drug is somehow lowered.

In our experiments we have surprisingly found a marked increase in the sodium channel blocking activity of some compounds when a MAO-B inhibitor compound is administered simultaneously. For example, combined administration of lamotrigine and deprenyl resulted in a more expressed neuroprotection than either of the two drugs alone, administered in the same dose. In addition the strong tremor inhibitory action of lamotrigine is very advantageous to alleviate movement and muscle tone abnormalities due to neuronal damage. An increased level of cholinergic synapses following the treatment was also noticed, which may be particularly advantageous in the treatment of Alzheimer's disease.

Accordingly the main object of this invention is to provide novel pharmaceutical combinations with enhanced efficaciousness that consist of a sodium channel blocker drug and a MAO-B inhibitor compound. Such combinations show increased activity in the therapy of diseases which are known therapeutic targets for sodium channel blockers (i.e. chronic pain, certain disturbances of the motor system, epilepsy, drug or alcohol addiction, incontinence of faces or urine, inflammation, itching, intracranial edema, ischemia and/or subsequent damage caused by reperfusion, retinopathy caused by glaucoma) but above all in neurodegenerative disorders (Parkinson's disease, sclerosis multiplex) and possessing more favorable side effect profile than the sodium channel blocker component alone. In the pharmaceutical compositions of to the invention the effective therapeutic doses of both the sodium channel blockers and MAO-B inhibitors can be lowered and their clinical efficaciousness thereof can be increased, respectively.

Sodium channel blockers for use in the pharmaceutical compositions according to the invention are substances known to have such mechanism of action. Examples of such substances are lamotrigine, crobenetine, carbamazepine, phenytoin, tolperisone, eperisone, oxcarbamazepine, phosphenytoin, preferably lamotrigine, riluzole, oxcarbamazepine,

phosphenytoin, or crobenetine, most preferably lamotrigine or riluzole. Optionally the mixtures of such substances for use in carrying out the invention are also within the scope of the invention.

MAO-B inhibitors which can be used are substances known to have such mechanism of action. Examples of such substances are deprenyl and rasagiline preferably deprenyl. Optionally the mixtures of such substances for use in carrying out the invention are also within the scope of the invention.

The use of the salts, solvates, polymorphsor stereoisomers of said sodium channel blockers or MAO-B inhibitors as well as the mixtures thereof is also within the scope of the invention.

The pharmaceutical compositions according to the invention can be efficient in the treatment and/or prevention of neurodegenerative diseases (e.g. ALS, HIV-related dementia, Parkinson's syndrome, Alzheimer's disease, Huntington's chorea, multiple sclerosis, prion diseases, stroke, cerebral and spinal cord injuries, cerebral ischemia), chronic pain (e. g. neuropathic pain, inflamed or rheumatic origin, trigeminal neuralgia, headache, fibromyalgia), and irritable bowel syndrome (IBS), in the treatment and prevention of the disorders of the motor system (e.g. spastic diseases, essential tremor, dystonia, tinnitus, extrapyramidal disorders, tics) and as well as in the treatment and prevention of drug or alcohol addiction, incontinence of faces and urine, inflammation, itching, intracranial edema, ischemia and/or subsequent damage caused by reperfusion or retinopathy caused by glaucoma, further in treatment and prevention of different forms of epilepsy, such as partial attacks, e.g. simple partial attacks (motor, somatosensorial-sensorial, autonomic, psychic symptoms), complex partial attacks (partial onset and/or loss of conciousness) or partial attacks with secondary generalization (generalized tonic or clonic attacks), generalized attacks, such as absance (typical or atypical), myoclonus, clonic, tonic-clonic (grand mal) attacks, loss of tonus (astatic attack), as well as further forms of attack which cannot be classified (International classification of epileptic seizures, Epilepsia, 22, 489-501, 1981).

The aforementioned diseases can successfully be treated not only by simultaneous administration of the sodium channel blockers and the MAO-B inhibitors (in which case said substances are present in two separate compositions or in a single one, i. e. in a combination) but also by sequential administration thereof, when any of the active ingredients may be administered first.

The active agents or the pharmaceutically acceptable derivatives thereof can be used without formulation or preferably in a form suitable for medical use, particularly for human treatment.

In addition to the active agents brought into suitable form the compositions may contain one or more pharmaceutically acceptable auxiliary material(s).

The compositions may be used in oral form, parenteral form, including intravenous, subcutaneous, intradermal, intramuscular, intrathecal, rectal, topical, buccal, dermal or sublingual forms, as well as in forms suitable for inhalation.

Formulations suitable for oral administration can be in unit dose form, such as capsules, tablets (e. g. tablet for chewing for pediatric use), can be in powder or in granulated form, in the form of aqueous or non-aqueous solution or suspension and water-in-oil or oil-in-water emulsion form.

Tablets can be prepared in compressed or molded form optionally using one or more auxiliary materials. Compressed tablets are prepared in an appropriate compressing machine in which the powdered or granulated active ingredients are optionally mixed with known auxiliary materials, such as binders, fillers, lubricants, disintegrators, wetting agents and flavouring substances. Examples of binding agents are the syrup, acacia, gelatine, sorbitol and polyvinylpirrolidone. Examples of fillers are different hydroxymethylcellulose fillers, lactose, sugar, microcrystalline cellulose, corn starch, calcium phosphate or hydroxymethylcellulose. Examples of lubricants are the magnesium stearate, stearic acid, talc, polyethylene glycol or silica gel. Examples of disintegrators are potato starch or sodium glycolate. Molded tablets can be prepared from the mixture of powdered active agents and an inert liquid solvent in an appropriate molding machine. Tablets optionally may be coated by methods known in the pharmaceutical industry. Tablets with slow or controlled release can also be prepared.

Compositions for oral administration may also be in liquid form, such as aqueous or oily suspensions, solutions, emulsions, syrups or elixir. Such compositions may be prepared also in dry form which can be brought into the liquid form by suitable means just before treatment.

Said liquid formulations may contain known additives, such as suspending agents (sorbitol, syrup, methylcellulose, glucose syrup, gelatine, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or edible hydrogenated fats), emulsifying agents (lecithin, sorbitan monooleate, acacia), non-aqueous materials (oil of sweet almond,

fractionated coconut oil, esters, propylene glycol, ethyl alcohol), preservatives (methyl or propyl-p-hydroxybenzoate, sorbitol) or flavouring additives.

Compositions in suppository form may contain traditional vehicles, such as cocoa butter, solid fats, polyethylene glycol or glycerol and derivatives thereof.

Compositions for parenteral use are aqueous or non-aqueous sterile solutions for injection and may contain antioxidants, buffers, bactericides and substances dissolved in isotonic solution. The composition is then filled e. g. in ampules (one or more unit dose) or can be stored in lyophilized form.

Examples of compositions suitable for topical use are in the form of cream, gel, ointment or transdermal plaster.

Examples of intranasal compositions are sprays, dusts or drops.

Composition suitable for use in the treatment may be an aerosol spray containing in addition to the active ingredient a propellant, such as carbon dioxide 1,1,1-trifluorethane, 1,1,1,2,3,3,3,-heptafluorpropane or the like.

Biological data

Inhibition of the spinal reflex

Experiments were performed according to the methods described by Otsuka and Konishi (Otsuka, M., Konishi, S. Electrophysiology of mammalian spinal cord in vitro. Nature 252, 733-734; 1974), with slight modifications (Kocsis, P. *et al.* Participation of AMPA- and NMDA-type excitatory amino acid receptors in the spinal reflex transmission, in rat. Brain Res. Bull. 60: 81-91; 2003). The L_5 dorsal root of the isolated, hemisected spinal cord preparation (six-day-old Wistar rats) was stimulated by supramaximal electrical impulse and the reflex potential from the L_5 ventral root was recorded. Different components of the reflex potential obtained are well distinguishable based on their post-stimulus latencies and durations. In our experiments the effect of sodium channel blockers on the amplitude of monosynaptic reflex (MSR) was measured.

Sodium channel blockers possess considerable spinal reflex inhibitory action in the hemisected spinal cord preparation, in vitro. This preparation is ideal for analyzing pharmacodynamic interactions between two substances, since metabolic factors take no part in the interaction.

Addition of the MAO-B inhibitor deprenyl induced significant increase in the reflex inhibitory action of the sodium channel blockers lamotrigine and riluzole as Figure 1. and 2. show.

Inhibition of maximal electroshock seizures

Inhibition of maximal electroshock seizures (MES; Swinyard, E.A., Brown, W.C., Goodman L.S. Comparative assay of antiepileptic drugs in mice and rats. J. Pharmacol. Exp. Ther. 106, 319-330; 1952) shows the antiepileptic potency of a compound. Experiments were carried out on male NMRI mice (19-21g).

Figure 3. shows the isobologram for the interaction between lamotrigine and deprenyl. The ED_{50} values of lamotrigine and deprenyl to inhibit MES are plotted on the abscissa and ordinate, respectively . The straight line connecting the two ED_{50} values is the isobolographic line. If the experimentally determined ED_{50} lies on the isobolographic line, then the drug effects are additive. If the ED_{50} lies below this line, it indicates supra-additivity and when the ED_{50} lies above the isobolographic line, there is infra-additivity. ED_{50} values were determined using probit analysis. The experimentally determined ED_{50} values lie below the isobolographic line, thus the interaction between the two compounds seems to be clearly supra additive.

These data indicate that pretreatment of the animals with a MAO-B inhibitor compound can cause a substantial increase in the potency of sodium channel blockers.

In vivo neuroprotective effect in an entorhinal cortex lesion model, in rat

Male Harlan Wistar rats (250-280 g) were used. NMDA injected into the entorhinal cortex of animals (40 nmol NMDA in 0.5 µl buffer (PBS: 0.01M phosphate buffer, pH 7.4, 0.9% NaCl)) caused an extensive lesion in the cortex and ventral thalamus. Rats were tested in behavioral pharmacological models for 13 days after the injection. Their brains were processed histologically on day 13.

Histological examination

Coronal sections were prepared from the brain after fixation. The evaluation of the extent of the lesion was performed at the levels of 7.6 and 6.4 mm from bregma, using a computer-controlled planimetric system (Paxinos G, Watson G. The Rat Brain in Stereotaxic

Coordinates. Academic Press, Sydney, 1982). In the majority of the animals both lamotrigine and deprenyl (10 mg/kg, 1 ml/kg; i.p. 60 min before the surgery; 90 min after the surgery; and twice a day during the next three days) decreased the extent of the lesion caused by NMDA. Co-administration of the two drugs in the volume of 1 ml/kg resulted in a stronger protective effect.

		Br -7.6		Br -6.4	
Group	(N)	area mm^2	decrease %	area mm^2	decrease %
control	(4)	3.075 ± 0.091		2.125 ± 0.083	
shame operated	(4)	3.256 ± 0.185		2.294 ± 0.086	
pulled control	(8)	3.166 ± 0.101		2.209 ± 0.064	
NMDA	(6)	2.304 ± 0.091	27	1.705 ± 0.085	23
NMDA+A	(5)	2.545 ± 0.110	20	1.805 ± 0.140	18
NMDA+B	(5)	2.490 ± 0.090	21	1.660 ± 0.099	25
NMDA+AB	(6)	2.563 ± 0.161	19	1.846 ± 0.116	16

mean ± SEM.

Table 1.

In addition, co-administration of the two drugs resulted in a surprisingly high increase of the number of cholinergic fibers and synapses (sprouting) in the area of the gyrus dentatus, sham operated animals serving as control. Cholin acetyl-transferase, the key-enzyme of acetylcholine synthesis, was used to mark cholinergic synapses.

Figure 4. shows the cholin acetyl transferase positive fibers and synapses in the area of gyrus dentatus from sham operated and NMDA lesioned animals treated with a combination of deprenyl and lamotrigine.

Behavioural pharmacology study

Before histological processing, behavioral pharmacology study was performed with NMDA treated animals. Two tests were applied to asses the functional damage caused by NMDA microinjection.

Novel object recognition in an open field

Male Harlan Wistar rats (250-280 g) were tested in a familiar environment in order to avoid the attention distracting effect of environmental changes (Myhrer T, Enger S, Aas P Cognitive side effects in rats caused by pharmacological agents used to prevent soman-induced lethality Eur. J. Pharmacol., 2004; 483: 271-279.). During the first training two identical aluminum cubes (5x5x5 cm) were placed in specified places of the cage and the time spent with exploration of the cubes, and the frequency of explorations were recorded during the first 5 minutes. Two hours later another training was performed. The cubes (known

objects) were exchanged (alternately in the case of each animal) to iron weights (1 kg; new object), and the time spent with exploration of the objects and the frequency of explorations were recorded again. Trainings lasted for 5 minutes. In another group of animals the first training was performed with the iron weights, which were exchanged to aluminum cubes in the second training, in an alternating manner, in order to neutralize object preference. The drug administration protocol was the same described in the "Histological examination" section.

Figure 5. shows the effect of lamotrigine and deprenyl on the recognition of new objects. NMDA treatment significantly decreased the time spent with exploring the new object. Neither deprenyl nor lamotrigine influenced significantly the exploratory time shortening effect of NMDA treatment. The combined treatment with deprenyl and lamotrigine significantly increased exploratory time, which practically returned to the control value measured with sham operated animals.

NMDA treatment significantly decreased the time spent with exploring the new object. Neither deprenyl nor lamotrigine influenced significantly the exploratory time shortening effect of NMDA treatment. The combined treatment with deprenyl and lamotrigine significantly increased exploratory time, which practically returned to the control value measured with sham operated animals.

Morris maze

The experimental device was a round basin (diameter: 153 cm) filled with water (28 C°; depth: 63 cm). In the middle of one quadrants of the basin (eccentrically) there was a platform (diameter: 10.8 cm) 1.5 cm beneath water level. Four starting points were marked on the edge of the basin in equal distances from each other. Before the first trial experimental animals (male Harlan Wistar rats 250-280 g) were placed on the platform for 30 seconds. Rats had four trials daily for 5 days. During the trials the animals, facing the wall, were placed into the water each time from different starting point. The sequence of starting points was the same in each experimental day, but randomly changed from day to day. The place of the platform was not changed during testing. Trials lasted until the animal reached the platform, but no longer than 90 seconds, and were followed by a 30-second period of orientation on the platform. The latency of finding the platform was recorded during each trial. The drug administration protocol was the same described in the "Histological examination" section.

Figure 6. shows the effect of lamotrigine and sertraline treatment on spatial learning deficit caused by NMDA induced brain lesion. After NMDA treatment the learning performance of the animals showed a significant decline. Deprenyl had some improving effect, but lamotrigine did not influence learning. On the other hand the latency returned to the control value following combined treatment.

After NMDA treatment the learning performance of the animals showed a significant decline. Deprenyl had some improving effect, but lamotrigine did not influence learning. On the other hand the latency returned to the control value following combined treatment.

We can conclude from the behavioral pharmacology data that combined treatment with deprenyl and lamotrigine has superior effects compared with single treatments either with lamotrigine or deprenyl.

Claims:

1. A pharmaceutical composition which comprises a sodium channel blocker in combination with a MAO-B inhibitor.

2. A pharmaceutical composition according to claim 1, wherein the MAO-B inhibitor is selected from the group consisting of deprenyl and rasagiline or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphs or stereoisomers as well as the mixtures thereof.

3. A pharmaceutical composition according to claim 1, wherein the sodium channel blocker is selected from the group consisting of lamotrigine, riluzole, crobenetine, oxcarbamazepine and phosphenytoin or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphs or stereoisomers as well as the mixtures thereof.

4. A pharmaceutical composition according to any of claims 1, 2 or 3, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is lamotrigine.

5. A pharmaceutical composition according to any of claims 1, 2 or 3, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is riluzole.

6. A pharmaceutical composition according to any of claims 1, 2 or 3, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is lamotrigine.

7. A pharmaceutical composition according to any of claims 1, 2 or 3, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is riluzole.

8. The use of a sodium channel blocker and a MAO-B inhibitor in a process for the preparation of a pharmaceutical composition suitable for the treatment and/or the prevention of neurodegenerative diseases (e.g. ALS, HIV-originated dementia, Parkinson's syndrome, Alzheimer's disease, Huntington's chorea, multiple sclerosis, prion diseases, stroke, cerebral and spinal cord injuries, cerebral ischemia), as well as in the treatment and prevention of drug or alcohol addiction, incontinence of faces and urine, inflammation, itching, intracranial edema, ischemia and/or subsequent damage caused by reperfusion or retinopathy, as a complication glaucoma in mammals.

9. The use of a sodium channel blocker and a MAO-B inhibitor in a process for the preparation of a pharmaceutical composition suitable for the treatment and/or the prevention of chronic pain, different forms of epilepsy or deriving from disorders and/or injuries of the motor system in mammals.

10. A pharmaceutical composition according to claim 8-9, wherein the MAO-B inhibitor is selected from the group consisting of deprenyl and rasagiline or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphs or stereoisomers as well as the mixtures thereof.

11. A pharmaceutical composition according to claim 8-9, wherein the sodium channel blocker is selected from the group consisting of lamotrigine, riluzole, crobenetine, oxcarbamazepine and phosphenytoin or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphs or stereoisomers as well as the mixtures thereof.

12. A pharmaceutical composition according to any of claims 8-9, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is lamotrigine.

13. A pharmaceutical composition according to any of claims 8-9, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is riluzole.

14. A pharmaceutical composition according to any of claims 8-9, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is lamotrigine.

15. A pharmaceutical composition according to any of claims 8-9, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is riluzole.

16. A method for the treatment and/or prevention of a disease occurring in a mammal, said disease involving chronic pain, epilepsy or deriving from disorders and/or injuries of the motor system, characterized in that a therapeutically effective amount of pharmaceutical composition comprising a sodium channel blocker and a MAO-B inhibitor is given to the subject in need of such treatment.

17. A method for the treatment and/or prevention of neurodegenerative diseases (e.g. ALS, HIV-originated dementia, Parkinson's syndrome, Alzheimer's disease, Huntington's chorea, multiple sclerosis, prion diseases, stroke, cerebral and spinal cord injuries, cerebral ischemia), as well as in the treatment and prevention of drug or

alcohol addiction, incontinence of faces and urine, inflammation, itching, intracranial edema, ischemia and/or subsequent damage caused by reperfusion or retinopathy, as a complication glaucoma a complication of glaucoma in mammals, characterized in that a therapeutically effective amount of pharmaceutical composition comprising a sodium channel blocker and selective serotonin uptake inhibitor is given to the subject in need of such treatment.

18. A method according to claim 16 or 17, wherein the MAO-B inhibitor is selected from the group consisting of deprenyl and rasagiline or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphsor stereoisomers as well as the mixtures thereof.

19. A method according to claim 16 or 17, wherein the sodium channel blocker is selected from the group consisting of lamotrigine, riluzole, crobenetine, oxcarbamazepine and phosphenytoin or their pharmaceutically acceptable derivatives like salts, esters, hydrates, solvates, polymorphsor stereoisomers as well as the mixtures thereof.

20. A method according to claim 16 or 17, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is lamotrigine.

21. A method according to claim 16 or 17, wherein the MAO-B inhibitor is deprenyl and the sodium channel blocker is riluzole.

22. A method according to claim 16 or 17, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is lamotrigine.

23. A method according to claim 16 or 17, wherein the MAO-B inhibitor is rasagiline and the sodium channel blocker is riluzole.

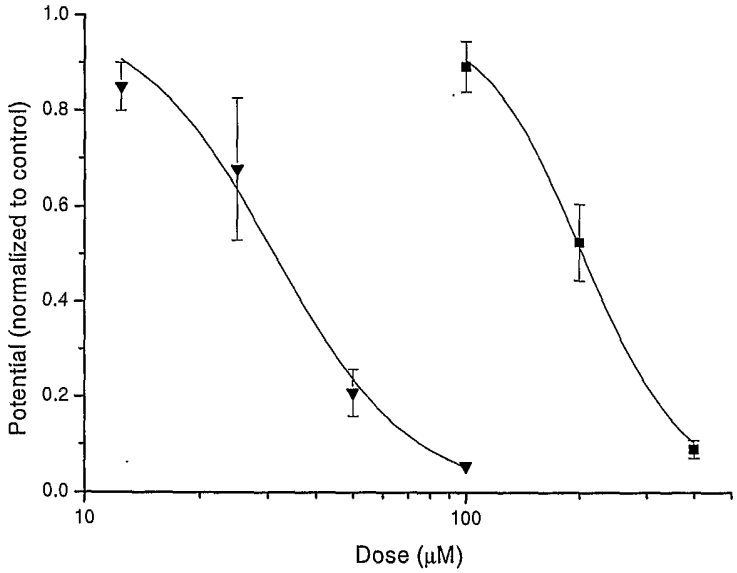

Figure 1.

Effect of deprenyl on the reflex inhibitory action of lamotrigine, in vitro. Effect of lamotrigine alone (■; IC50=203.8 μM) and in the presence of 10 μM deprenyl (▼; IC50=31.3 μM).

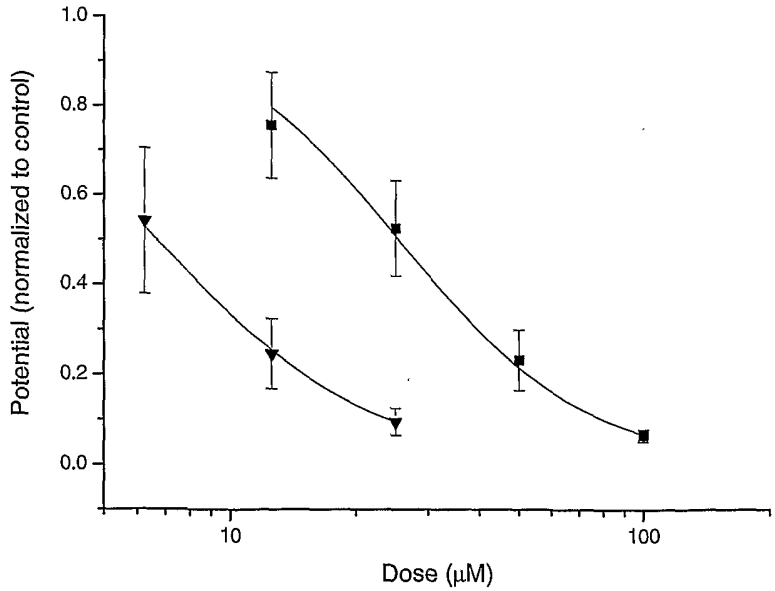

Figure 2.

Effect of deprenyl on the reflex inhibitory action of riluzole, in vitro. Effect of riluzole alone (■; IC50=25.5 μM) and in the presence of 10 μM deprenyl (▼; IC50=6.7 μM).

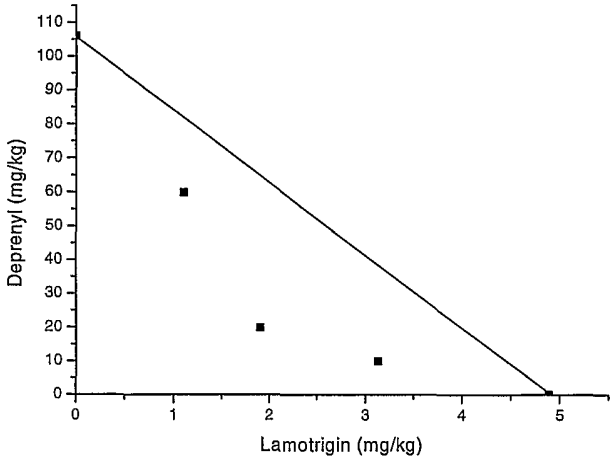

Figure 3.
the isobologram for the interaction between lamotrigine and deprenyl

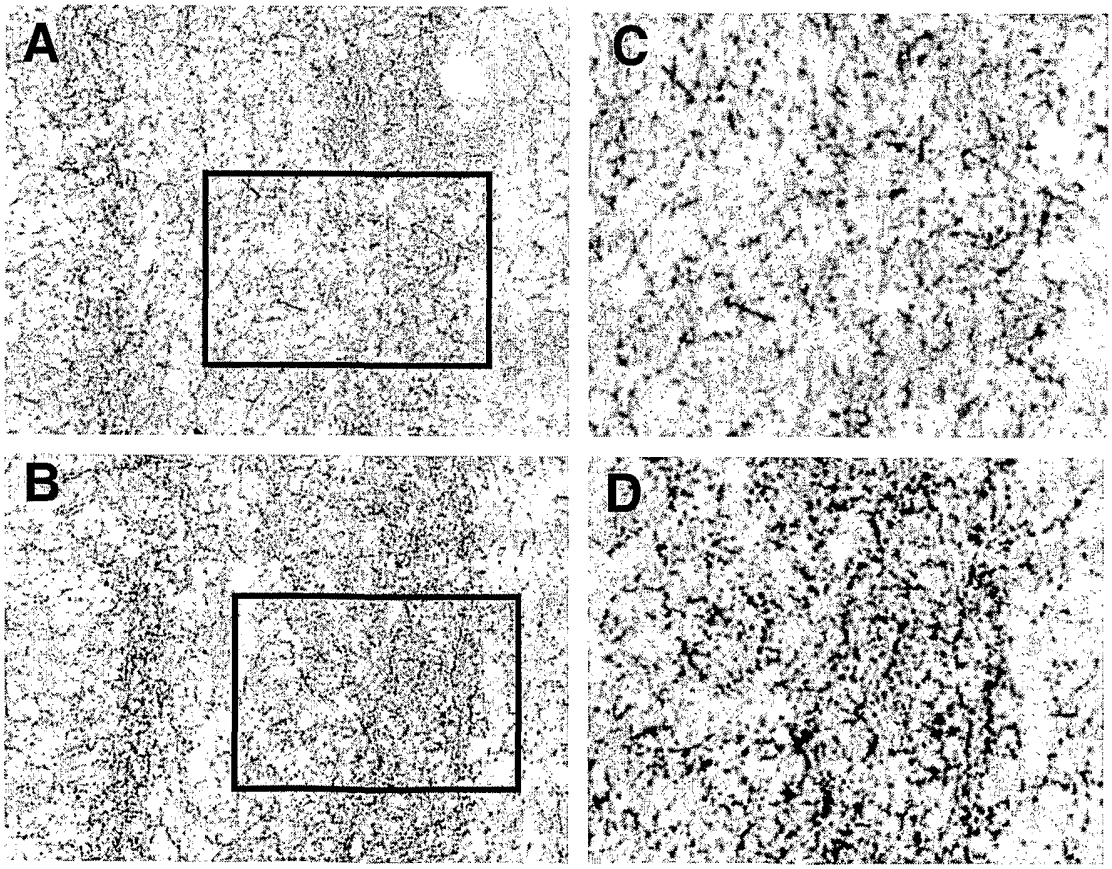

Figure 4.

A and C: from sham operated, B and D: from NMDA lesioned animals treated with a combination of deprenyl and lamotrigine. C and D show the same areas as A and B, respectively, with higher magnification.

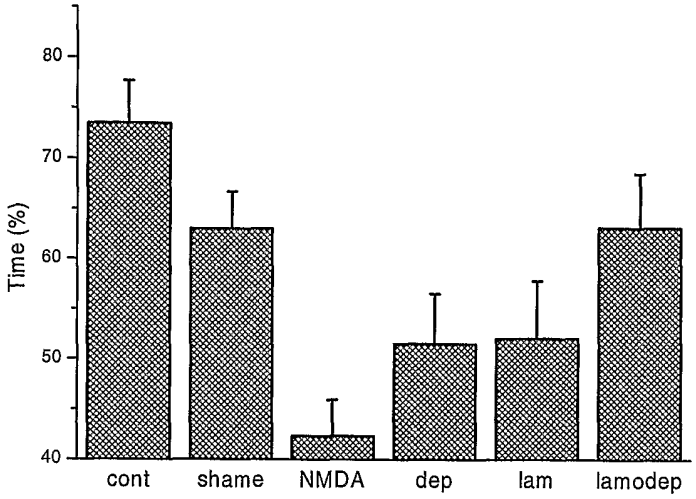

Figure 5.

Control animal (cont); shame operated (shame); NMDA treated control (NMDA); NMDA treated + deprenyl (2.5 mg/kg, dep); NMDA treated + lamotrigine (10 mg/kg), NMDA treated + lamotrigine (10 mg/kg) and deprenyl (2,5 mg/kg, lamodep)

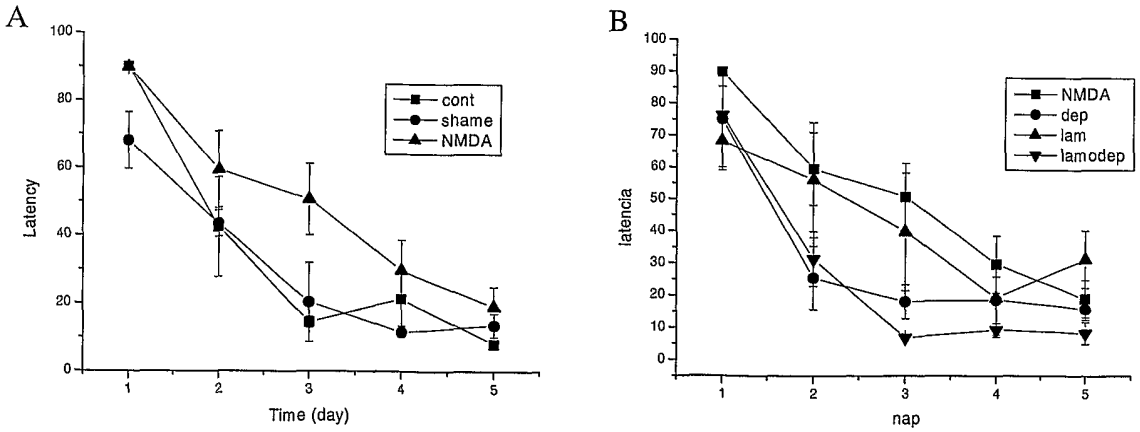

Figure 6.

A: control animals (cont); shame operated (shame); NMDA treated control (NMDA)
B: NMDA treated control (NMDA); NMDA treated + deprenyl (2.5 mg/kg; dep); NMDA treated + lamotrigine (10 mg/kg; lam); NMDA treated + lamotrigin (10 mg/kg) and deprenyl (2.5 mg/kg; lamodep)