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54	AGENTS WITH AN ANTIDEPRESSIVE EFFECT

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FOR ABSTRACT SEE THE NEXT SHEET

(57) **Abstract**

The invention relates to the use of 2–amino–4,5,6,7–tetrahydro–6–propylamino–benzothizole (pramipexol), its (+) or (–) enantiomers or one of its pharmacologically compatible salts, combined with sertralin, for treating depression and depressive conditions more effectively.

Remedy with antidepressant effects

The present invention relates to an agent with an antidepressant activity containing 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, the (+) or (-) enantiomer thereof, the pharmacologically acceptable acid addition salts thereof and a conventional antidepressant. The combination of pramipexole and sertraline is of particular interest.

Prior art

Pramipexole – (-)-2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzo-thiazole – is an dopamine-D_3/D_2 agonists, the synthesis of which is described in European Patent 186 087 and US 4,886,812. Pramipexole is known primarily for treating schizophrenia and particularly for the treatment of Parkinson's disease. German Patent Application DE 38 43 227 discloses that pramipexole lowers the prolactin serum level, and it is also known from German Patent Application DE 39 33 738 to use pramipexole to lower high TSH levels. Its transdermal administration is disclosed in US Patent 5,112,842, and WO Patent Application PCT/EP93/03389 describes the use of pramipexole as an antidepressant.

Details of the preparation of the title compound can be found in EP-A 85 116 016, and reference is hereby made specifically to the literature cited therein.

Description of the invention

It has now been found that, surprisingly, pramipexole, the (+) or (-) enantiomer thereof, or the pharmacologically acceptable acid addition salts thereof, combined with another antidepressant has a significantly greater antidepressant activity than either of the two individual components taken alone. The fact that the combination of active substances takes effect immediately should be particularly emphasised.

The improvement in the effect of pramipexole by the simultaneous administration of another antidepressant was discovered by testing rats that have been applied a

combination of pramipexole and sertraline according to the so-called "forced swimming test". Details of this test method can be found, for example, in Willner, Psychopharmacology 83, 1-16 (1984) or Borsini and Meli, Psychopharmacology 94, 147-160 (1988).

For the particular preferred combination of pramipexole and sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, their acid addition salts respectively, the test was carried out as follows. The animals were divided up into different groups and each group was given either a saline solution, a therapeutically effective amount of pramipexole, a therapeutic amount of sertraline or a combined dose of both antidepressants in the same therapeutic amount as the animals that received only one of the two active substances.

The combination of 2-amino-4,5,6,7-tetrahydro-6-n-propyl-amino-benzothiazole, the (+) or (-) – enantiomer thereof, the acceptable acid addition salts thereof and (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine (sertraline) and the acid addition salts thereof is particularly preferred, while the combination of pramipexole and sertraline in the form of their hydrochlorides is most particularly preferred.

Despite sertraline another antidepressent can be used in combination with pramipexole as well. Preferably these other antidepressants are selected from the following known compounds:

alprazolam,
chlordiazepoxide,
clomipramine,
chinpirol,
dibenzepin,
doxepin,
fluvoxamine,
lofepramine,
maprotiline,
mirtazapine,
moclobemide,
nefazodone,
nortriptyline,
opipramol,
paroxetine,
sertraline,
sulpiride,
tranylcypromine,
trimipramine,
tryptophan,
venlafaxine or
viloxazine

mianserin, trazodone,

The term combination for the purposes of the invention refers to an active substance combination of the two active substances (pramipexole and the second antidepressivum) in a formulation and also as a combination in the sense of individual formulations of the active substances administered at specified intervals from one another in a therapeutic measure.
Orally administered pharmaceutical formulations for pramipexole are known from the prior art and are obtainable f.e. in the German or US-market.

The individual active substances may also be packaged in kit form as a combined pack of the individual drugs, as well as separately.

The combination of pramipexole and another antidepressant may be formulated analogously to conventional galenic preparations, generally together with a pharmaceutical carrier. In other words an effective dose of the individual components and optionally a pharmaceutical carrier are formulated as plain or coated tablets, lozenges, powders, solutions, suspensions, emulsions, syrups, suppositories etc. For pramipexole the pharmaceutically effective dose per patient is between 0.01 and 10 mg, preferably between 0.08 and 5 mg.

The therapeutically effective doses of the second antidepressant in the combination are given in the Table which follows.

(25-100mg)	alprazolam,	(20mg)	paroxetin,
(5mg)	chlordiazepoxide,	(50mg)	sertraline,
(10-25mg)	clomipramine,	(50-200mg)	sulpiride,
(1-5mg)	chinpirol,	(10 mg)	tranylcypromine,
(10-250mg)	dibenzepin,	(25-100mg)	trazodone,
(5-50mg)	doxepin,	(25-250mg)	trimipramine,
(50-100mg)	fluvoxamine,	(500mg-2.5g)	tryptophan,
(35-75mg)	lofepramine,	(30-75mg)	venlafaxine or
(10-75mg)	maprotiline,	(100mg)	Viloxazine.

(10-30mg)	mianserin,
(30mg)	mirtazapine,
(150-300 mg)	moclobemide,
(100-300mg)	nefazodone,
(10-25mg)	nortriptyline,
(50mg)	opipramol,

In the combination according to the invention the recommended dose may in individual cases be below the single dose previously recommended for the monopreparation.

Description of the experiments

Pramipexole was used in doses of 0.1 and 0.3 mg/kg. In addition, trials were carried out using 0.05 mg/kg pramipexole. Sertraline was used in doses of 5 and 10 mg/kg as mentioned in the Tables. The tests were carried out on rats (male Wistar, 250-270 g) at RT while maintaining a natural day-night rhythm. Pramipexole (HCl) was dissolved in a physiological saline solution and sertraline (HCl) was dissolved in distilled water, and both substances were injected in a volume of 2 ml/kg.

Forced swimming test in rats

The total immobility time was determined according to Porsolt et al. (1978) within a five-minute observation period. Pramipexole (0.05, 0.1 and 0.3 mg/kg) and sertraline (5 or 10 mg/kg) were given three times at intervals of 24 hours, 5 hours and 1 hour before the test.

In separate groups pramipexole was also injected three times in the abovementioned dosage together with sertraline (5 or 10 mg/kg) as described above. Each group consisted of 10 rats.

Results

Pramipexole – 0.1 mg/kg – does not alter the immobility time in the forced swimming test, whereas higher doses (0.3 mg) bring about a significant reduction in the immobility time.

A dosage of 5 mg/kg sertraline on its own likewise does not reduce the immobility time. However, the joint administration of 5 mg/kg of sertraline and 0.1 mg/kg of pramipexole noticeably reduces the immobility time. This effect is considerably more marked at higher doses of sertraline.

Sertraline alone in a dose of 10 mg/kg was inactive in the forced swimming test, but given in conjunction with pramipexole (0.1, 0.3 mg/kg). This effect is increased at higher doses of pramipexole. Pramipexole in a dosage of 0.05 mg/kg shows no effect on the immobility time but there is a reduction in the immobility time when it is combined with sertraline.

These results demonstrate the unexpected synergistic effect of pramipexole in conjunction with sertraline as an antidepressant.

Table 1. Effect of pramipexole (0.1 and 0.3 mg/kg) on its own or in conjunction with sertraline (5 mg/kg) on the immobility time in the forced swimming test in rats.

Compounds (mg/kg)	Immobility time(s)	
	mean ± SEM	P
1. carrier	239.9 ± 3.1	____
2. sertraline 5	257.0 ± 7.0	ns vs 1
3. pramipexole 0.1	223.4 ± 6.2	ns vs 1
4. pramipexole 0.3	171.5 ± 9.2	<0.001 vs 1
5. sertraline 5 + pramipexole 0.1	96.1 ± 10.3	<0.001 vs 3
6. sertraline 5 + pramipexole 0.3	18.1 ± 3.5	<0.001 vs 4

Pramipexole (0.1 or 0.3 mg/kg s.c.) and sertraline (5 mg/kg i.p.) are administered three times (24 hours, 5 hours and 1 hour) before the test.

Table 2. Effect of pramipexole (0.1 and 0.3 mg/kg) on its own or in conjunction with sertraline (10 mg/kg) on the immobility time in the forced swimming test in rats.

Compounds (mg/kg)	Immobility time(s)	
	mean ± SEM	P
1. carrier	237.9 ± 2.7	____
2. sertraline 10	223.6 ± 9.9	Ns vs 1
3. pramipexole 0.1	212.5 ± 6.9	Ns vs 1
4. pramipexole 0.3	142.9 ± 7.9	<0.001 vs 1
5. sertraline 10 + pramipexole 0.1	133.3 ± 6.9	<0.001 vs 3
6. sertraline 10 + pramipexole 0.3	11.8 ± 2.3	<0.001 vs 4

Pramipexole (0.1 or 0.3 mg/kg s.c.) and sertraline (10 mg/kg i.p.) are administered 3 times (24 hours, 5 hours and 1 hour) before the test.

Table 3. Effect of pramipexole (0.05 mg/kg) on its own or in conjunction with sertraline (5 and 10 mg/kg) on the immobility time in the forced swimming test in rats.

Compounds (mg/kg)	Immobility time(s)	
	mean ± SEM	P
1. carrier	235.3 ± 4.8	____
2. pramipexole 0.05	245.5 ± 7.8	ns vs 1
3. sertraline 5	247.5 ± 3.0	ns vs 1
4. sertraline 10	223.7 ± 2.8	ns vs 1
5. sertraline 5 + pramipexole 0.05	187.7 ± 11.2	<0.001 vs 2
6. sertraline 10 + pramipexole 0.05	163.9 ± 10.0	<0.001 vs 2

Pramipexole (0.05 mg/kg s.c.) and sertraline (5 and 10 mg/kg i.p.) are administered 3 times (24 hours, 5 hours and 1 hour) before the test.

Patent Claims

1. Agent for treating depression, containing 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, one of the enantiomers thereof or acid addition salts thereof in conjunction with a conventional antidepressant selected from the group

alprazolam,
chlordiazepoxide,
clomipramine,
chinpirol,
dibenzepin,
doxepin,
fluvoxamine,
lofepramine,
maprotiline,
mianserin,
mirtazapine,
moclobemide,
nefazodone,
nortriptyline,
opipramol,
paroxetine,
sertraline,
sulpiride,
tranylcypromine,
trazodone,
trimipramine,
tryptophan,
venlafaxine or
viloxazine.

or one of the pharmacologically acceptable salts thereof .

2. Agent according to claim 1, characterised in that it contains the (+)-enantiomer of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole or one of the acid addition salts thereof.

3. Agent according to claim 1, characterised in that it contains the (-)-enantiomer of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole or one of the acid addition salts thereof.

4. Agent according to one of claims 1 to 3, characterised in that it contains 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole-dihydrochloride, particularly 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole-dihydrochloride monohydrate.

5. Agent according to claim 1, characterised in that the formulation contains 0.05-10 mg of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, one of the enantiomers or one of the acid addition salts thereof, pramipexole or pramipexole-dihydrochloride-monohydrate.

6. Pharmaceutical formulation according to claim 1, characterised in that the formulation contains 0.088 – 1.5mg of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, one of the enantiomers or one of the acid addition salts thereof, pramipexole or pramipexole-dihydrochloride-monohydrate.

7. Agent containing 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, one of the enantiomers, one of the acid addition salts thereof, pramipexole or pramipexole-dihydrochloride-monohydrate and sertraline or a pharmaceutically acceptable acid addition salt thereof.

8. Agent containing pramipexole or pramipexole dihydrochloride and sertraline or a pharmaceutically acceptable acid addition salt thereof.

9. Agent according to claim 8, characterised in that it contains between 0.088 and 1.1mg of pramipexole or between 0.125 and 1.5mg of pramipexole dihydrochloride monohydrate monohydrate.

10. Agent according to one of claims 8 to 9, characterised in that it contains between 25 and 200mg of sertraline.

11. Agent according to claim 13, characterised in that it contains 50 mg of sertraline.

12. Use of an agent according to one of the preceding claims for treating depression or depressive states.

13. Use of an agent according to one of the preceding claims for preparing a pharmaceutical composition for treating depression.

14. Method of treating depression in patients suffering from such a complaint, characterised in that a combination of active substances according to one of the preceding claims is administered.

15. Method according to claim 14, characterised in that the active substances are taken as individual compounds one after the other over time.