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Psychopharmacologic Drugs

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Abstract

This month's *Annual Review* is dedicated to updated information on psychopharmacologic drugs. The following table lists 86 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been marketed for an indication other than that discussed in the review. Information on the following 17 products is updated here: **aripiprazole, blonanserin, deramciclane fumarate, duloxetine hydrochloride, E-5842, escitalopram oxalate, gepirone hydrochloride, iloperidone, lamotrigine, lesopitron dihydrochloride, MDL-100907, nemifitide ditriflutate, Org-5222, pagoclone, perospirone hydrochloride, pregabalin** and **vilazodone hydrochloride.** A new addition to the *Annual Review* series, entitled Spotlights, begins this month and provides profiles of drugs which have not been previously published in the journal but are under active development in the area under review. Drugs featured in the Spotlights section this month are: **abaperidone hydrochloride, ACR-16, agomelatine, ANPH-101, ANPH-102, aprepitant, AR-A2, AVE-5997, bifeprunox, cannabidiol, CEE-310, CP-122721, CX-516, DOV-216303, DU-125530, E-6039, elzasonan hydrochloride, EMR-62218, eplivanserin, eszopiclone, gaboxadol, GW-353162, GW-597599, indiplon, itriglumide, levetiracetam, LU-36,138, LY-156735, LY-354740, melatonin, NBI-34041, NE-100, NGD-96-3, ocinaplon, olanzapine/fluoxetine, OPC-14523, Org-24448, Org-34167, Org-34517, osanetant, R-673, R-1204, saredutant, SB-271046, SB-723620, secretin (synthetic human), SEP-174559, sertindole, (*R*)-sibutramine metabolite, SL-65.1498, SLV-308, SLV-310, SLV-313, SLV-314, SLV-319, SM-13496, SNEC-2, sodium oxybate, SR-58611, SR-144190, TAK-375, talnetant** and **valproic acid sodium salt**.

We remind our readers that the Prous Science **Integrity** database provides continously updated information on the products covered in this *Annual Review*.

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Drug	Source	Indication/Action	Phase
Abaperidone Hydrochloride	Ferrer	Antipsychotic	I
ACR-16	Carlsson Research	Antipsychotic	I
Agomelatine	Servier	Antidepressant	III
ANPH-101	Ancile	Sleep disorders	II/III
ANPH-102	Ancile	Anxiolytic	II
Aprepitant[1]	Merck & Co.	Antidepressant	III
AR-A2	AstraZeneca	Antidepressant	I
Aripiprazole[1]	Otsuka/Bristol-Myers Squibb	Antipsychotic	R-2002
		Bipolar disorder	III
AVE-5997	Aventis Pharma	Antipsychotic	I
Bifeprunox	Solvay/Lundbeck	Antipsychotic	II
Blonanserin[1]	Dainippon Pharmaceutical	Antipsychotic	III
Cannabidiol	GW Pharmaceuticals	Antipsychotic	I
CEE-310	CeNeS	Sleep disorders	II
CP-122721	Pfizer	Antidepressant	II
CX-516	Cortex/Organon	Antipsychotic	II
	Rush Presbyterian-St. Luke's Med. Center	Autism	II
Deramciclane Fumarate[1]	Orion Corp./Pharmacia	Generalized anxiety disorder	III
DOV-216303	DOV Pharmaceutical	Antidepressant	I
DU-125530	Solvay	Antidepressant	II
Duloxetine Hydrochloride[1]	Lilly/Shionogi	Antidepressant	Prereg
E-5842[1]	Esteve	Antipsychotic	II
E-6039	Esteve	Antidepressant	I
Elzasonan Hydrochloride	Pfizer	Antidepressant	II
EMR-62218	Merck KGaA	Antipsychotic	I
Eplivanserin	Sanofi-Synthélabo	Antipsychotic	II
Escitalopram Oxalate[1]	Lundbeck/Forest	Antidepessant	L-2002
	Lundbeck/Forest	Panic disorder	L-2002
	Lundbeck	Social anxiety disorder	III
Eszopiclone	Sepracor	Sedative/Hypnotic	III
Gaboxadol	Lundbeck	Sleep disorders	II/III
Gepirone Hydrochloride[1]	Organon	Antidepressant	Prereg
GW-353162	GlaxoSmithKline	Antidepressant	I
		Bipolar disorder	I
GW-597599	GlaxoSmithKline	Antidepressant	II
		Anxiolytic	II
Iloperidone[1]	Novartis/Titan	Antipsychotic	III
Indiplon	DOV Pharmaceutical/Neurocrine Biosciences	Sleep disorders	III
Itriglumide[1]	Rotta	Anxiolytic	I
Lamotrigine[1,2]	GlaxoSmithKline	Bipolar disorder	III
Lesopitron Dihydrochloride[1]	Esteve	Generalized anxiety disorder	II
Levetiracetam[1,2]	UCB	Bipolar disorder	Clinical
LU-35-138	Lundbeck	Antipsychotic	I
LY-156735	Lilly/Phase 2 Discovery	Sedative/Hypnotic	I
LY-354740	Lilly	Anxiolytic	I
MDL-100907[1]	Aventis Pharma	Sleep disorders	I
Melatonin	Paladin/Neurim	Sleep disorders	Prereg
NBI-34041	Neurocrine Biosciences	Antidepressant	I
	Neurocrine Biosciences/GlaxoSmithKline	Anxiolytic	I
NE-100	Taisho	Antipsychotic	II
Nemifitide Ditriflutate[1]	Innapharma	Antidepressant	II/III
NGD-96-3	Neurogen/Pfizer	Sleep disorders	I
Ocinaplon	DOV Pharmaceutical/Elan	Generalized anxiety disorder	II
Olanzapine/Fluoxetine	Lilly	Antidepressant	III
OPC-14523	Otsuka	Antidepressant	II
Org-24448	Cortex/Organon	Antipsychotic	II
Org-34167	Organon	Antidepressant	II
Org-34517	Organon	Antidepressant	II
Org-5222[1]	Organon	Antipsychotic	III
Osanetant	Sanofi-Synthélabo	Antidepressant	II
		Antipsychotic	II

Continued

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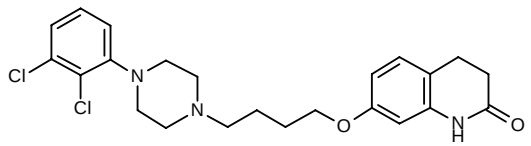
Drug	Source	Indication/Action	Phase
Pagoclone[1]	Indevus	Anxiolytic	III
		Generalized anxiety disorder	II
Perospirone Hydrochloride[1]	Sumitomo Pharmaceuticals/Mitsubishi Pharma		Antipsychotic
L-2001			
Pregabalin[1]	Pfizer	Generalized anxiety disorder	II
R-673	Roche	Antidepressant	II
R-1204	Roche	Anxiolytic	I
	Roche	Antidepressant	I
Saredutant[1]	Sanofi-Synthélabo	Antidepressant	II
SB-271046	GlaxoSmithKline	Antipsychotic	I
SB-723620	GlaxoSmithKline	Antidepressant	I
		Anxiolytic	I
Secretin, Synthetic Human	ChiRhoClin/Repligen	Autism	III
SEP-174559	Sepracor	Anxiolytic	I
Sertindole	Lundbeck	Antipsychotic	R-2001
(*R*)-Sibutramine Metabolite	Sepracor	Antidepresant	II
SL-65.1498	Sanofi-Synthélabo	Anxiolytic	II
SLV-308[1]	Solvay	Antidepressant	II
		Anxiolytic	II
SLV-310	Solvay	Antipsychotic	I
SLV-313	Solvay	Antipsychotic	I
SLV-314	Solvay	Antipsychotic	I
SLV-319	Solvay	Antipsychotic	I
SM-13496	Sumitomo Pharmaceuticals	Antipsychotic	II
SNEC-2	Synaptic	Antidepressant	I
Sodium Oxybate	Orphan Medical	Antinarcoleptic	L-2002
SR-58611	Sanofi-Synthélabo	Antidepressant	II
SR-144190	Sanofi-Synthélabo	Antidepressant	I
	Sanofi-Synthélabo	Anxiolytic	I
TAK-375	Takeda	Sedative/Hypnotic	II
Talnetant	GlaxoSmithKline	Antipsychotic	II
Valproic Acid Sodium Salt[1,2]	Dainippon Pharmaceutical	Bipolar disorder	R-2002
Vilazodone Hydrochloride[1]	Merck KGaA/GlaxoSmithKline	Antidepressant	II

[1]Previously published in Drugs of the Future. [2]Launched for another indication.

Aripiprazole



The first of a new generation of atypical antipsychotics, aripiprazole (OPC-14597, Abilify®) acts as a dopamine D_2 and 5-HT_{1A} receptor partial agonist and a 5-HT_2 receptor antagonist. The compound has been suggested to act as a dopamine/5-HT system stabilizer (1-4). The FDA just approved the NDA filed by Otsuka and licensee Bristol-Myers Squibb for its use in the treatment of schizophrenia. It is also undergoing phase III clinical testing by both companies for the treatment of bipolar disorder. An MAA is under review in Europe (5-7).

The cardiovascular effects of aripiprazole were compared to those of haloperidol in a halothane-anesthetized canine model. The drugs were infused over 10 min at escalating doses of 0.03, 0.3 and 3.0 mg/kg with 20-min intervals between doses. Aripiprazole at doses of 0.03-0.3 mg/kg had positive chronotropic, inotropic and dromotropic effects and resulted in shortening of the ventricular effective refractory period and repolarization phase. Dose-dependent decreases in total peripheral resistance were also observed. At 0.1 mg/kg/min, esmolol antagonized these changes. The 3.0 mg/kg dose of aripiprazole attenuated the cardiac effects produced by the lower doses and induced negative chronotropic, dromotropic and hypotensive actions and prolongation of the ventricular effective refractory period and repolarization phase. The only significant change seen with the lowest dose of haloperidol was a decrease in peripheral resistance. Haloperidol 0.3-3.0 mg/kg produced dose-dependent negative chronotropic, inotropic and hypotensive effects, intraventricular conduction delay and prolongation of the ventricular effective refractory period and repolarization phase. These effects were accompanied by a further decrease in peripheral resistance. Aripiprazole had less potent inhibitory effects on cardiovascular parameters than haloperidol at clinically relevant exposure, and appeared to be safer than haloperidol as it did not induce afterdepolarization or prolong the ventricular electrical vulnerable period (8).

Patients with stable chronic schizophrenia treated with 15 mg/day of aripiprazole presented greater improvement in efficacy parameters (PANSS [Positive And Negative Syndrome Scale] total score and PANSS positive subtotal score) and a lower relapse rate than placebo-treated patients. Aripiprazole showed a favorable safety and tolerability profile comparable to placebo (9).

The safety, tolerability and pharmacokinetics of aripiprazole were assessed in 12 children and 11 adolescents with conduct disorder. Dosing was revised according to weight due to nausea and sedation in younger subjects to 1 mg if < 25 kg, 2 mg if 25-50 kg, 5 mg if 50-70 kg and 10 mg if > 70 kg. The drug was safe and well tolerated, with no serious adverse events or clinically relevant changes in vital signs, ECG or laboratory parameters, and accumulation was comparable among children, adolescents and adults (10).

A multicenter, double-blind, placebo-controlled trial in 404 patients with acute exacerbations of schizophrenia or schizoaffective disorder randomized patients to receive once-daily aripiprazole 20 or 30 mg, twice-daily risperidone 6 mg or placebo for 4 weeks following a washout period. Aripiprazole and risperidone proved to be significantly more effective than placebo in terms of changes from baseline in the total PANSS and the positive and negative subscales of the PANSS, as well as the Clinical Global Impression severity of illness and improvement scores. The active treatment groups also showed a significantly higher responder rate compared to placebo. Aripiprazole was not associated with worsening of extrapyramidal symptoms, increase in serum prolactin or changes in Q-Tc interval compared to placebo, whereas risperidone produced a significant increase in prolactin levels (11, 12). The results of this study and some that follow are summarized in Table I.

The effects of short- and long-term administration of aripiprazole on weight were evaluated in a meta-analysis of several 4-6-week studies (n=1648), as well as a 1-year study (n=1294) and a 26-week trial (n=255). Patients either experienced slight gain in weight or weight loss when treated with aripiprazole. Studies with an active control showed that aripiprazole-related weight gain was similar to that with haloperidol and less than that with olanzapine. Neither short- nor long-term administration of aripiprazole was associated with prolongation of the Q-T interval, and its low potential for extrapyramidal symptoms, prolactin elevation and somnolence was also confirmed (13-16).

In the 1-year study in patients (n=1294) with acute relapse of chronic schizophrenia, aripiprazole 30 mg/day resulted in higher response rates than haloperidol 10 mg/day (62.4% *vs.* 54.9%) and induced significant improvements in negative symptom scores and depressive symptom. Doses could be reduced to 20 and 7 mg/day, respectively (17, 18).

Aripiprazole was safe, effective, well tolerated and demonstrated linear pharmacokinetics at doses of 30-90 mg/day in a randomized, double-blind study in 40 patients with stable schizophrenia or schizoaffective disorder. In this study, doses of 30, 45, 60, 75 and 90 mg/day were evaluated over 15 days. The only adverse event associated with a gradual increase in the aripiprazole dose from 30 mg/day to 90 mg/day was a higher incidence of

Table I: Clinical studies of aripiprazole (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Schizophrenia	Randomized, double-blind, multicenter	Aripiprazole, 20 mg od x 4 wk (n=101) Aripiprazole, 30 mg od x 4 wk (n=191) Risperidone, 3 mg bid x 4 wk (n=99) Placebo (n=103)	404	Aripiprazole was safe and as effective as risperidone in the treatment of positive and negative symptoms of patients with relapsed schizophrenia or schizoaffective disorder	12
Schizophrenia	Pooled/ meta-analysis	Aripiprazole x 4-52 wk Haloperidol, 10 mg od x 4-52 wk Risperidone, 6 mg/d x 4-6 wk Olanzapine, 6 mg od x 4-26 wk Placebo	1648	Aripiprazole induced a minimal weight gain when compared with haloperidol, with a greater difference *versus* olanzapine, in patients with schizophrenia or schizoaffective disorder. Both short- and long-term treatment with aripiprazole were associated with a low potential for EPS, weight gain, increase in prolactin levels, QTc prolongation and somnolence	13-16, 30
Schizophrenia	Randomized, double-blind, multicenter	Aripiprazole, 30 mg od x 52 wk (n=861) Haloperidol, 10 mg od x 52 wk (n=433)	1294	Greater response rates, lower discontinuation rates and higher improvements in negative subscale scores and depressive symptoms were found for aripiprazole compared with haloperidol in patients with schizophrenia. The incidence of extrapyramidal adverse events was lower with aripiprazole	15, 18
Schizophrenia	Randomized, double-blind	Aripiprazole, 30 mg/d x 15 d (n=12) Aripiprazole, 45 mg/d x 15 d (n=7) Aripiprazole, 60 mg/d x 15 d (n=7) Aripiprazole, 75 mg/d x 15 d (n=7) Aripiprazole, 90 mg/d x 15 d (n=7)	40	Treatment with aripiprazole 30-90 mg/d was safe, well tolerated and effective in controlling symptoms in patients with schizophrenia or schizo-affective disorder, although there was an increased incidence of akathisia and tachycardia in the 90-mg dose group	19, 20
Schizophrenia	Randomized, double-blind, multicenter	Aripiprazole, 15 mg/d x 26 wk Placebo	310	Aripiprazole was well tolerated , with an adverse event profile similar to that of placebo and effective in decreasing the number of patients with relapse, increasing the time to relapse by 2-fold and improving the PANSS score in patients with stable chronic schizophrenia	21
Bipolar disorder, mania	Randomized, double-blind, multicenter	Aripiprazole, 30 mg (decreased to 15 mg if not tolerated) x 3 wk Placebo	262	Aripiprazole was well tolerated and effective in inducing significant improvements in the Young Mania Rating Scale Total score in patients with acute and bipolar mania	22, 23
Schizophrenia	Randomized	Aripiprazole, 30 mg/d (abrupt discontinuation of other antipsychotics) x 8 wk (n=104) Aripiprazole, 30 mg/d + current antipsychotics (tapering off over 2 wk) x 8 wk (n=104) Aripiprazole, 10-30 mg/d (titrated over 2 wk) + current antipsychotics (tapering off over 2 wk) x 8 wk (n=103)	311	Switching to aripiprazole was safe, well tolerated and effective in improving PANSS and CGI scores in patients with schizophrenia or schizo-affective disorder, showing less extrapyramidal events, reduced weight and decreased serum prolactin levels	24, 25
Schizophrenia	Open, multicenter	Aripiprazole, 30 mg od x 26 wk (n=76) Olanzapine, 15 mg o.d. x 26 wk (n=93)	169	Compared with olanzapine, aripiprazole significantly improved secondary verbal memory and induced less weight gain in patients with stable schizophrenia	26
Schizophrenia	Open, pooled/ meta-analysis	Aripiprazole, 30 mg/d x 14 d → Aripiprazole, 30 mg/d x 22 d + Lithium (titrated from 900 mg until serum concentrations 1.0-1.4 mEq/l for >/=5 d) x 22 d (n=7) Aripiprazole, 30 mg/d x 14 d → Aripiprazole, 30 mg/d x 22 d + Valproate semisodium, 50-125 mg/l x 22 d (n=6)	13	Concomitant administration of aripiprazole and either lithium or valproate semisodium was safe and well tolerated by patients with schizophrenia or schizoaffective disorder	27

Continued

Table I (Cont.): Clinical studies of aripiprazole (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Schizophrenia	Pooled/ meta-analysis	Aripiprazole, 2 mg od x 4-6 wk (n=59) Aripiprazole, 10 mg od x 4-6 wk (n=165) Aripiprazole, 15 mg od x 4-6 wk (n=207) Aripiprazole, 20 mg od x 4-6 wk (n=199) Aripiprazole, 30 mg od x 4-6 wk (n=263) Haloperidol, 10 mg od x 4-6 wk (n=167) Risperidone, 6 mg od x 4-6 wk (n=100) Placebo (n=380)	1540	All aripiprazole doses higher than 2 mg od significantly improved the positive and negative symptoms of schizophrenia and schizoaffective disorder just 1 week after beginning therapy	28, 29

akathisia and tachycardia that resulted in no discontinuations (19, 20).

A multicenter, randomized, double-blind, placebo-controlled trial in 310 chronic, stable schizophrenic patients was conducted to assess relapse after treatment with aripiprazole 15 mg/day for 3 months. Compared with placebo, significantly fewer patients taking aripiprazole relapsed (57% and 34%, respectively), and the drug doubled the time to relapse. Aripiprazole was well tolerated (21).

Aripiprazole 30 mg/day or placebo was administered to 262 patients with acute bipolar mania for 3 weeks in a randomized, double-blind phase III trial. Aripiprazole was well tolerated and significantly superior to placebo in the primary efficacy measure, the Y-MRS total score, as well as in the response rate (40% *vs.* 19%). The drug was effective within the first week of treatment (22, 23).

A multicenter, randomized, open-label phase III study compared the effects of switching from typical or atypical antipsychotic monotherapy to aripiprazole monotherapy in a population of 311 patients suffering from chronic, stable schizophrenia or schizoaffective disorder. Switching was equally safe and effective when it was done abruptly or over a 2-week period (tapering off the previous antipsychotic with or without gradually increasing the aripiprazole dose administered to the patients) (24, 25).

Aripiprazole 30 mg once daily was better than olanzapine 15 mg once daily in improving the secondary verbal memory of patients with schizophrenia, although both treatments were equally effective in improving general cognitive function and the clinical situation of the patients (26).

The pharmacokinetics and safety of coadministration of aripiprazole and lithium or divalproex sodium were investigated in 2 open-label studies in patients with schizophrenia or schizoaffective disorder. Aripiprazole 30 mg/day was given on days 1-14 and either lithium or divalproex sodium on days 15-36. While the mood-stabilizing agents affected pharmacokinetic variables of aripiprazole, the pharmacokinetics of the active metabolite were only slightly altered. Coadministration of these agents was deemed safe by the investigators (27).

Meta-analyses of multicenter, double-blind, placebo-controlled studies of aripiprazole treatment in patients with acute relapse of schizophrenia or schizoaffective disorder found that the drug was significantly better than placebo in antipsychotic efficacy at doses over 2 mg/day. Significant efficacy was seen 1 week after initiating treatment. It also showed a good safety and tolerability profile, with no significant changes in akathisia scale scores, plasma prolactin or Q-Tc prolongation compared to placebo or reference drugs (haloperidol, risperidone). Moreover, aripiprazole was associated with a lower increase in body weight (28-30).

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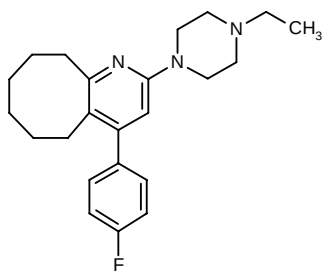
Blonanserin



An antipsychotic agent with potent dopamine D_2 and 5-HT_{2A} receptor-antagonist properties, blonanserin (AD-5423) was developed by Dainippon Pharmaceutical, which has licensed the drug to Almirall Prodesfarma for exclusive development and marketing worldwide except for Japan, China, Taiwan and South Korea. Blonanserin is expected to be effective against both positive and negative symptoms of schizophrenia, as well as to have few adverse effects, *i.e.*, extrapyramidal symptoms and hypotension. It is currently in phase III trials in Japan and phase I evaluation in Europe for the treatment of schizophrenia (1).

Pharmacokinetic/pharmacodynamic data from 11 schizophrenic patients treated with blonanserin at a mean daily dose of 12 ± 6.0 mg/day were analyzed. The results demonstrated significant correlations between daily dose and plasma levels, between plasma level and anti-D_2 activity, between plasma levels and anti-5-HT_{2A} activity, and between anti-D_2 and anti-5-HT_{2A} activity, indicating that the pharmacological activity of the drug is due to the parent compound. It also showed relatively balanced activity against 5-HT and dopamine. Little intra- and inter-individual variation was observed (2, 3).

Blonanserin was compared with haloperidol in an 8-week, double-blind study that included 263 patients with schizophrenia. Treatment with blonanserin at doses of 8-24 mg/day was at least as effective as haloperidol (4-12 mg/day) in improving the Final Global Improvement Rating (FGIR) score (61.2% *vs.* 51.3% of patients having at least moderate improvement) and was associated with a lower incidence of extrapyramidal adverse reactions (52.7% *vs.* 75.4%) (4).

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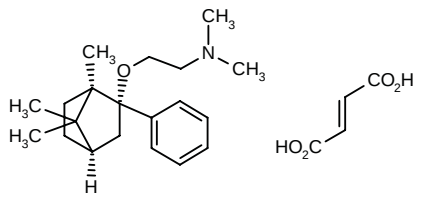
Original monograph - Drugs Fut 1992, 17(1): 9.

Deramciclane Fumarate



Deramciclane fumarate (EGIS-3886, EGYT-3886) is an anxiolytic agent with antagonist activity at 5-HT_{2A} and 5-HT_{2C} receptors, which also acts as a GABA reuptake inhibitor. Currently in phase III clinical evaluation in Europe, the drug is being jointly developed by Orion and Pharmacia under license from Egis as a treatment for generalized anxiety disorder. Phase III studies are scheduled to begin soon in the U.S. (1-3).

The pharmacokinetics of deramciclane and the fate of its side chain were evaluated in rats using [^{3}H]- and [^{14}C]-labeled deramciclane and [^{14}C]-dimethylaminoethanol radioisomers. Plasma concentration-time curves revealed intensive cleavage (30-40%) of the side chain at the ether bond, with slow elimination ($t_{1/2\beta}$ = 99 h) as compared with the core of deramciclane, which was almost totally eliminated after 24 h. Time-related changes in tissue concentrations of the radioisomers were found to be highest in the hypophysis, with similar characteristics in plasma and brain (4).

The pharmacokinetics of deramciclane fumarate (10 mg/kg) have been evaluated in rats. C_{max} values for i.p., i.v. and orally administered drug were 44.9 ng/ml, 177.8 ng/ml or greater and 2643 ng/ml or greater, respectively. Corresponding values for its *N*-desmethyl metabolite were 32.0 ng/ml, 25.4 ng/ml or greater and 51.0 ng/ml, respectively. Fast absorption was evident and plasma levels were found to be dependent on administration route. Low availability of the parent drug suggested fast and strong first-pass metabolism, and strong tissue binding was indicated by the apparent volume of distribution (5).

Deramciclane 10, 30 or 60 mg once daily or placebo was administered to 212 patients with generalized anxiety disorder (GAD) for 8 weeks in a multicenter, randomized, double-blind phase II trial. Treatment with deramciclane was well tolerated and the optimal dose was determined to be 30 mg once daily (6).

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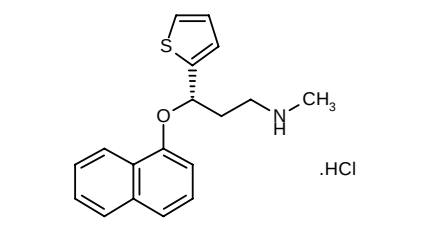
Original monograph - Drugs Fut 1990, 15(12): 1174.

Duloxetine Hydrochloride



Lilly is awaiting approval in the U.S. and Shionogi in Japan for duloxetine hydrochloride (Cymbalta®, LY-264453, LY-248686) for the treatment of major depressive disorder. Duloxetine is a dual 5-HT and noradrenaline reuptake inhibitor which is also being investigated for stress urinary incontinence (see *Drugs of the Future* 2002, 27(6): 599), with a submission targeted for late this year (1, 2).

Table II: Clinical studies of duloxetine hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Duloxetine, 10 mg bid po x 14 d Duloxetine, 30 mg bid (titrated from 10 mg b.i.d. over 7 d) p.o. x 14 d Clomipramine, 50 mg bid (titrated from 25 mg/d over 7 d) po x 14 d Placebo	30	Duloxetine acted as a selective serotonin reuptake inhibitor at the doses tested in healthy volunteers, showing no effect on norepinephrine reuptake. Nevertheless, at the 60 mg daily dose, duloxetine increased supine systolic blood pressure, possibly representing the threshold regimen for norepinephrine reuptake	4
Depression	Double-blind, pooled/ meta-analysis	Duloxetine, 40-120 mg/d x 12 (max) wk (n=1032) Placebo (n=723)	1755	Duloxetine was safe and well tolerated in patients with major depression. Adverse events more frequently observed with duloxetine than with placebo included nausea, dry mouth, fatigue, dizziness, constipation, somnolence, decreased appetite and sweating	7
Depression	Randomized, double-blind, multicenter	Duloxetine, 60 mg po od x 9 wk (n=123) Placebo (n=122)	245	Duloxetine was safe, well tolerated and effective in improving HAMD-17 scores and reducing the severity of pain in patients with major depression	8
Depression	Randomized, double-blind	Duloxetine, 20 mg bid x 8 wk Duloxetine, 40 mg bid x 8 wk Paroxetine, 20 mg od x 8 wk Placebo		Duloxetine administered at a daily dose of 80 mg for 8 weeks significantly reduced overall pain and was more effective than paroxetine or placebo in improving HAMD-17, MADRS, CGI-S and PGI-I scores in patients with major depression. Insomnia was the only adverse event significantly more frequent with duloxetine 80 mg/day than with paroxetine	9, 10
Anxiety, depression	Randomized, double-blind, multicenter, pooled/ meta-analysis	Study 1: Duloxetine, 60 mg bid Fluoxetine, 20 mg/d Placebo Study 2: Duloxetine, 20 mg bid Duloxetine, 40 mg bid Paroxetine, 20 mg/d Placebo Study 3: Duloxetine, 60 mg/d Placebo		HAMD-10 (anxiety/somatization subfactor and anxiety item) and HAMA scores improved significantly more with duloxetine than placebo, fluoxetine or paroxetine (only HAMD-10 in the latter case) in patients with anxiety and depression	11

In mice exposed to a novel open-field environment, citalopram, fluoxetine, paroxetine, fluvoxamine, litoxetine, zimelidine, venlafaxine, duloxetine and S-33005 (all 5-HT or 5-HT/noradrenaline reuptake inhibitors) enhanced spontaneous locomotor activity. Other classes of drugs had different effects: a lesser effect on locomotor activity was seen with clomipramine, while imipramine and amitriptyline had no effect. Reboxetine, desipramine, maprotiline, nisoxetine, nortriptyline, mianserin, mirtazapine, nefazodone and trazodone also did not increase locomotor activity in this model (3).

The effects of duloxetine on 5-HT and noradrenaline uptake were evaluated in 27 healthy volunteers. Male volunteers with no history of psychiatric disorder were randomized to placebo, clomipramine 100 mg/day, duloxetine 20 mg/day or duloxetine 60 mg/day. Administration of clomipramine and both doses of duloxetine decreased blood 5-HT concentrations, but only clomipramine inhibited the increase in blood pressure following i.v. infusion of tyramine. Duloxetine therefore acted as a selective 5-HT reuptake inhibitor without affecting the noradrenaline reuptake process (4). The results of this study and some that follow are summarized in Table II.

Findings from a multicenter, double-blind, placebo-controlled study in 245 patients have shown duloxetine hydrochloride, at a dose of 60 mg/day, to provide rapid relief of depressive symptoms as early as 2 weeks into treatment. In the trial, duloxetine afforded rapid and sustained relief of the primary emotional symptoms of depression, with significant differences from placebo by

the second week and improving throughout the 9-week study. Significant improvement was also noted in depressive symptoms regardless of the initial severity of the patients' symptoms. Rapid and sustained relief of the common physical symptoms associated with depression was noted, with significant differences from placebo in terms of complaints such as muscle soreness, abdominal cramps and headache. Duloxetine showed a 44% probability of remission, three times that of placebo. Patients treated with duloxetine with a Hamilton Depression Rating Scale HAMD-17 baseline score less than 19 showed a 6.53 average reduction in their score, while those with a greater HAMD-17 score had an average reduction of 10.1, both results being statistically significant compared to placebo. According to AUC analysis, duloxetine gave significant reductions in the severity of shoulder pain, back pain and pain that interferes with daily activities. Duloxetine was also generally well tolerated. Other clinical data on duloxetine suggest that it may reduce the symptoms of anxiety in depressed patients at the starting dose. At the dose of 60 mg once daily, duloxetine was associated with significant reductions in anxiety symptoms compared to placebo on the HAMD Anxiety subscale (3.0 *vs*. 1.99). Also, patients on duloxetine experienced significant improvement in depressive symptoms regardless of the initial severity of their anxiety symptoms. Furthermore, data from 7 double-blind, placebo-controlled trials in 1755 patients were aggregated for analysis and the findings suggest that patients taking duloxetine did not experience clinically significant weight gain. Further analysis revealed no clinically meaningful cardiovascular effects following duloxetine treatment, although it reduced corrected Q-T interval. Adverse events such as nausea, dry mouth, fatigue, dizziness, constipation, somnolence, decreased appetite and sweating were more common on duloxetine than on placebo, and a total of 14.6% of patients on duloxetine compared to 5.0% of those on placebo discontinued therapy due to adverse events (5-7).

A multicenter, double-blind, placebo-controlled, parallel study in patients with major depressive disorder established that treatment with duloxetine 60 mg once daily for 9 weeks was significantly superior to placebo in terms of reduction in HAMD-17 scores and gave an estimated remission rate of 44%. A significant decrease in the severity of overall pain was also reported (8).

In a randomized, double-blind, controlled study in outpatients with major depressive disorder, the reduction in the HAMD-17 score was significantly higher with duloxetine 80 mg/day compared to either placebo or paroxetine 20 mg/day, and the remission rates estimated after 8 weeks of therapy were 50%, 37% and 30%, respectively, for duloxetine, paroxetine and placebo (9, 10).

Lilly reported encouraging results from phase II and phase III trials which suggest that duloxetine is superior to placebo in reducing the severity of depressive symptoms. One hundred and seventy-three patients with DSM-IV-defined major depression were randomized in a multisite, double-blind, placebo-controlled phase II trial to receive duloxetine, fluoxetine (positive control) or placebo for 8 weeks. Results indicated that duloxetine produced statistically significantly greater improvement in depressive symptoms compared to placebo as measured by the HAMD-17 scale. In addition, statistically significantly more patients receiving duloxetine achieved remission from their depression as compared to those receiving placebo (remission was prospectively defined in the study protocol as a score of 7 or less in the HAMD-17). Adverse effects were generally mild and the drug was well tolerated. Lilly also reported that a multisite, double-blind, placebo-controlled phase III trial with duloxetine has been completed and results from the study are consistent with those seen in the phase II trial. The trial randomly assigned 353 patients with DSM-IV-defined major depression to receive duloxetine at doses of 40 or 80 mg/day, paroxetine 20 mg/day or placebo for 8 weeks. Remission was defined the same way as in the phase II trial. Patients receiving 80 mg/day duloxetine experienced statistically significantly greater improvement in depressive symptoms on the HAMD-17 than those randomized to placebo or paroxetine. In addition, a significantly higher rate of duloxetine-treated patients (50%) achieved remission from depression compared to patients receiving placebo (29.5%). No statistically significant differences between the duloxetine- and placebo-treated patients were reported in the incidence of sustained hypertension (2% for both groups) (11, 12).

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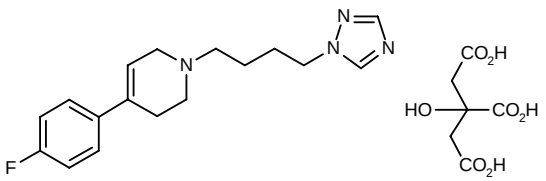
Original monograph - Drugs Fut 2000, 25(9): 907.

E-5842



Phase II clinical trials with Esteve's atypical antipsychotic E-5842, a preferential sigma$_1$ receptor ligand and glutamate receptor modulator, are ongoing in treatment-resistant schizophrenia in Europe (1).

Results from a study in rats showed that chronic administration of E-5842 for 21 days upregulated fibroblast growth factor-2 (FGF-2) mRNA in the prefrontal cortex and striatum, and downregulated FGF-2 mRNA in the hypothalamus. Acute administration resulted in transient dose-dependent upregulation of FGF-2 mRNA in the prefrontal cortex, striatum, hypothalamus and hippocampus, which disappeared 24 h postdosing (2).

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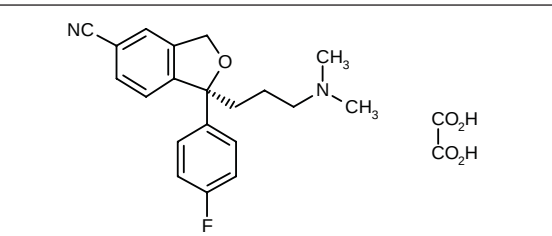
Original monograph - Drugs Fut 1999, 24(4): 386.

Escitalopram Oxalate



A selective serotonin reuptake inhibitor, escitalopram oxalate was recently launched by Lundbeck as Cipralex(R) for the treatment of depression and panic disorder in several European countries, including the U.K., Switzerland and Sweden, as well as for major depressive disorder in the U.S. by licensee Forest under the tradename Lexapro™. Lundbeck also has marketing agreements with Mochida in Japan, Recordati in Italy, Almirall Prodesfarma in Spain and Abbott in Latin American markets (1-12).

Forest has begun an 8-week, open-label trial known as EXCEED (EXamining Clinical Experience with Escitalopram in Depression). The trial will evaluate escitalopram in a standard clinical practice setting. Several thousand patients with major depressive disorder will be enrolled in the U.S. and will be evaluated for the effect of escitalopram on their quality of life (13).

In vitro, escitalopram inhibited the 5-HT transporter (SERT) more selectively than other selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline. Further experiments with the selective SERT ligand [^{3}H]-MADAM showed that escitalopram also has high affinity for SERT *in vivo* (14).

Escitalopram was at least twice as effective as citalopram in inhibiting 5-HT reuptake *in vivo* and *in vitro*, and also in models predictive of anxiolytic and antidepressant activity. Its onset of action was much faster than that of other antidepressants, suggesting that it might be more effective than citalopram in depression and anxiety disorders (15).

The potentiation of 5-HTP-induced behavioral changes (5-HT reuptake), locomotor stimulation (dopamine reuptake) and antagonism of tetrabenazine ptosis (noradrenaline reuptake) were used as parameters to correlate the *in vitro* and *in vivo* activities of escitalopram, paroxetine and sertraline in mice. Escitalopram was the most potent 5-HT reuptake inhibitor (ED_{50} = 0.36 mg/kg) and was devoid of *in vivo* activity mediated by other receptors or binding sites (16).

The effects of acute administration of paroxetine (1 and 10 mg/kg), venlafaxine (5 mg/kg) and escitalopram (5 mg/kg) on erectile function were evaluated in a rat model. Paroxetine produced significant impairment (62.4%) and inhibition (34.6%) of erectile responses at the lower and higher doses, respectively. Venlafaxine significantly inhibited cavernosal nerve stimulation-induced erectile response (62.9%), while escitalopram did not

Table III: Clinical studies of escitalopram oxalate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Depression, major	Randomized, double-blind, multicenter	Escitalopram, 10 mg/d (double dose if needed after 4-6 wk) x 8 wk (n=155) Citalopram, 20 mg/d (double dose if needed after 4-6 wk) x 8 wk (n=160) Placebo (n=154)	469	Escitalopram was effective for the treatment of depression, and its effect occurred earlier than that of citalopram	18
Panic disorder	Randomized, double-blind, multicenter	Escitalopram Placebo	237	Compared with placebo, escitalopram was well tolerated, decreased the symptoms of anxiety associated with panic disorder, reduced panic attack frequency and severity and phobic avoidance and improved quality of life in patients with DSM-IV panic disorder	19
Depression, major	Randomized, multicenter	Escitalopram, 10 mg/d x 8 wk (n=191) Placebo (n=189)	380	Escitalopram was well tolerated and demonstrated significantly superior efficacy to placebo in patients with major depressive disorder	20
Anxiety	Randomized, double-blind	Escitalopram, 10 mg/d (doubled at 4, 6 or 8 wk if needed) x 12 wk (n=181) Placebo (n=177)	358	Escitalopram at doses ranging from 10-20 mg/d was well tolerated and effective in improving Clinical Global Impression of Severity and Improvement and Liebowitz Social Anxiety Scale-avoidance and fear/anxiety scores in patients with social anxiety disorder	21
Depression	Randomized, double-blind, multicenter, pooled/ meta-analysis	Escitalopram, 10-20 mg/d x up to 8 wk Placebo	715	Escitalopram was safe and well tolerated in patients with depression	23

affect erectile responses (99.9%). Results support the favorable profile of escitalopram in clinical studies (17).

Although both treatments were effective, escitalopram 5 mg/kg/day had a faster onset of action than citalopram 10 mg/kg/day in a chronic mild stress model of depression in rats. In a randomized, double-blind, placebo-controlled study of the same treatments in primary care patients with major depressive disorder, escitalopram again had a faster onset of action and showed superior therapeutic efficacy compared to citalopram (18).

A randomized, double-blind, placebo-controlled, multicenter trial in 237 patients with panic disorder with or without agoraphobia revealed that escitalopram was well tolerated and significantly reduced the frequency and severity of panic attacks, anticipatory anxiety and phobic avoidance, thereby improving both overall status and quality of life of the patients (19). The results if this study and some that follow are summarized in Table III.

In a randomized, double-blind, placebo-controlled trial, 380 patients with major depressive disorder were given placebo or escitalopram 10 mg/day for 8 weeks. The Montgomery-Asberg Depression Rating Scale (MADRS) total score was significantly improved on escitalopram compared to placebo. Escitalopram was superior to placebo at week 1 according to the Clinical Global Impression of Improvement (CGI-I) score and at week 2 according to the MADRS score. Escitalopram was well tolerated, nausea being the only adverse event occurring significantly more frequently on escitalopram than on placebo (20).

In a phase II study, escitalopram at a daily dose of 10 mg (later increased to 20 mg) for 12 weeks was well tolerated and significantly improved efficacy scale scores (such as LSAS, CGI-S, CGI-I and the Sheehan Disability Scale) of outpatients with a primary diagnosis of social anxiety disorder (21).

Analysis of pooled data from three 8-week, double-blind trials comparing escitalopram, citalopram and placebo for treating severe depression revealed that while both active treatments had significantly superior efficacy to placebo, escitalopram separated from placebo earlier and was significantly better than citalopram at endpoint. In all studies, including a total of 546 severely depressed patients, the treatments were well tolerated (22).

A meta-analysis of several randomized, placebo-controlled clinical trials in a total of 715 depressed outpatients revealed that escitalopram was well tolerated at doses of 10-20 mg/day. The discontinuation rates of drug-treated and placebo-treated patients were similar, and only nausea was more common with escitalopram (23).

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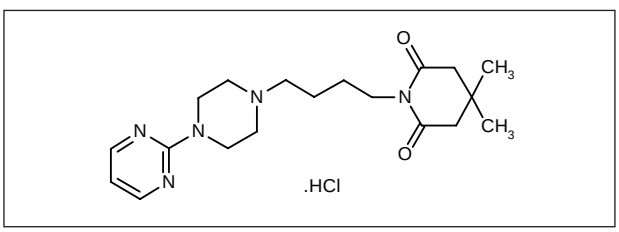
Original monograph - Drugs Fut 2001, 26(2): 115.

Gepirone Hydrochloride



Gepirone hydrochloride (BMY-13805, MJ-13805, Org-33062) acts as a partial agonist at 5-HT_{1A} receptors and was developed by Organon (Akzo Nobel) for the treatment of major depressive disorders. Organon recently announced that it will take longer than expected to complete the regulatory file for gepirone (extended-release tablets; previously known as Ariza[R]) in the U.S. The company now expects to submit the data in the third quarter of 2003 and to launch the product in 2004 (1, 2).

Gepirone has been reported to have the preclinical profile of an effective antidepressant. In rats, the compound acted as a full agonist at postsynaptic 5-HT_{1A} receptors and in some forebrain structures. Its metabolite 3'-OH-gepirone crossed the blood-brain barrier, could induce desensitization of 5-HT_{1A} receptors after prolonged administration, and was as effective as the parent compound as a 5-HT_{1A} receptor agonist in rat hippocampus (3).

In vivo, both gepirone and 3'-OH-gepirone induced changes in the pattern of sleep-wake distribution in rats that suggested a quick onset of antidepressant and anxiolytic properties (*e.g.*, reduction in REM sleep, increased passive walking and prolongation of REM sleep latency). It was concluded that both compounds display a nonsedative profile with mild stimulant properties (4).

Extended-release gepirone was effective in patients with major depressive disorder. The therapeutic response induced by the drug was greater in patients with atypical features of major depressive disorder (5). The results of this study and the ones that follow are summarized in Table IV.

A multicenter study assessed the efficacy and safety of extended-release gepirone (gepirone ER) in 204 patients with major depressive disorder. Administration of gepirone ER for 56 days at doses ranging from 20-80 mg once daily significantly improved the HAMD-17 and HAMD-25 scores of the patients, without inducing weight change, sedation, sexual dysfunction or serious adverse events, suggesting its potential use in the short-term treatment of major depressive disorder (6, 7).

Table IV: Clinical studies of gepirone hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Depression		Gepirone-XR, 70 (mean) mg/d Placebo	202	Gepirone was effective in patients with major depressive disorder and seemed to be especially effective in depression with overeating or oversleeping	5
Depression	Randomized	Gepirone, 29 mg od x 3 d → 40 mg od x 3 d → 60 mg o.d. x 7 d → 80 mg (later adjusted to 40-80 mg] od x 43 d Placebo	204	Gepirone was well tolerated and significantly improved HAMD-17 and HAMD-25 scores in patients with major depression, thereby suggesting that it is a good therapeutic option for short-term treatment of this condition. No weight gain, sedation, sexual dysfunction or serious adverse events were found among patients treated with gepirone	6, 7

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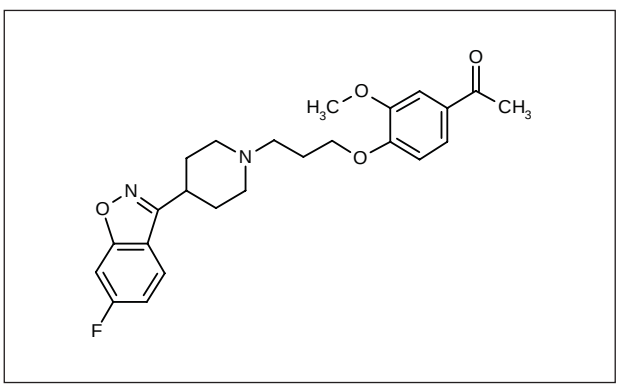
Iloperidone



A member of a new class of drugs for schizoprenia known as the SDAs (serotonin/dopamine receptor antagonists), iloperidone (ILO-522, HP-873, Zomaril™) is a new, broad-spectrum antipsychotic agent presently completing a global phase III development program for the treatment of schizophrenia. Novartis acquired the worldwide rights to the product from Titan in 1997. A depot formulation is in phase II clinical trials (1-3).

Titan and Novartis recently announced plans to initiate trials including once-a-day dosing to further strengthen the profile of iloperidone for the treatment of schizophrenia. The companies reported that the clinical trials conducted to date support the favorable efficacy, safety and tolerability profile of iloperidone in the treatment of acute schizophrenia, but that additional studies will further investigate once-daily dosing, demonstrate a favorable safety profile when switching from other antipsychotic agents to iloperidone, and support the competitive profile of the compound. Data from these studies will be included in the initial regulatory submissions. The first submission is anticipated in the U.S. towards the end of 2002, followed by filings elsewhere. Studies in additional indications such as acute mania are also planned. The most recently completed placebo-controlled trial investigated two dose ranges of iloperidone for 6 weeks. Results from the high-dose arm (20-24 mg/day) showed a statistically significant improvement in symptoms measured by the 18-item Brief Psychiatric Rating Scale (BPRS) and the Positive And Negative Symptom Scale (PANSS). Results from the low-dose arm (12-16 mg/day) showed statistically significant results for iloperidone compared with placebo at weeks 3, 4 and 5, as well as a numerical trend at week 6. The favorable safety and

Table V: Clinical studies of iloperidone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Schizophrenia	Randomized, double-blind	Iloperidone, 2 mg bid Iloperidone, 4 mg bid Iloperidone, 6 mg bid Haloperidol, 7.5 mg bid Placebo bid	621	Twice-daily iloperidone 2-6 mg was safe and well tolerated by patients with schizophrenia or schizoaffective disorder. Risk/benefit of iloperidone 6 mg bid was superior to lower doses and haloperidol. Studies to confirm these findings are in progress	8
Dementia	Randomized, double-blind	Iloperidone, 0.5-6 mg/d bid (n=68) Risperidone, 0.5-4 mg/d bid (n=43)	111	Efficacy was seen in more patients treated with iloperidone, and fewer patients in this group withdrew due to adverse events. Also, extrapyramidal symptoms worsened in the risperidone group while remaining stable in the iloperidone group	9
Dementia, psychosis	Randomized, double-blind	Iloperidone, 0.5-6.0 mg/d bid (titrated up to maximum tolerated, then tapered) (n=10) Placebo (n=5)	15	Iloperidone was safe and well tolerated up to and including the maximum 6.0 mg/d dose in elderly patients with dementia and psychosis	10
Schizophrenia	Randomized, double-blind, multicenter	Iloperidone, 2-8 mg bid x 52 wk Haloperidol, 2.5-10 mg bid x 52 wk	600	Psychotic symptoms were improved to a similar extent by both treatments. Fewer iloperidone-treated patients, however, experienced adverse events and fewer discontinued because of adverse events. In addition, fewer extrapyramidal symptoms were seen in these patients compared with haloperidol treatment	11

tolerability profile of iloperidone was confirmed in this study, with an overall low incidence of extrapyramidal symptoms (EPS) and cardiovascular effects, little weight gain and little sedation. Analysis of safety and efficacy data from phase III clinical trials involving more than 3500 patients at some 300 sites around the world showed that iloperidone is effective and possesses a favorable safety and tolerability profile. Overall, the development program has studied a range of doses from 4-24 mg/day. Long-term data from 3 double-blind safety studies in approximately 1200 patients show that patients in the iloperidone arm experienced a mean weight gain of only 1.6-3.7 kg at 52 weeks and minimal EPS, which remained stable or even improved over 52 weeks. There was no increase in serum prolactin, no seizures and minimal effects on heart rate and blood pressure over 52 weeks (4).

The binding of new and established antipsychotic drugs was investigated at 9 different receptors in normal human brain tissue in radioligand binding assays. Iloperidone was found to be the most active at α_1- and α_2-adrenoceptors (K_d = 0.31 ± 0.02 and 3.0 ± 0.2 nM, respectively), Org-5222 the most active at dopamine D_2 and 5-HT_{2C} receptors (K_d = 2.0 ± 0.3 and 0.27 ± 0.03 nM, respectively) and ziprasidone the most active at 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2A} receptors (K_d = 1.9 ± 0.1, 2.4 ± 0.2 and 0.12 ± 0.01 nM, respectively). Olanzapine was the most active at the histamine H_1 receptor (K_d = 0.087 ± 0.005 nM) and clozapine at the muscarinic receptor (K_d = 9 ± 1 nM). The other compounds tested were haloperidol, melperone, pimozide, quetiapine, risperidone, 9-OH-risperidone, sertindole and zotepine (5).

The effect of iloperidone on the agonist activity of LSD was studied in HEK-293 and CHO-K1 cells expressing the human D_{2A} receptor and human alpha$_{2C}$-adrenoceptor, respectively. The full agonist activity of LSD at the D_2 receptor and α_{2C}-adrenoceptor (pIC_{50} = 8.69 ± 0.08 and 8.73 ± 0.05, respectively) was blocked by iloperidone with a pK_B of 8.684 ± 0.14 and 8.13 ± 0.03, respectively. Blockade of α_{2C}-adrenoceptors therefore may enhance the antipsychotic activity of D_2 receptor blockade (6).

In radioligand receptor binding assays, iloperidone displayed high affinitiy for α_1-adrenoceptors and dopamine D_3 and 5-HT_{2A} receptors, indicating the its potential as a broad-spectrum antipsychotic with a favorable side effect profile (7).

A randomized, double-blind, placebo-controlled trial assessed treatment of 621 patients with schizophrenia or schizoaffective disorders with fixed doses of twice-daily iloperidone 2, 4 or 6 mg, placebo or haloperidol 7.5 mg. Iloperidone was safe and well tolerated and the risk/benefit ratio of the 6-mg dose was superior to the other doses and haloperidol (8). The results of this study and those that follow are summarized in Table V.

A randomized, double-blind trial compared administration of iloperidone 0.5-6 mg b.i.d. to risperidone 0.5-4 mg b.i.d. in elderly patients with psychotic or behavioral symptoms associated with dementia. Doses were adjusted over 4 weeks, maintained for 9 weeks and then

titrated down to 0 over 4 days. Efficacy was seen in more patients treated with iloperidone, and fewer patients in this group withdrew due to adverse events. Also, EPS worsened in the risperidone group while remaining stable in the iloperidone group (9).

A randomized, double-blind, placebo-controlled study evaluated the safety and tolerability of iloperidone in 15 elderly patients with dementia. Iloperidone doses of 0.5-6 mg b.i.d. were titrated up every 3 days to the maximum tolerated dose followed by a tapering period. The treatment was safe and well tolerated at all doses, without increasing the risk of laboratory or ECG abnormalities (10).

Iloperidone (2-8 mg b.i.d.) or haloperidol (2.5-10 mg b.i.d.) was administered to 600 patients with schizophrenia or schizoaffective disorder in a 1-year, multicenter, randomized, double-blind trial. Psychotic symptoms were improved to a similar extent by both treatments. Fewer iloperidone-treated patients experienced adverse events and fewer discontinued because of adverse events. In addition, fewer EPS were seen in these patients compared with haloperidol treatment (11).

Novartis has completed a study of the potential effect of iloperidone on the EKG profile of schizophrenia patients. The 6-week study randomized approximately 150 schizophrenia patients to receive iloperidone at doses of 8 mg b.i.d., 12 mg b.i.d. or 24 mg/day, or another currently approved drug. The primary endpoint was change in Q-Tc interval from baseline at 6 weeks. Iloperidone was found to be roughly comparable to ziprasidone, one of the approved drugs in the study (12).

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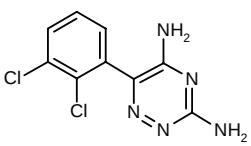
Original monograph - Drugs Fut 2000, 25(1): 29.

Lamotrigine



Lamotrigine is currently indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients. It is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with an enzyme-inducing antiepileptic drug. It is also being evaluated for chronic pain states (see *Drugs of the Future* 2002, 27(4): 416). The compound acts via use-dependent inhibition of voltage-dependent neuronal sodium channels (1).

GlaxoSmithKline recently filed a supplemental NDA with the FDA for lamotrigine (Lamictal®) for the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes. The application is supported by two 18-month, double-blind, placebo-controlled studies in 638 adult patients in which lamotrigine significantly delayed the relapse/recurrence of mood episodes, particularly depressive episodes, in patients with bipolar I disorder (1).

In a recent update of its guidelines for the treatment of bipolar disorder, the American Psychiatric Association (APA) indicated that it considers lamotrigine or lithium as first-line monotherapy for acute bipolar depression in patients not already on a mood stabilizer. In addition to recommending these drugs as monotherapy for acute bipolar disorder, the guidelines also advise using lamotrigine as one of three therapy options for acute depressive episodes in initial nonresponders, as a monotherapy treatment alternative for rapid cycling and as a treatment

alternative along with carbamazepine or oxcarbazepine in bipolar patients requiring maintenance therapy. Treatment alternatives are to be used when first-line therapy is not fully effective, not tolerated or inappropriate for the patient. Adjunctive therapy in initial responders is recommended when patients do not fully respond to treatment after the dose is optimized (2).

The isolated chick embryo retina model was used to evaluate the neuroprotective effects of lamotrigine and remacemide against glutamate agonist-induced excitotoxicity. The two agents and the desglycinyl metabolite of remacemide decreased excitotoxicity, suggesting that they may have therapeutic potential (3).

Lamotrigine blocked stress responses in a cell culture model of seizure-like activity utilizing primary cultured hippocampal neurons from rats (4).

In an *in vitro* model of cerebral ischemia (rat hippocampal slice cultures subjected to oxygen/glucose deprivation), phenobarbital, phenytoin, ethosuximide, chlordiazepoxide and midazolam significantly reduced cell death. Carbamazepine, tiagabine and lamotrigine demonstrated significant neuroprotective effects in this model, while levetiracetam and gabapentin did not reduce cell death (5).

Researchers investigated the effect of lamotrigine (100 mg p.o.) on the pharmacokinetics of carbamazepine (2 x 200 mg p.o. for 7 days) and the active metabolite carbemazepine-epoxine in dogs. No pharmacokinetic interaction was found between the two drugs or the metabolite (6).

Researchers estimated the population pharmacokinetics of lamotrigine using data from 129 patients on oral lamotrigine therapy with drug concentration monitoring. Population estimates of apparent clearance (2.14 ± 0.81 l/h) and volume of distribution of (78.1 ± 5.1 l/kg) were calculated (7).

A pharmacokinetic study of lamotrigine was conducted in 28 epileptic patients who received lamotrigine therapy in combination with an inductor and/or an inhibitor. Drug clearance values were twice as high for patients receiving a concomitant inductor than those measured in healthy subjects receiving only lamotrigine. In addition, low lamotrigine clearance values were noted with administration of valproic acid (8).

Long-term mood stabilization was achieved on lamotrigine or lithium in 2 studies in patients with bipolar I disorder. After achieving stabilization in an open-label treatment phase, 638 patients (currently or recently symptomatic or manic/hypomanic/mixed) were randomized to lamotrigine (either fixed dose of 50, 200 or 400 mg/day or flexible dose of 200-400 mg/day), lithium (0.8-1.1 mEq/l) or placebo for 18 months. Both agents significantly delayed the time to treatment intervention and increased overall survival; lamitrigine significantly delayed the time to intervention for depressive and manic/hypomanic/mixed events while lithium did so only for manic/hypomanic/mixed events (9-15). The results of these studies are summarized in Table VI.

An analysis of the course of illness, familty history and comorbidities of 164 patients with bipolar disorder indicated that those responding to lamotrigine and those responding to lithium may have different subtypes of the disorder (16).

Patients with rapid-cycling bipolar disorder (n=14) received lithium (mean plasma level after 12 months = 0.84 ± 0.08 mmol/l) or lamotrigine (mean of 425 mg/day at 12 months) for 1 year in an open longitudinal study. While 6 of 7 lamotrigine-treated patients had fewer than 4 episodes during 1-year of follow-up, this was true of only 3 of 7 patients treated with lithium. In addition, 3 of 7 patients in the lamotrigine group had no affective episodes (17).

Lamotrigine was evaluated in rapid-cycling bipolar disorder patients in a 2-phase clinical study. Initially, open-label lamotrigine 100-300 mg/day was added to therapy in 324 patients. After 4-8 weeks of lamotrigine therapy, other psychotropic agents were tapered off. Eligible patients (n=182) were then randomized in a double-blind fashion to 26 weeks of lamotrigine 100-500 mg/day or placebo. Lamotrigine treatment was well tolerated and was significantly superior to placebo in overall survival in study. Also, significantly more patients remained clinically stable for 6 months with lamotrigine treatment than with placebo. No difference was seen in time to additional pharmacotherapy (18).

In the first report of its kind, a 17-year-old woman with a 2-year history of bipolar disorder experienced severe reactions to treatment with lamotrigine, including fever, lymphadenopathy, skin rash, diarrhea and acute renal failure. Interstitial nephritis with focal granulomas was found upon renal biopsy, and colonic biopsy revealed colitits and ileitis with non-necrotizing epithelioid granulomas. Discontinuation of lamotrigine and steroids allowed the patient to recover (19).

In a randomized, double-blind trial, 30 inpatients with bipolar I disorder and currently manic were treated with lamotrigine (25 mg once daily for 1 week, 50 mg once daily the next week and 100 mg once daily for 2 more weeks) or lithium (400 mg b.i.d.). The drugs were found to be equally effective in improving mania symptoms and neither was associated with significant adverse events (20).

Depressed patients (n=40) reported improvements in their depressed mood, guilt feelings, work and interest after treatment with lamotrigine plus paroxetine compared to paroxetine alone in a double-blind study (21).

A meta-analysis of the side effects reported in all placebo-controlled clinical trials conducted to date with lamotrigine in bipolar disorder found a very small increase in the incidence of rash compared to placebo. It was suggested that this effect might be avoided by using a low starting dose followed by gradual titration (22).

A 61-year-old inpatient with severe psychosis and clinical features of confusional psychosis who did not respond to neuroleptics or mood stabilizers achieved notable reductions in clinical signs and symptoms when lamotrigine was added to therapy. Three other patients

Table VI: Clinical studies of lamotrigine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Bipolar I disorder, depression, mania	Randomized, double-blind, pooled/ meta-analysis	Lamotrigine, 50, 200 or 400 mg/d (fixed dose) x 18 mo (n=280) Lamotrigine, 200-400 mg/d (flexible dose) x 18 mo Lithium, 0.8-1.1 mEq x 18 mo (n=167) Placebo (n=191)	638	Lamotrigine significantly delayed the time to intervention for depressive and manic/hypomanic/mixed events while lithium did so only for manic/ hypomanic/mixed events	10, 12
Bipolar I disorder	Randomized, double-blind, multicenter	Lamotrigine, 100-400 mg po od x 18 mo Lithium, 0.8-1.1 mEq/l x 18 mo Placebo	175	Lamotrigine and lithium were safe and effective in stabilizing mania or hypomania, showing longer periods to intervention for a depressive or manic episode	11
Bipolar I disorder	Randomized, double-blind, open	Lamotrigine x 8-16 wk (discontinuation of other psychotrops) → Lamotrigine, 50 mg/d x 18 (max) mo Lamotrigine x 8-16 wk (discontinuation of other psychotrops) → Lamotrigine, 200 mg/d x 18 (max) mo Lamotrigine x 8-16 wk (discontinuation of other psychotrops) → Lamotrigine, 400 mg/d x 18 (max) mo Lamotrigine x 8-16 wk (discontinuation of other psychotrops) → Lithium, 0.8-1.1 mEq/l x 18 (max) mo Lamotrigine x 8-16 wk (discontinuation of other psychotrops) → Placebo	463	Both lamotrigine and lithium were more effective than placebo in delaying relapse or recurrence of mood episodes in recently depressed bipolar I patients. Lamotrigine, but not lithium, also prolonged the time to a depressive episode	13
Bipolar disorder	Retrospective	Lamotrigine Lithium	164	Analysis of the course of illness, family history and comorbidities of bipolar disorder patients indicated that those responding to lamotrigine and those responding to lithium may have different subtypes of the disorder	16

with confusional psychoses also benefited from lamotrigine treatment (23).

A double-blind, randomized, placebo-controlled, crossover clinical trial revealed that a daily dose of 200 mg of lamotrigine administered as add-on therapy effectively reduced positive and general psychopathological effects in patients with olanzapine-resistant schizophrenia (24).

A prospective study evaluated outcomes in 275 pregnancies exposed to lamotrigine during the first trimester. Major birth defects following lamotrigine monotherapy, lamotrigine polytherapy involving valproic acid and lamotrigine polytherapy without valproic acid were found in 3/120 (2.5%), 5/48 (10.4%) and 5/107 (4.9%) pregnancies, respectively (25).

The incidence of serious rash associated with lamotrigine use was examined in data pooled from placebo-controlled trials of the agent. Of 10,611 adult patients enrolled in the studies, 0.26% had serious rash and 0.10% had rashes which were possibly Stevens-Johnson syndrome. Among the 5798 adult patients whose dosing adhered to current guidelines, these rates were reduced to 0.12 and 0.05% for serious rash and Stevens-Johnson syndrome, respectively (26).

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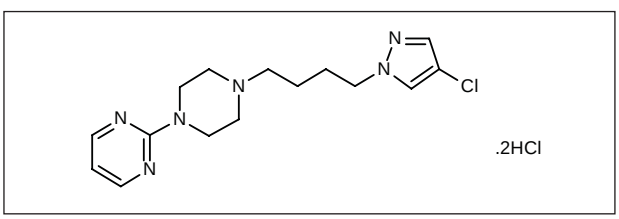
Original monograph - Drugs Fut 1986, 11(6): 456.

Lesopitron Dihydrochloride



Esteve's lesopitron dihydrochloride (E-4424) is a new nonbenzodiazepine anxiolytic agent with potent 5-HT_{1A} receptor-agonist activity and lacking sedative effects. The company is conducting phase II clinical trials of this compound for the treatment of GAD.

Lesopitron 40-80 mg/day was compared with lorazepam 2-4 mg/day and placebo in GAD outpatients including a subgroup who had a documented history of anxiety. The study had a randomized and double-blind design and lasted for 6 weeks. The active treatments were not significantly more effective than placebo. In the subgroup analysis, however, lesopitron and lorazepam appeared to have beneficial effects (1).

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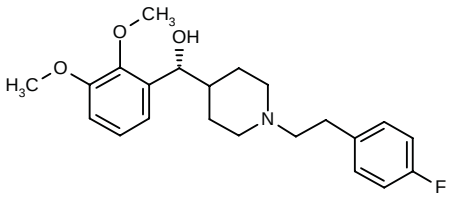
Original monograph - Drugs Fut 1994, 19(7): 651.

MDL-100907



MDL-100907 (M-100907, 100907) is a piperidine-based, highly selective 5-HT_{2A} receptor antagonist which is in phase I evaluation at Aventis for enhancing sleep quality.

The effects of a number of antipsychotics and other compounds interacting with monoaminergic receptors on acetylcholine (ACh) efflux were examined using *in vivo* microdialysis methods in rat hippocampus, following reports of improved cognition in schizophrenic patients treated with atypical antipsychotics. Olanzapine and clozapine produced marked increases in ACh outflow compared to only modest increases for the antipsychotic agents haloperidol, thioridazine, chlorpromazine, risperidone and ziprasidone, the 5-HT_{2A} antagonist MDL-100907, the 5-HT_{2C} antagonist SB-242084, the 5-HT_6 antagonist Ro-04-6790, the 5-HT^{1A} agonist *R*-(+)-8-OH-DPAT, the dopamine D_2 antagonist raclopride and the α_1-adrenoceptor antagonist prazosin. It is concluded that the improvement in cognition reported for atypical antipsychotics may be partly attributable to their effects on ACh efflux (1).

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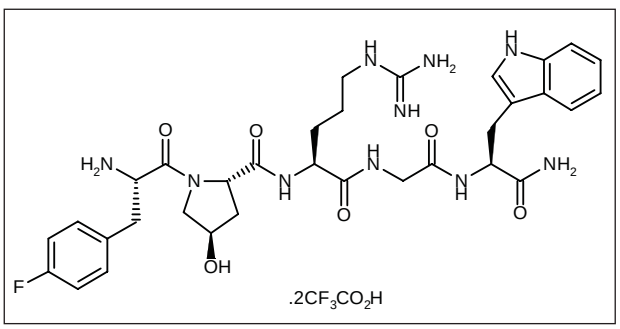
Original monograph - Drugs Fut 1998, 23(9): 955.

Nemifitide Ditriflutate



A low-molecular-weight pentapeptide compound, nemifitide ditriflutate (INN-00835, netamiftide trifluoroacetate) is undergoing phase II/III clinical evaluation at Innapharma for the treatment of depression.

Preclinical research using animal models of depression revealed that nemifitide was more active than fluoxetine and sertraline in the Porsolt test, a stress-induced animal model of depression (1).

Administration of nemifitide to male Sprague-Dawley rats decreased 5-HT levels and turnover in the hippocampus, suggesting that a serotonergic pathway is involved in the pharmacological properties of this drug (2).

Incubation of rat and human tissue preparations with nemifitide at concentrations of 0.01 and 0.1 mM for 60 min revealed that the compound is extensively metabolized in liver and intestine. Multiple pathways involving the cytochrome P-450 isoforms CYP1A2, CYP2C19 and CYP2D6 appear to be responsible for metabolizing nemifitide, which suggests that the drug is not likely to interact significantly with known CYP-inhibitory drugs (3).

The antidepressant-like activity of nemifitide (0.3, 0.8 or 1.2 mg/kg over a period of 14 consecutive days) was evaluated in a genetic rat model of depression. The lowest but not the higher doses significantly increased swimming time in a swim mobility test. No changes in neuropeptide Y (NPY) concentrations were observed in any of the brain regions tested as compared to control animals. Nemifitide did not increase NPY-like immunoreactivity but was found to cross the blood-brain barrier, reduce food intake and to be localized in the hippocampal and amygdala regions of the rat brain. These findings suggest a novel mechanism of action (4).

The pharmacokinetic profile of nemifitide was established based on data from 5 phase I and 3 phase II studies in healthy volunteers and depressed patients. The drug is rapidly absorbed and eliminated from the body, and both AUC and C_{max} were dose-proportional at doses ranging from 8-320 mg s.c. Nemifitide also had a favorable safety profile, as no serious adverse events were reported; only transient skin reactions at the injection site were related to the drug (5).

Researchers randomized 52 patients with major depression to nemifitide (0.2 mg/kg s.c. for 5 days) or placebo in a phase II pilot study. Treatment was well tolerated, with no serious adverse events. There was a strong pharmacodynamic correlation between plasma concentration of the agent and reduction in the severity of depression 1 h after dosing. The estimated mean

effective concentration was 5 ng/ml, with peak drug concentrations observed 7-14 days postdosing (6).

The safety, pharmacokinetics, mechanism of action and antidepressant activity of nemifitide were evaluated in a series of preclinical and clinical studies. More than 100 healthy volunteers were treated (8-320 mg) in 5 phase I studies and over 200 in current or completed phase II studies (15-240 mg in 5-day cycles), including 2 double-blind, placebo-controlled, single-center, parallel studies, 1 open-label extension study and an open-label pilot study. Nemifitide was well tolerated and produced rapid (within 3-5 days) and sustained clinical response (7).

In an ongoing open-label pilot study in patients with major depression, treatment consisted of daily doses of nemifitide of 40-240 mg s.c. in two 5-day dosing cycles, separated by 2 days and followed by 2 additional 5-day cycles when necessary. A positive response to treatment with nemifitide was seen in 41.2% of the patients and the drug also showed a good safety profile, confirming its potential as an antidepressant for severe treatment-resistant depression (8).

In a double-blind, randomized, placebo-controlled study including 55 patients with major depression, netamiftide 18 mg/day s.c. was administered to 22 patients for 10 days and to 11 patients for 5 days followed by placebo for 5 days. Placebo alone was given to 22 patients for 10 days. Netamiftide treatment was safe and demonstrated a rapid onset of action. A strong pharmacodynamic correlation between plasma drug concentrations and response to treatment was observed (9-11).

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4. Overstreet, D.H., Mathe, A.A., Nicolau, G., Feighner, J.P., Jimenez-Vasquez, P.A., Hlavka, J., Morrison, J., Abajian, H. *Effects of nemifitide on brain NPY levels and swim test immobility in a genetic animal model of depression*. Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.1.179.

5. Morrison, J., Feighner, J.P., Nicolau, G., Sverdlov, L., Abajian, H., Cardillo, N., Hlavka, J., Tonelli, G. Jr., Faria, G., DiSpirito, C. *Clinical pharmacokinetic studies with nemifitide, a novel pentapeptide antidepressant*. Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.4.W.013.

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8. Feighner, J.P., Sverdlov, L., Abajian, H., Nicolau, G., Hlavka, J., Freed, J. *Pilot study with nemifitide in patients with severe treatment-resistant depression*. Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.4.W.016.

9. Feighner, J.P., Sverdlov, L., Abajian, H., Hlavka, J., Nicolau, G. *Discriminant analysis to separate a study population by treatment subgroups in a pilot clinical trial with a new pentapeptide antidepressant (INN 00835)*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.1.003.

10. Sverdlov, L., Feighner, J.P., Abajian, H., Hlavka, J. *Discriminant analysis to separate a study population by treatment subgroups in a pilot clinical trial with a new antidepressant (nemifitide)*. Int J Neuropsychopharmacol 2002, 5(Suppl. 1): Abst P.4.W.015.

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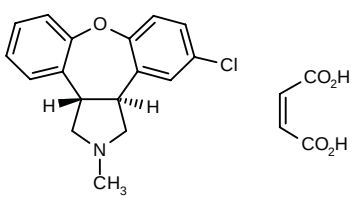
Original monograph - Drugs Fut 1997, 22(12): 1314.

Org-5222



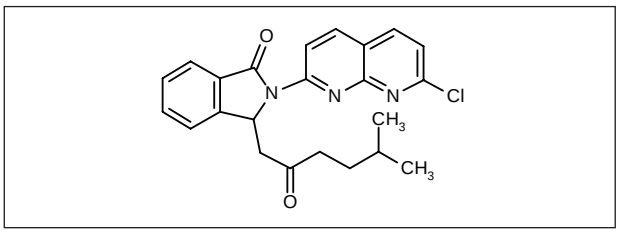
Org-5222 is a highly potent dopamine D_1/D_2 and 5-HT_{2C} receptor antagonist with potential as an antipsychotic agent. Organon (Akzo Nobel) is currently evaluating its efficacy in psychosis in phase III clinical studies.

The binding of new and established antipsychotic drugs was investigated at 9 different receptors in normal human brain tissue using radioligand binding assays. Iloperidone was found to be the most active at α_1- and α_2-adrenoceptors (K_d = 0.31 ± 0.02 and 3.0 ± 0.2 nM, respectively), Org-5222 the most active at dopamine D_2 and 5-HT_{2C} receptors (K_d = 2.0 ± 0.3 and 0.27 ± 0.03 nM, respectively) and ziprasidone the most active at 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2A} receptors (K_d = 1.9 ± 0.1, 2.4 ± 0.2 and 0.12 ± 0.01 nM, respectively). Olanzapine was the most active at the histamine H_1 receptor (K_d = 0.087 ± 0.005 nM) and clozapine at muscarinic receptors (K_d = 9 ± 1 nM). The other compounds tested were haloperidol, melperone, pimozide, quetiapine, risperidone, 9-OH-risperidone, sertindole and zotepine (1).

1. Richelson, E., Souder, T. *Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds*. Life Sci 2000, 68(1): 29.

Original monograph - Drugs Fut 1993, 18(12): 1117.

Pagoclone



Pagoclone (CI-1043, IP-456, RP-62955, RP-59037) belongs to the cyclopyrrolone class of compounds and is a novel GABA receptor agonist in advanced clinical testing for anxiety disorders.

The former Interneuron, now Indevus Pharmaceuticals, licensed pagoclone from Rhone-Poulenc Rorer (now Aventis) in 1994, and in 1999 licensed exclusive worldwide rights to Warner-Lambert (now Pfizer). Earlier this year, Pfizer returned to Indevus the rights to pagoclone following results of recent clinical trials in GAD (phase II) and panic disorder (phase III) which did not reach the level of efficacy established in previous trials. Pagoclone has completed 3 positive phase II trials, 2 in panic disorder conducted by Indevus and 1 in GAD by Pfizer. Aventis then declined to exercise its contractual option to develop pagoclone, allowing Indevus to pursue a new worldwide development partnership for the drug's commercialization. Indevus continues discussions with several companies regarding partnering opportunities for pagoclone (1-4).

A double-blind, randomized, placebo-controlled, crossover study established the efficacy and safety of pagoclone in the treatment of DSM-IV panic disorder. After a 2-week screening period, 16 patients were randomized to receive either 0.1 mg t.i.d. pagoclone or placebo for 2-week periods, separated by a 1-week washout period. Pagoclone significantly decreased the number of full panic attacks compared to baseline values, while showing a safety profile similar to that of placebo and better than that of classical benzodiazepines. No serious adverse events or abnormalities in ECG, vital signs, clinical chemistry, hematology or urinalysis were found (5).

Results from a 6-week trial of pagoclone for the treatment of GAD have shown it to produce a statistically significant improvement in symptoms over placebo, and to be well tolerated, nonsedating and devoid of withdrawal effects. The trial, carried out by Pfizer, was conducted in 200 patients and involved a flexible dose regimen ranging from 0.3-1.2 mg/day. Patient entry criteria included Hamilton Anxiety Scale (HAM-A) scores of 18 or more. In comparison with placebo-treated patients, pagoclone-treated patients had a mean 2.3-point decrease in HAM-A scores at week 3, a mean 3.3-point decrease at week 4 and a mean 3.2-point decrease at week 6. At this time, the mean reduction in HAM-A score among pagoclone patients was 11.7 compared to 8.5 for placebo (6).

1. *Pfizer returns pagoclone rights to Indevus*. DailyDrugNews.com (Daily Essentials) June 11, 2002.

2. *Aventis declines option to develop pagoclone*. DailyDrugNews.com (Daily Essentials) Aug 30, 2002.

3. *Pagoclone enters phase II for treatment of GAD*. DailyDrugNews.com (Daily Essentials) Jan 17, 2001.

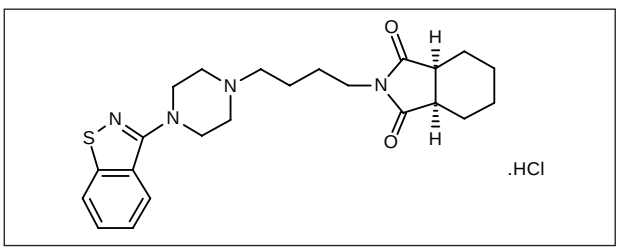
4. *Continued progress in product pipeline reported at Interneuron*. DailyDrugNews.com (Daily Essentials) Feb 15, 2001.

5. Sandford, J.J., Forshall, S., Bell, C., Argyropoulos, S., Rich, A., D'Orlando, K.J., Gammans, R.E., Nutt, D.J. *Crossover trial of pagoclone and placebo in patients with DSM-IV panic disorder*. J Psychopharmacol 2001, 15(3): 205.

6. *Pagoclone shows promising results in treatment of generalized anxiety disorder*. DailyDrugNews.com (Daily Essentials) Dec 21, 2001.

Original monograph - Drugs Fut 2001, 26(7): 651.

Perospirone Hydrochloride



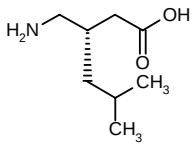
Perospirone is a dual 5-HT_2 and dopamine D_2 receptor antagonist which alleviates both positive and negative symptoms of schizophrenia and exhibits a low incidence of extrapyramidal side effects.

The atypical antipsychotic perospirone hydrochloride hydrate (SM-9018), developed at Sumitomo, was launched last year in Japan as Lullan® following its approval in late December 2000. The product is copromoted by Sumitomo and Mitsubishi Pharma as tablets of 4 and 8 mg (1).

1. *Japanese introduction announced for new atypical antipsychotic*. DailyDrugNews.com (Daily Essentials) Feb 23, 2001.

Original monograph - Drugs Fut 1991, 16(2): 122.

Pregabalin



The GABA analogue pregabalin (CI-1008, PD-144723; see *Drugs of the Future* 2002, 27(9): 898) is in late-stage clinical evaluation at Pfizer for use as an adjunct in epilepsy and for neuropathic pain and GAD. NDA filing, originally scheduled for this year, is now expected to occur in Europe in March 2003 and subsequently in the U.S., allowing for the inclusion of requested toxicological studies.

Pregabalin (150 and 600 mg/day) was the subject of 4 phase II trials (3 in generalized anxiety disorder and 1 in social anxiety disorder) in patients with anxiety disorders. In all the trials, pregabalin proved to be effective and well tolerated. Adverse events were mild or moderate and consisted of somnolence and dizziness (1).

The efficacy of pregabalin (150 mg t.i.d.) in the long-term treatment of GAD was evaluated in 624 patients who were randomized to double-blind treatment with pregabalin or placebo for 26 weeks following an initial 8-week open-label phase. Treatment was well tolerated and effective in preventing relapse of GAD (2). The results of this study and those that follow are summarized in Table VII.

A randomized, double-blind, 6-week study compared the efficacy and safety of pregabalin 400 or 600 mg/day to that of venlafaxine 75 mg/day and placebo in 426 patients with GAD. All treatments were given twice daily. The pregabalin doses were equally effective and as effective as venlafaxine in improving symptoms of GAD. More withdrawals due to adverse events were seen in the venlafaxine group (3, 4).

1. Lydiard, R.B., Feltner, D.E., Robinson, P., Liu-Dumaw, M., Pande, A.C. *Pregabalin, a novel agent in the treatment of anxiety disorders.* Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst S.21.04.

2. Smith, W., Feltner, D., Kavoussi, R. *Pregabalin in generalized anxiety disorder: Long term efficacy and relapse prevention.* Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.3.047.

3. Kasper, S., Blagden, M., Seghers, S. et al. *A placebo-controlled study of pregabalin and venlafaxine treatment of GAD.* Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.3.027.

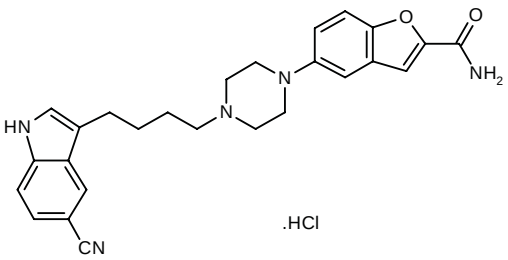
4. Kasper, S., Blagden, M., Seghers, S., Veerman, A., Volz, H.P., Geniaux, A., Strubb, N. *A placebo-controlled study of pregabalin and venlafaxine treatment of GAD.* Annu Meet Am Psychiatr Assoc (May 18-23, Philadelphia) 2002, Abst NR202.

Original monograph - Drugs Fut 1999, 24(8): 862.

Table VII: Clinical studies of pregabalin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Anxiety	Randomized, double-blind	Pregabalin, 150 mg tid x 8 wk → (in responders) Pregabalin x 26 wk (n=168) Pregabalin, 150 mg tid x 8 wks → (in responders) Placebo x 26 wk (n=170)	624	Pregabalin was well tolerated and significantly prolonged the time to relapse compared with placebo in patients with generalized anxiety disorder. Efficacy was maintained during the placebo-controlled study in significantly more patients given pregabalin than placebo	2
Anxiety	Randomized, double-blind	Pregabalin, 200 mg bid x 6 mo (n=98) Pregabalin, 300 mg bid x 6 mo (n=111) Venlafaxine, 37.5 mg bid x 6 mo (n=114) Placebo (n=103)	426	Pregabalin and venlafaxine given bid were safe and effective in improving the HAM-A total score in patients with generalized anxiety disorder	3, 4

Vilazodone Hydrochloride



The antidepressant vilazodone hydrochloride (EMD-68843, SB-659746-A) is being developed under a collaboration between GlaxoSmithKline and Merck KGaA. The compound, currently in phase II trials, was discovered and advanced into early clinical development by Merck. Vilazodone combines the properties of an SSRI with those of a 5-HT_{1A} partial agonist. Under the terms of the agreement, GlaxoSmithKline will be responsible for continuing development worldwide and for commercialization. Merck will receive milestone payments and royalties on sales and will retain the option to jointly commercialize the compound in certain markets outside North America. Merck will also be responsible for manufacturing the drug (1).

Prior to the plus-maze and shock-probe anxiety tests, rats were injected with vehicle, diazepam (2.5 mg/kg i.p.) or vilazodone (10, 20 or 40 mg/kg). While diazepam and vilazodone dose-dependently reduced burying in the shock-probe test, only diazepam induced a significant increase in open arm exploration in the plus-maze (2).

Healthy young male volunteers (n=10) were randomized to 20 mg vilazodone or placebo in a study of the drug's effects on sleep EEG. These effects were found to correlate with the pharmacological profile of vilazodone (3).

1. *Merck KGaA licenses antidepressant to GlaxoSmithKline*. DailyDrugNews.com (Daily Essentials) Feb 15, 2001.

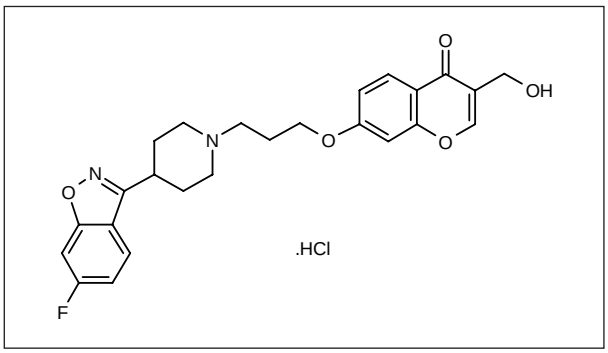
2. Treit, D., Degroot, A., Kashluba, S., Bartoszyk, G.D. *Systemic EMD 68843 injections reduce anxiety in the shock-probe, but not the plus-maze test*. Eur J Pharmacol 2001, 414(2-3): 245.

3. Murck, H., Friboes, R.M., Antonijevic, I.A., Steiger, A. *Distinct temporal pattern of the effects of the combined serotonin-reuptake inhibitor and 5-HT_{1A} agonist EMD 68843 on the sleep EEG in healthy men*. Psychopharmacology 2001, 155(2): 187.

Original monograph - Drugs Fut 2001, 26(3): 247.

Spotlights

Abaperidone Hydrochloride

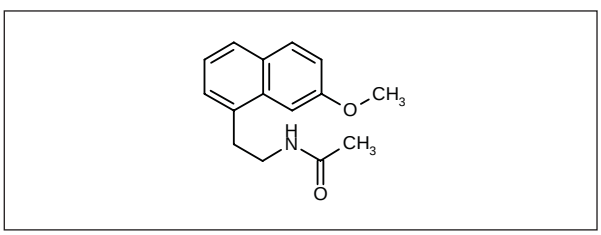


Ferrer's abaperidone hydrochloride (FI-8602) is currently undergoing clinical evaluation as a new treatment for schizophrenia and other psychotic disorders. Its biochemical and pharmacological profile are indicative of highly potent antipsychotic activity along with reduced side effects compared to conventional drugs. Abaperidone displays a mixed CNS receptor binding profile, with dopamine D_2 receptor-antagonist activity, high affinity for D_3 receptors and α_1-adrenoceptors, and greater affinity for 5-HT_2 receptors than D_2 receptors, the latter thought to be responsible for the reduced incidence of extrapyramidal side effects (see *Drugs of the Future* 2001, 26(4): 335).

ACR-16

A dopaminergic transmission stabilizer, ACR-16 recently completed phase I clinical testing at Carlsson Research in Sweden and is advancing to trials in patients with schizophrenia. Indications are that the drug may be useful for the full range of symptoms of schizophrenia, including both positive and negative symptoms.

Agomelatine



Agomelatine (S-20098) is a potential new antidepressant with a novel pharmacological profile, combining melatonin receptor-agonist and selective 5-HT_{2C} receptor-antagonist activity. It is undergoing phase III clinical trials by Servier.

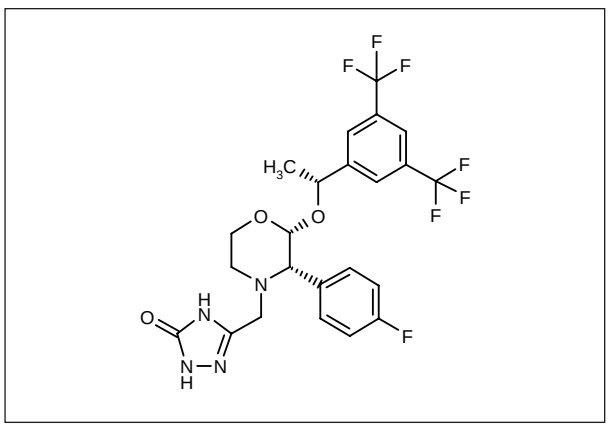
ANPH-101

ANPH-101 is being evaluated by Ancile as a potential treatment for sleep disorders in phase II/III clinical trials in the U.S.

ANPH-102

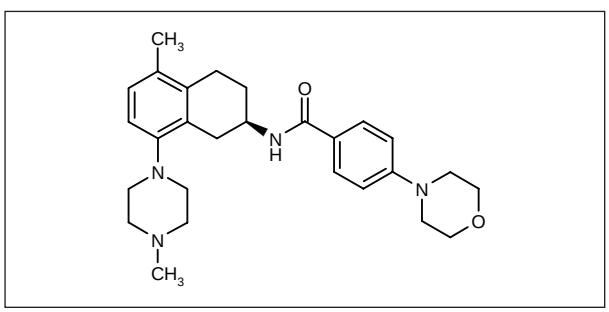
A potential anxiolytic agent from Ancile, ANPH-102 is undergoing phase II clinical trials in the U.S.

Aprepitant



Merck & Co.'s aprepitant (L-754030, MK-0869, MK-869) is a selective tachykinin NK_1 receptor antagonist in phase III clinical trials as a treatment for depression, and also for chemotherapy-induced nausea and vomiting.

AR-A2



AstraZeneca is conducting early clinical trials with AR-A2 (AR-A000002), a highly selective 5-HT_{1B} receptor antagonist with potential in the treatment of depression and anxiety.

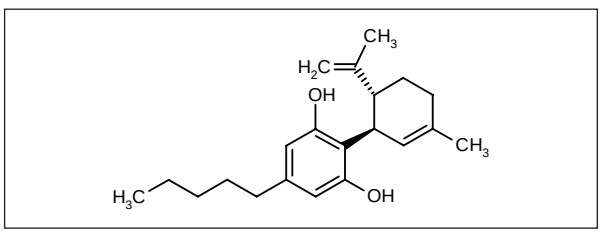
AVE-5997

AVE-5997 is a potential antispychotic agent with dopamine D_3 receptor-antagonist activity, presently in phase I evaluation at Aventis.

Bifeprunox

Bifeprunox (DU-127090) is an atypical antipsychotic agent that combines potent partial agonist/antagonist effects at the dopamine D_2 receptor with 5-HT_{1A} receptor-agonist effects. It is undergoing phase II evaluation at Solvay and licensee Lundbeck for the treatment of schizophrenia, and is scheduled to enter phase III testing in 2003 for both schizophrenia and Parkinson's disease.

Cannabidiol

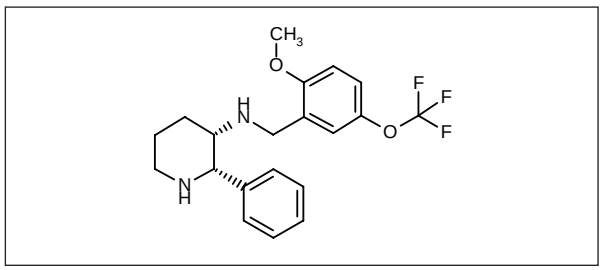


Cannabidiol (CBD) is a nonpsychoactive neuroprotective cannabinoid derived from cannabis with potential as an antipsychotic. The compound is an effective blood-brain barrier-permeable antioxidant which is in phase I clinical trials at GW Pharmaceuticals as a treatment for schizophrenia.

CEE-310

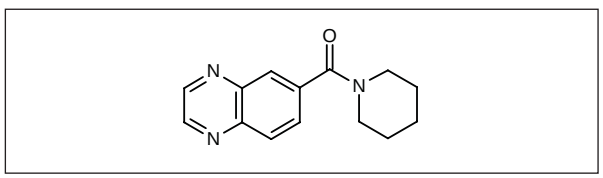
A selective dopamine D_1 receptor antagonist discovered by Novo Nordisk, CEE-310 (CEE-03-310) had reached phase II clinical trials in the U.S. at CeNeS for the treatment of sleep disorders and alcohol abuse. Development is currently on hold while the company looks for a partner.

CP-122721



Pfizer is conducting phase II clinical trials with CP-122721, a potent and selective tachykinin NK_1 receptor antagonist with potential in the treatment of depression.

CX-516

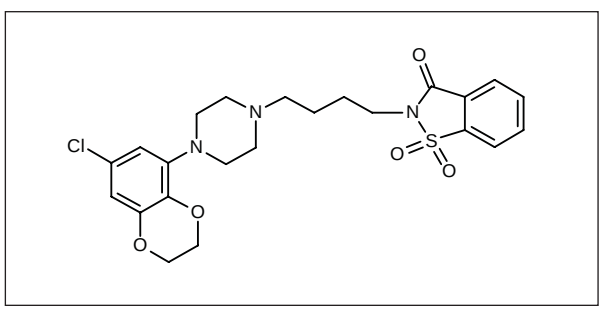


CX-516 (Ampalex®) is a positive AMPA receptor modulator (Ampakine®) that is being developed jointly by Organon (Akzo Nobel) and Cortex in phase II trials for schizophrenia. It is also being evaluated in phase II clinical trials for the treatment of autism and Alzheimer's disease.

DOV-216303

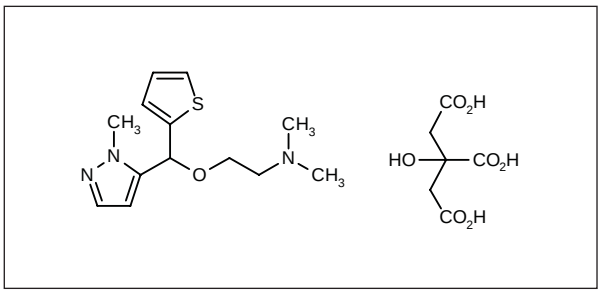
DOV Pharmaceutical is conducting phase I clinical studies with DOV-216303, a noradrenaline, 5-HT and dopamine reuptake inhibitor licensed from Wyeth-Ayerst (now Wyeth Research) in 1998, as a potential antidepressant.

DU-125530



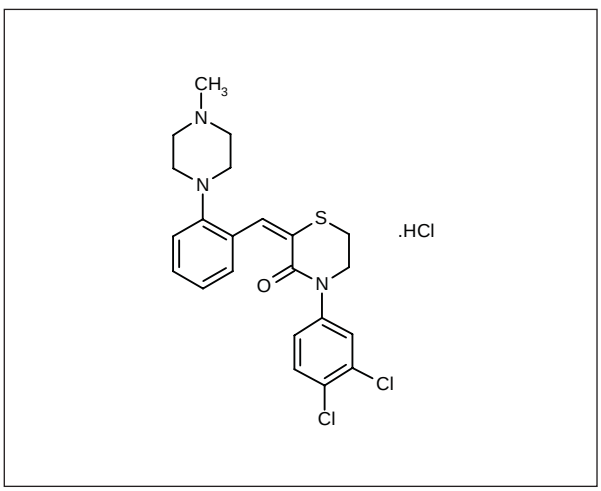
DU-125530 is a selective 5-HT_{1A} receptor antagonist developed by Solvay and currently in phase II clinical evaluation for the treatment of major depressive disorder.

E-6039



E-6039 (E-6006 citrate) is a potential anxiolytic and antidepressant that entered phase I testing in 2001 at Esteve for the treatment of depression.

Elzasonan Hydrochloride

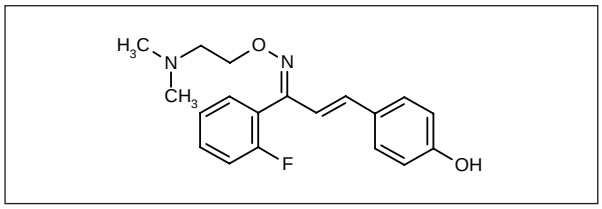


Phase II clinical trials are under way at Pfizer for elzasonan hydrochloride (CP-448187), a 5-HT_{1D} receptor antagonist for depression.

EMR-62218

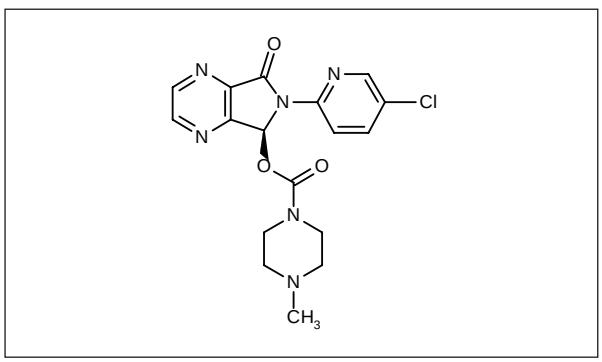
EMR-62218 is a potential new antipsychotic agent developed at Merck KGaA and currently in phase I testing.

Eplivanserin



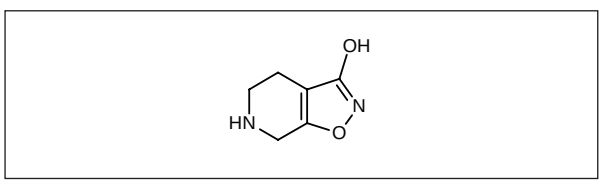
Sanofi-Synthélabo is conducting phase IIb trials of eplivanserin (SR-46349) in the U.S. for the treatment of schizophrenia. The development of this selective 5-HT_{2A} receptor antagonist for the treatment of sleep apnea hypopnea syndrome was discontinued last year.

Eszopiclone



A rapid-acting, nonbenzodiazepine hypnotic discovered at Aventis and indicated for the treatment of sleep disorders, eszopiclone (Estorra™), the (+)- or (*S*)-enantiomer of zopiclone, is being prepared for NDA filing in the U.S. by licensee Sepracor. The company plans to develop two doses, one intended for the maintenance of a full sleep cycle and the other for patients who have difficulty falling asleep.

Gaboxadol



Gaboxadol (Lu-02-030, THIP) is a selective GABA-A receptor agonist currently in phase II/III trials at Lundbeck for the treatment of insomnia, with regulatory submission scheduled for 2004.

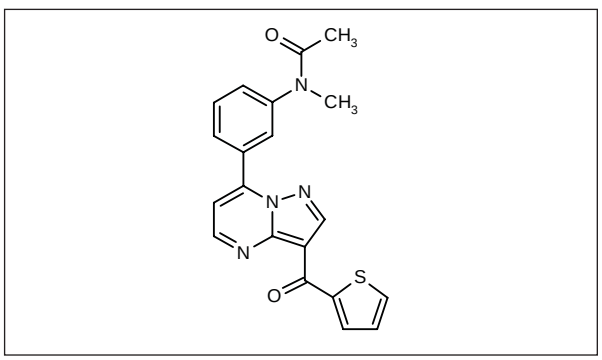
GW-353162

GW-353162 is a dopamine/noradrenaline reuptake inhibitor from GlaxoSmithKline that is being tested in phase I trials as a potential treatment for depression and bipolar disorder.

GW-597599

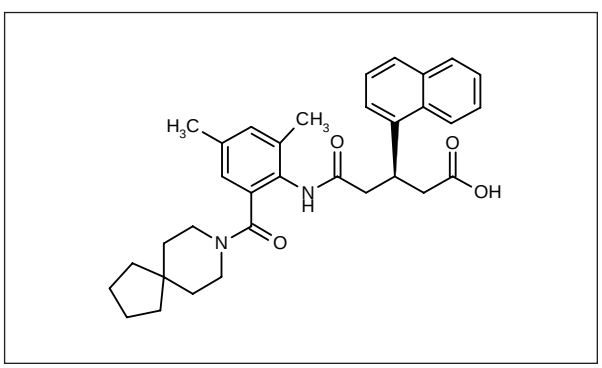
A tachykinin NK_1 antagonist, GW-597599 is in phase II clinical development at GlaxoSmithKline for the treatment of anxiety and depression.

Indiplon



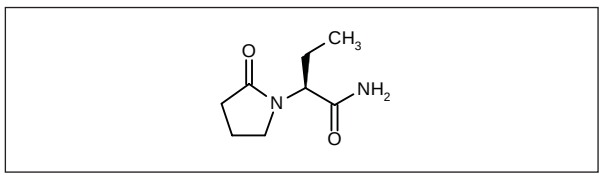
Neurocrine Biosciences is conducting multiple phase III clinical trials with immediate-release (IR) and modified-release (MR) formulations of indiplon (NBI-34060), a non-benzodiazepine sleep-promoting compound developed by DOV Pharmaceutical that acts as an agonist at a specific site of the GABA-A receptor. The compound is indicated for the treatment of primary (chronic) and transient insomnia. NDA filing in the U.S. is scheduled for 2003.

Itriglumide



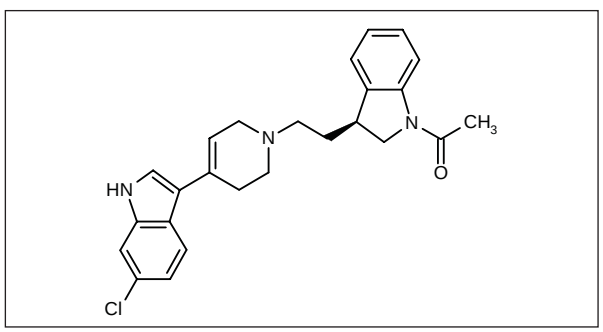
A CCK-B receptor and gastrin antagonist developed by Rotta, itriglumide (CR-2945) is undergoing phase I clinical evaluation for the treatment of anxiety, and also for gastric ulcer and gastric cancer.

Levetiracetam



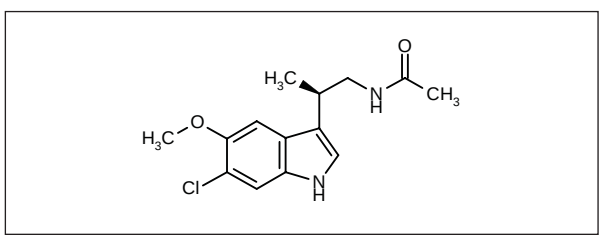
The antiepileptic drug levetiracetam (Keppra®), the *levo*-isomer of etiracetam, was discovered by UCB and has been available for the treatment of partial-onset seizures in adults for several years in the U.S. and certain European countries. Exploratory studies are also being conducted in new indications, including bipolar disorder, as well as migraine and neuropathic pain (see *Drugs of the Future* 2002, 27(4): 419).

LU-35-138



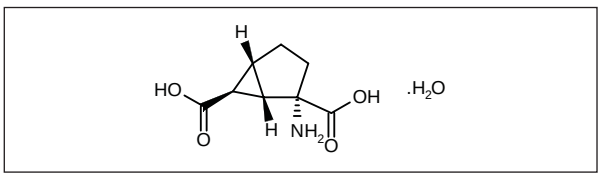
The dopamine D_4 receptor antagonist and 5-HT reuptake inhibitor Lu-35-138 is in phase I clinical trials at Lundbeck as a potential antipsychotic agent. Phase II trials are scheduled to begin next year, with phase III evaluation in 2004.

LY-156735



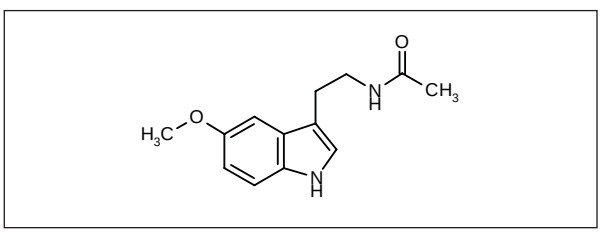
A melatonin analogue and melatonin receptor agonist, LY-156735 was discovered by Lilly and is licensed for development and marketing to Phase 2 Discovery. The compound has given positive results in preliminary phase I trials in patients with sleep-onset insomnia and is poised to advance into larger trials.

LY-354740



The potent and selective metabotropic glutamate mglu2 and mglu3 agonist LY-354740 has demonstrated significant anxiolytic activity and potential for use in drug withdrawal in animal models and is currently in phase I clinical studies.

Melatonin

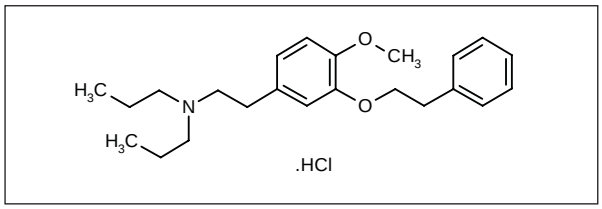


Neurim's sustained-release melatonin formulation, Circadin™, is nearing market launch in Canada for use in elderly patients suffering from primary insomnia. It mimics the body's physiological secretion profile of melatonin in younger healthy adults and reconstitutes the decreased melatonin levels in the elderly, resulting in improved quality of sleep and subsequent daytime functioning. Unlike in the U.S., where melatonin is considered a health food supplement, the Canadian authorities regard it as a drug. Paladin holds rights to the product in Canada and filed for approval earlier this year.

NBI-34041

NBI-34041 is a corticotropin-releasing factor CRF_1 receptor antagonist discovered as part of a collaboration between Neurocrine Biosciences and GlaxoSmithKline, and is currently in phase I development for the treatment of anxiety disorders and depression.

NE-100

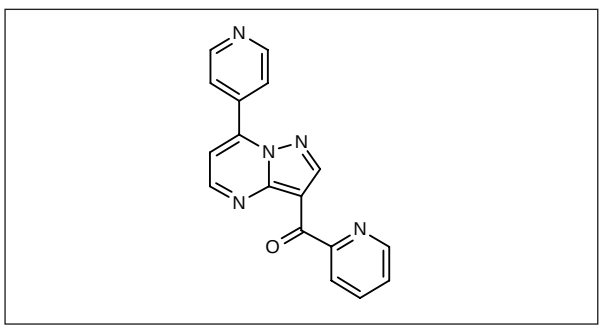


An antipsychotic agent that acts as a potent and selective sigma receptor antagonist, Taisho's NE-100 is in phase II clnical testing for the treatment of schizphrenia.

NGD-96-3

Originally discovered at Neurogen, NGD-96-3, a selective GABA-A receptor modulator, is being evaluated by licensee Pfizer in phase I trials as a potential treatment for insomnia.

Ocinaplon

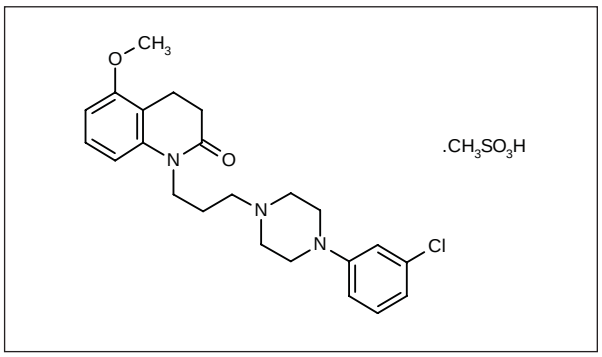


The selective GABA-A receptor modulator ocinaplon (CL-273547) was originally licensed from the former Wyeth-Ayerst (now Wyeth) and is being developed through a joint venture between DOV Pharmaceutical and Elan. In trials to date, ocinaplon has demonstrated good safety and tolerability, with no evidence of sedation or other side effects. It is now in phase II clinical evaluation for the treatment of GAD.

Olanzapine/Fluoxetine

The combination of the atypical antipsychotic agent olanzepine and the antidepressent fluoxetine is in phase II development at Lilly for the treatment of psychotic depression and an NDA for the treatment of bipolar depression was recently submitted to the FDA for review.

OPC-14523

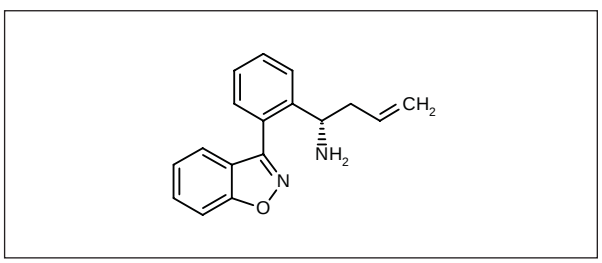


Otsuka is developing OPC-14523, a potent sigma/5-HT_{1A} receptor agonist and 5-HT reuptake inhibitor, in phase II clinical trials for the treatment of major depressive disorder.

Org-24448

An AMPA receptor modulator (Ampakine®) developed by Cortex, Org-24448 is in phase II evaluation by Organon (Akzo Nobel) as a potential new antipsychotic agent.

Org-34167

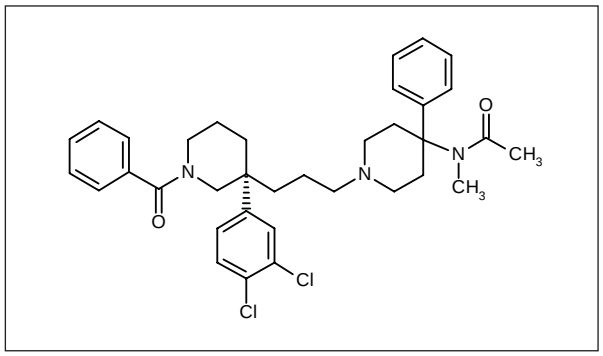


A potential new antidepressant, Org-34167 is an ion channel modulator in phase II development at Organon (Azko Nobel).

Org-34517

A selective glucocorticoid receptor antagonist, Org-34517 has advanced to phase II clinical studies at Organon (Akzo Nobel) as a potential treatment for depression. The product is scheduled for launch in 2006.

Osanetant



Osanetant (SR-142801) is a new tachykinin NK_3 receptor antagonist currently in phase IIb development at Sanofi-Synthélabo as a potential treatment for schizophrenia and major depressive disorder.

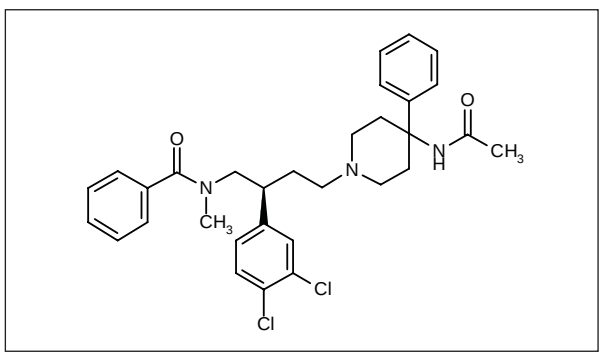
R-673

Roche is conducting phase II clinical trials with the potential new antidepressant R-673, a tachykinin NK_1 receptor antagonist.

R-1204

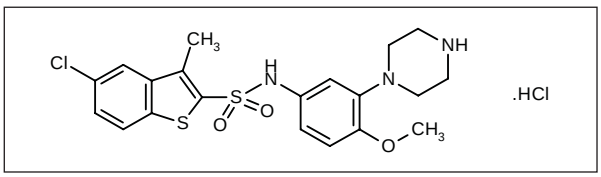
Roche's R-1204 is a new G-protein-coupled receptor (GPCR) modulator undergoing phase I trials for anxiety and depression.

Saredutant



Saredutant (SR-48968), a selective, nonpeptide tachykinin NK_2 receptor antagonist, is being studied in phase II trials by Sanofi-Synthélabo for depression and irritable bowel syndrome.

SB-271046



GlaxoSmithKline's SB-271046 is a highly potent and selective 5-HT_6 receptor antagonist which has reached phase I clinical evaluation as a potential treatment for schizophrenia and Alzheimer's disease.

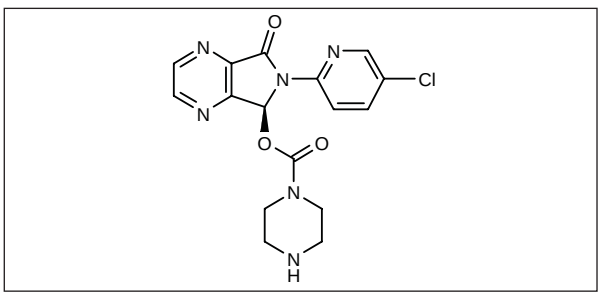
SB-723620

SB-732620 is a new CRF_1 receptor antagonist in phase I clinical development at GlaxoSmithKline for the treatment of depression and anxiety disorders, as well as irritable bowel syndrome.

Secretin, Synthetic Human

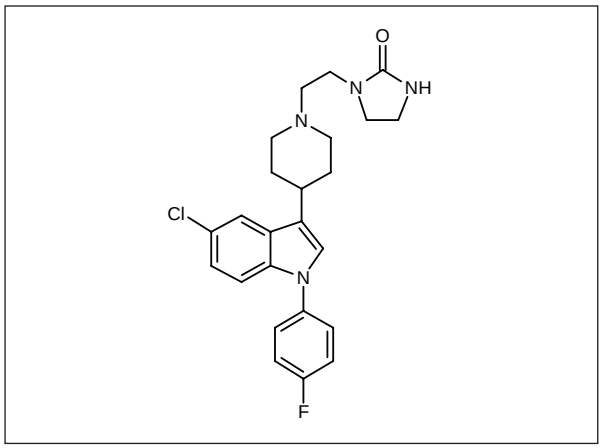
The hormone secretin is produced by the intestine and stimulates the pancreas as part of the normal process of digestion. Synthetic human secretin (RG-1068) has been found to activate several regions of the brain, including the amygdala, implicated in autism. It is undergoing phase III clinical evaluation at Repligen and ChiRhoClin for the treatment of autism.

SEP-174559



In preclinical studies, SEP-174559, or (+)-*N*-desmethylzopiclone ([*S*]-DMZ), an isomer of a metabolite of zopiclone discovered at Aventis, demonstrated anxiolytic effects at doses well below levels causing sedation. Licensee Sepracor has commenced phase I clinical trials of the drug for the treatment of acute and chronic anxiety.

Sertindole

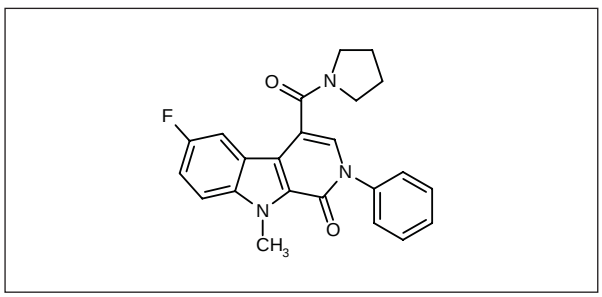


Sertindole (Serdolect®) is an antipsychotic agent which acts as a 5-HT_{2A} receptor and dopamine D_2 receptor antagonist and was approved and launched by Lundbeck in 1996, but subsequently withdrawn by the company after serious cardiac events were reported. Further studies are in progress and it is scheduled for relaunch in 2004.

(*R*)-Sibutramine Metabolite

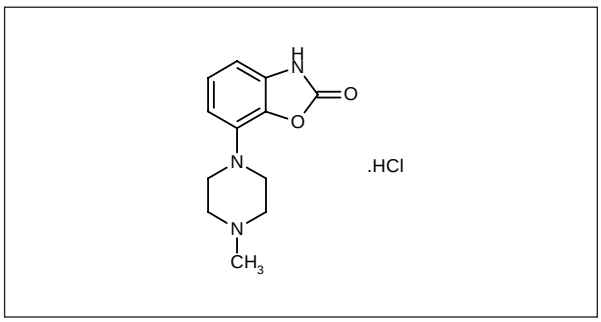
An isomer of an active metabolite of sibutramine, this compound is a potent monoamine (5-HT, noradrenaline and dopamine) reuptake inhibitor. It was well tolerated in phase I trials and Sepracor is currently conducting a large-scale phase II clinical trial for the treatment of depression. Launch is scheduled for 2004.

SL-65.1498



SL-65.1498 is a full agonist at α_2 and α_3 GABA-A receptor subunits and a partial agonist at α_1 and α_5 subunits. It is undergoing phase II clinical evaluation at Sanofi-Synthélabo for the treatment of anxiety.

SLV-308



A highly potent dopamine D_2 receptor partial agonist with weak full 5-HT_{1A} receptor-agonist effects, SLV-308 (SME-308) is being developed by Solvay and Meiji Seika primarily for the treatment of Parkinson's disease (see *Drugs of the Future* 2002, 27(9): 909). It is also being studied in phase II clinical trials for the treatment of major depressive disorder and panic attacks.

SLV-310

Solvay is conducting phase I trials of SLV-310, a potent dopamine D_2 antagonist and 5-HT reuptake inhibitor with potential as an antipsychotic agent.

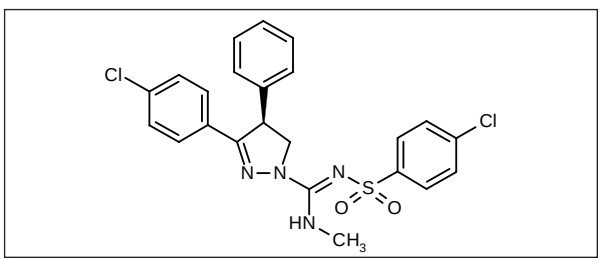
SLV-313

A dopamine D_2 antagonist and 5-HT_{1A} agonist, SLV-313 is in phase I clinical development at Solvay as a potential antipsychotic agent.

SLV-314

SLV-314 is a potential new antispychotic agent from Solvay that acts as a dual dopamine D_2 receptor antagonist and 5-HT reuptake inhibitor and is in phase I trials for the treatment of schizophrenia.

SLV-319



SLV-319 is another compound from Solvay that is undergoing phase I trials as an antispychotic agent. SLV-319 is a cannabinoid CB_1 receptor antagonist with very high selectivity over CB_2 receptors.

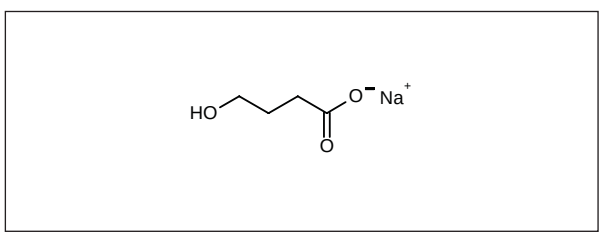
SM-13496

SM-13496, an agent with preferential 5-HT_{2A} receptor- and dopamine D_2 receptor-antagonist effects, is in phase II evaluation by Sumitomo in Japan and the U.S. for use in the treatment of schizophrenia.

SNEC-2

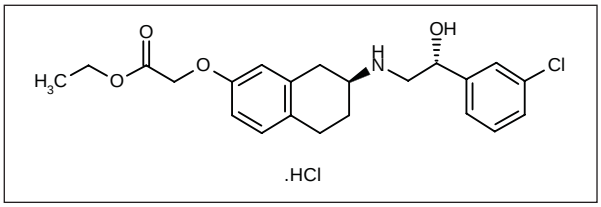
Synaptic's SNEC-2 is a new antidepressant targeting the SCT-11 receptor, a G-protein-coupled receptor (GPCR) which is presently in phase I clinical evaluation in the U.S.

Sodium Oxybate



Just launched in the U.S., Orphan Medical's sodium oxybate (Xyrem®) is indicated for the treatment of cataplexy associated with narcolepsy. This drug is designated a Schedule III controlled substance for medical use only.

SR-58611

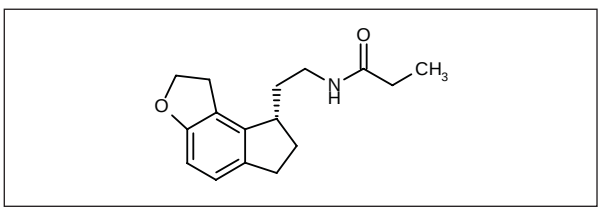


A selective beta$_3$-adrenoceptor agonist, SR-58611 (SR-58611A) is presently being tested in phase II clinical trials by Sanofi-Synthélabo for the treatment of major depressive disorder.

SR-144190

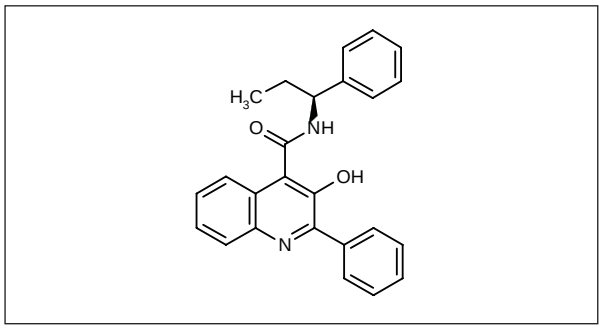
SR-144190 is a nonpeptide tachykinin NK_2 receptor antagonist in phase I clinical development at Sanofi-Synthélabo for depression and anxiety.

TAK-375



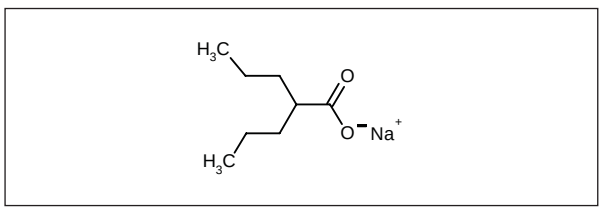
TAK-375 (Takeda) is a potent melatonin MT_1 and MT_2 receptor agonist undergoing phase II clinical trials in Japan, Europe and the U.S. for the treatment of primary insomnia and circadian rhythm disorders.

Talnetant



Talnetant (SB-223412), undergoing phase II clinical trials by GlaxoSmithKline for the treatment of schizophrenia, and also for chronic obstructive pulmonary disease, irritable bowel syndrome and cough, is a potent and selective, nonpeptide tachykinin NK_3 receptor antagonist.

Valproic Acid Sodium Salt



Valproic acid sodium salt is a known anticonvulsant agent marketed by Abbott as Depacon® and by Dainippon Pharmaceutical as Valerin®. It was approved in Japan in 2002 as a mood stabilizer for the treatment of manic-depressive psychosis and bipolar disorder.