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Annual Update 2003: Drugs for Psychiatric Disorders and Substance Abuse

CONTENTS

Abstract

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Introduction

This month's Annual Update 2003, dedicated to Drugs for Psychiatric Disorders and Substance Abuse, is comprised of a compendium of 137 drugs for the treatment of anxiety disorders, depression, bipolar disorder, schizophrenia, autism, attention deficit hyperactivity disorder, sleep disorders, alcohol abuse and alcoholism, drug abuse and addiction, and smoking cessation. The table of drugs includes products which have been launched for the first time since 2002 and others that were previously marketed for another indication. Products featured in the monograph updates section include agomelatine, aripiprazole, blonanserin, duloxetine hyrochloride, escitalopram oxalate, eszopiclone, gepirone hydrochloride, indiplon, INN-00835, lamotrigine, nalmefene, naltrexone hydrochloride, ocinaplon, olanzapine, pregabalin, quetiapine fumarate, TAK-375 and venlafaxine hydrochloride.

Annual Update 2003: Drugs for Psychiatric Disorders and Substance Abuse

Drug	Source	Condition	Phase
679769	GlaxoSmithKline	Anxiety	I
	GlaxoSmithKline	Depression	I
AAG-561	Novartis	Anxiety	I
	Novartis	Depression	I
Abaperidone Hydrochloride[2]	Ferrer	Psychosis	I
ABT-089	Abbott	Attention deficit hyperactivity disorder	II
AC-5216	Dainippon/Novartis	Anxiety	I
	Dainippon	Depression	I
ACR-16	Carlsson Research/Merck & Co.	Schizophrenia	I
Adrogolide Hydrochloride[2]	DrugAbuse Sciences	Cocaine dependency	II
Agomelatine[2]	Servier	Depression, major	III
Alprazolam (nasal spray)[1,2]	Questcor	Anxiety	Clinical
Alprazolam[1,2]	Pfizer	Panic disorder	L-2003
AP-521	Asahi Kasei	Anxiety	II
AR-A000002	AstraZeneca	Anxiety	II
	AstraZeneca	Depression	II
Aripiprazole[1,2]	Bristol-Myers Squibb/Otsuka	Schizophrenia	L-2002
	Bristol-Myers Squibb/Otsuka	Bipolar disorder	Prereg.
Asenapine Maleate[2]	Organon/Pfizer	Bipolar disorder	III
	Organon/Pfizer	Schizophrenia	III
Atomoxetine Hydrochloride[2]	Lilly	Attention deficit hyperactivity disorder	L-2003
	Lilly	Autism	Clinical
AVE-5997	Aventis Pharma	Schizophrenia	I
Bifeprunox Mesilate[2]	Solvay/Lundbeck	Schizophrenia	III
Blonanserin[2]	Dainippon	Schizophrenia	III
BP-897	Bioprojet	Cocaine dependency	II
BTG-1640	Abiogen/BTG	Anxiety	I
BTS-74398 (SPD-473)	Shire Pharmaceuticals	Attention deficit hyperactivity disorder	I
Bupropion Hydrochloride[1,2]	GlaxoSmithKline	Depression, major	L-2003
	National Institutes of Health	Attention deficit hyperactivity disorder (with comorbid alcoholism)	II
	National Institutes of Health	Alcoholism (with comorbid ADHD)	II
	National Institutes of Health	Drug addiction	II
	Biovail	Smoking cessation	III
Cabergoline[1,2]	National Institutes of Health	Cocaine dependency	II
Cannabidiol	GW Pharmaceuticals	Schizophrenia	I
CEE-03-310	Addex Pharmaceuticals (licensed from CeNeS)	Alcoholism	II
Chromium Picolinate[1]	Nutrition 21	Depression	Clinical
CJ-17493	Pfizer	Depression	I/II
TA-CD	Xenova	Cocaine dependency	II
CP-601927	Pfizer	Drug addiction	I/II
CP-730330	Pfizer	Insomnia	I/II
CX-516	Cortex/Organon	Schizophrenia	II
	Cortex	Autism	II
Dexmethylphenidate Hydrochloride	Celgene/Novartis	Attention deficit hyperactivity disorder	L-2002
Donepezil hydrochloride[1,2]	National Institute of Mental Health	Autism	I
DOV-216303	DOV Pharmaceutical	Depression, major	II
DOV-21947	DOV Pharmaceutical	Depression	I
DP-VPA	D-Pharm	Bipolar disorder	I
Duloxetine Hydrochloride[2]	Lilly/Shionogi/Boehringer Ingelheim	Depression	Prereg.
E-6006 Citrate	Esteve	Depression	I
Eglumegad Hydrate	Lilly	Anxiety	I
Elzasonan Hydrochloride	Pfizer	Depression	II
EMR-62218	Merck KGaA	Schizophrenia	I
Eplivanserin	Sanofi-Synthélabo	Insomnia	II
Escitalopram Oxalate[1,2]	Forest/Lundbeck	Panic disorder	L-2002
	Forest/Lundbeck	Depression, major	L-2002
	Forest/Lundbeck	Anxiety, generalized	Prereg.
	Forest/Lundbeck	Phobia, social	III
Eszopiclone[2]	Sepracor	Insomnia	Prereg.
Felbamate[1,2]	National Institutes of Health	Bipolar disorder	II
Fluoxetine Hydrochloride[1,2]	Lilly	Panic disorder	R-2002

Continuation

Annual Update 2003: Drugs for Psychiatric Disorders and Substance Abuse

Drug	Source	Condition	Phase
	Lilly	Stress, posttraumatic	III
	FDA Office of Orphan Products Development	Autism	Clinical
Fluvoxamine Maleate[1,2]	Meiji Seika	Phobia, social	Prereg.
Gabapentin[1,2]	National Institutes of Health	Alcoholism	II
Gaboxadol	Lundbeck	Insomnia	III
Sodium Oxybutyrate	Orphan Medical	Narcolepsy	L-2002
Gepirone Hydrochloride[2]	Organon	Depression, major	Prereg.
GW-353162	GlaxoSmithKline	Depression	I
	GlaxoSmithKline	Bipolar disorder	I
GW-468816	GlaxoSmithKline	Smoking cessation	I
GW-597599	GlaxoSmithKline	Anxiety	II
	GlaxoSmithKline	Depression	II
Iloperidone[2]	Titan/Novartis	Schizophrenia	III
Indiplon	Neurocrine Biosciences/Pfizer	Insomnia	III
Itriglumide[2]	Rotta	Anxiety	I
Lamotrigine[1,2]	GlaxoSmithKline	Bipolar disorder	Prereg.
Levetiracetam[1,2]	UCB	Bipolar disorder	Clinical
Lithium Carbonate[1]	GlaxoSmithKline	Bipolar disorder	L-2002
LU-35-138[2]	Lundbeck	Schizophrenia	I/II
LY-156735	Lilly/Phase 2 Discovery	Insomnia, sleep onset	I
Methylphenidate Hydrocholoride*	Shire Laboratories/Noven	Attention deficit hyperactivity disorder	Prereg.
Mifepristone[1,2]	National Institutes of Health	Stress, posttraumatic	II
	National Institutes of Health	Bipolar disorder	II
Nalmefene[1,2]	BioTie Therapies	Alcoholism	III
Naltrexone Hydrochloride[1,2]	Alkermes	Alcoholism	III
	DrugAbuse Sciences	Alcoholism	III
	DrugAbuse Sciences	Drug addiction	II
NBI-34041	Neurocrine Biosciences	Anxiety	I
	Neurocrine Biosciences	Depression	I
INN-00835	Innapharma	Depression, major	II/III
NGD-96-3	Neurogen/Pfizer	Insomnia	I
NGI-101	Afecta	Anxiety	II
	Afecta	Depression	II
NGI-221	Afecta	Attention deficit hyperactivity disorder	II
NGI-909	Afecta	Drug addiction	II
NicVAX	Nabi Biopharmaceuticals/National Institute on Drug Abuse	Smoking cessation	II
NKP-608	Novartis	Phobia, social	II
NPI-028	National Center for Complementary and Alternative Medicine	Alcoholism	II
NS-2359	NeuroSearch	Attention deficit hyperactivity disorder	II
Ocinaplon[2]	DOV Pharmaceutical	Anxiety, generalized	II
Olanzapine[1,2]	FDA Office of Orphan Products Development	Autism	II
	Lilly	Bipolar disorder (combination therapy)	L-2003
	Lilly	Bipolar disorder (long-term-maintenance)	R-2003
	Lilly	Agitation (in psychotic patients)	Prereg.
Olanzapine/Fluoxetine	Lilly	Bipolar disorder	Prereg.
Ondansetron Hydrochloride[1,2]	National Institutes of Health	Alcoholism	II
OPC-14523	Otsuka	Depression	II
Org-24448	Cortex/Organon	Schizophrenia	II
Org-34167	Organon	Depression	II
Org-34517	Akzo Nobel	Depression	II
Osanetant	Sanofi-Synthélabo	Schizophrenia	II
Pagoclone[2]	Indevus	Anxiety, generalized	II
	Indevus	Panic disorder	III
Paroxetine Hydrochloride[1,2]	GlaxoSmithKline	Premenstrual dysphoric disorder	R-2003
	GlaxoSmithKline	Panic disorder	L-2002
	GlaxoSmithKline	Phobia, social	R-2003
PD-200390	Pfizer	Insomnia	I/II
PD-299685	Pfizer	Insomnia	I/IIP
PH-399733	Pfizer	Schizophrenia	I/II

Continuation

Annual Update 2003: Drugs for Psychiatric Disorders and Substance Abuse

Drug	Source	Condition	Phase
PH-80	Pherin/Organon	Premenstrual dysphoric disorder	II
PH-94B	Pherin	Phobia, social	II
Pramipexole Hydrochloride[1,2]	National Institutes of Health	Bipolar disorder	II
Pregabalin[2]	Pfizer	Anxiety, generalized	Prereg.
Quetiapine Fumarate[1,2]	AstraZeneca	Bipolar disorder	R-2003
R-1204	Roche	Anxiety	I
	Roche	Depression	I
R-673	Roche	Depression	II
Rimonabant Hydrochloride	Sanofi-Synthélabo	Smoking cessation	III
Risperidone[1,2]	Janssen	Bipolar disorder	Prereg.
SA-4503	M's Science	Depression	I
	M's Science	Drug addiction	I
Saredutant[2]	Sanofi-Synthélabo	Depression	II
SB-271046	GlaxoSmithKline	Schizophrenia	I
SB-723620	GlaxoSmithKline	Anxiety	I
	GlaxoSmithKline	Depression	I
Sertindole	Lundbeck	Schizophrenia	Clinical
Sertraline Hydrochloride[1,2]	Pfizer	Phobia, social	R-2003
	Pfizer	Premenstrual dysphoric disorder	L-2002
SL-65.1498	Sanofi-Synthélabo	Anxiety	II
SLV-310	Solvay	Schizophrenia	II
SLV-313[2]	Solvay	Schizophrenia	II
SLV-314	Solvay	Bipolar disorder	I
	Solvay	Schizophrenia	I
SLV-319	Solvay	Schizophrenia	I
SM-13496	Sumitomo	Schizophrenia	II
SNEC-2	Synaptic (Lundbeck)	Depression	I
SPD-465	Shire Pharmaceuticals	Attention deficit hyperactivity disorder	I
SPD-503[1]	Shire Laboratories	Attention deficit hyperactivity disorder	III
SR-58611A	Sanofi-Synthélabo	Depression	III
SSR-125047	Sanofi-Synthélabo	Schizophrenia	I
SSR-146977	Sanofi-Synthélabo	Depression	I
	Sanofi-Synthélabo	Schizophrenia	I
SSR-181507	Sanofi-Synthélabo	Schizophrenia	I
SSR-591813	Sanofi-Synthélabo	Smoking cessation	I
RG-1068	Repligen	Autism	III
	Repligen	Schizophrenia	I
TAK-375	Takeda	Insomnia	III
	Takeda	Circadian rhythm sleep disorder	II
Talnetant	GlaxoSmithKline	Schizophrenia	II
Tamoxifen Citrate[1]	National Institutes of Health	Bipolar disorder	II
TA-NIC	Xenova	Smoking cessation	I
TAU	Repligen	Depression, major	I/II
	Repligen	Bipolar disorder	I/II
Tetrodotoxin	Esteve/International Wex Technologies	Withdrawal syndrome	II
The Straw	Recovery Pharmaceuticals	Smoking cessation	I/II
Tiagabine Hydrochloride	Cephalon	Anxiety, generalized	II
(*S*)-Tofisopam	Vela Pharmaceuticals	Anxiety	I
Transdermal Selegiline[1]	Somerset	Depression	Prereg.
Triazolam (nasal spray)[1,2]	Questcor	Insomnia	II
Valproic Acid Sodium Salt[1]	Dainippon Pharmaceutical	Bipolar disorder	R-2002
Vanoxerine Hydrochloride	National Institutes of Health	Cocaine dependency	I
Varenicline	Pfizer	Smoking cessation	III
Venlafaxine Hydrochloride[1,2]	Wyeth Pharmaceuticals	Phobia, social	R-2003
	Wyeth Pharmaceuticals	Stress, posttraumatic	III
YKP-1358	SK Bio-Pharmaceuticals	Schizophrenia	IND filed
Ziprasidone Hydrochloride[1,2]	Pfizer	Bipolar disorder	Prereg.

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

Compendium of Drugs for Psychiatric Disorders and Substance Abuse

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Anxiety disorders

Anxiety is the pathological counterpart of normal fear and may be manifested by alterations in mood, thinking, behavior and physiological activity. Whereas fear is an acute response to a known, external and well-defined threat, anxiety is a chronic response to an unknown, internal and vague threat. Several different anxiety disorders exist, but all are characterized by extreme or pathological anxiety as the principal alteration in mood or emotional tone.

Several anxiety disorders exist and are characterized by different symptoms. The most common types include generalized anxiety disorder (GAD), panic disorder, agaraphobia, obsessive-compulsive disorder (OCD), acute stress disorder, posttraumatic stress disorder (PTSD), social phobia (also known as social anxiety disorder) and specific phobias.

As a group, anxiety disorders are the most frequent of all mental disorders encountered in clinical practice. According to the U.S. Surgeon General, the 1-year prevalence among adults (aged 18-54) for all anxiety disorders is in excess of 16%. The associated costs are equally impressive: as a group, anxiety disorders cost the USD 46.6 billion in 1990 alone, representing nearly one-third of the nation's total mental heath expenditures.

Anxiety disorders are usually treated with psychotherapy or counseling, drug therapy or some combination thereof. Benzodiazepines and antidepressants are currently the most widely used drugs for anxiety disorders. Benzodiazepines have a faster onset of effect, while antidepressants tend to have improved safety and tolerability. The efficacy of a given drug depends upon the nature of the disorder being treated.

Benzodiazepines

The benzodiazepines are a large class of relatively safe drugs with fast-acting and significant anxiolytic and sedative/hypnotic effects. These compounds bind to benzodiazepine receptor sites on the $GABA_A$ receptor complex, acting as agonists, and are thought to act by enhancing the inhibitory neurotransmitter systems that use GABA.

The utility of benzodiazepines is often limited by toxicities, which include dependency, tolerance and withdrawal symptoms. This finding has led to the exploration in recent years of other classes of GABAergic drugs whose actions do not directly involve $GABA_A$ receptor modulation. A newer generation of GABAergic drugs, many of which have already been successfully developed and marketed for other indications such as epilepsy, are now being evaluated in the clinic for the treatment of anxiety and other affective disorders.

Benzodiazepines and other GABAergic drugs in active development for the treatment of anxiety disorders are presented in Table I.

Drugs acting on 5-HT receptors

Serotonin (5-HT) plays an undisputed role in the etiology of anxiety disorders, and drugs modulating 5-HT receptors in some way are used extensively in their treatment. Anxiety symptoms have been suggested to result from excessive 5-HT activity in the raphe nucleus, hypothalamus, thalamus, basal ganglia and limbic system, and serotonergic drugs including $5\text{-}HT_2$ antagonists, $5\text{-}HT_3$ antagonists and selective serotonin reuptake inhibitors (SSRIs) have shown some effect in treating anxiety.

Table II presents recent progress in the development of serotonergic drugs for the treatment of anxiety disorders, together with the specific disorder (if known) for which they are being developed. Some compounds are already marketed for another indication, as noted in the table.

Table I: Anxiolytic drugs acting on benzodiazepine and other receptors in the GABA receptor complex.

Drug Name	Source	Mechanism of Action	Status (indication)
Alprazolam*	Pfizer	$GABA_A$ BZ site receptor agonist	L-2003 (panic disorder)
Pregabalin	Pfizer	GABA analogue	Prereg. (GAD)
Pagoclone	Indevus	$GABA_A$ BZ site receptor partial agonist	Phase III (panic disorder) Phase II (GAD)
Ocinaplon	DOV Pharmaceutical	$GABA_A$ receptor modulator	Phase II (GAD)
SL-65.1498	Sanofi-Synthélabo	$GABA_A$ BZ site receptor agonist	Phase II (anxiety)
Tiagabine hydrochloride	Cephalon	GABA reuptake inhibitor	Phase II (GAD)
AC-5216	Dainippon/Novartis	$GABA_A$ BZ site receptor agonist	Phase I (anxiety)
Alprazolam nasal spray**	Questcor	GABA-A BZ site receptor agonist	Clinical (anxiety)

*Marketed for another indication(s). **New formulation.

Table II: Serotonergic drugs recently launched and in active development for the treatment of anxiety disorders.

Drug Name	Source	Mechanism of Action	Status (indications)
Escitalopram oxalate	Lundbeck/Forest	Selective 5-HT reuptake inhibitor	L-2002 (panic disorder) Prereg. (GAD) Phase III (social phobia)
Paroxetine hydrochloride*	GlaxoSmithKline	Selective 5-HT reuptake inhibitor	L-2002 (panic disorder) R-2003 (social phobia)
Fluoxetine hydrochloride*	Lilly	Selective 5-HT reuptake inhibitor	R-2002 (panic disorder) Phase III (posttraumatic stress disorder)
Sertraline hydrochloride*	Pfizer	Selective 5-HT reuptake inhibitor	R-2003 (social phobia)
Venlafaxine hydrochloride*	Wyeth Pharmaceuticals	5-HT and NE reuptake inhibitor	R-2003 (social phobia)
Fluvoxamine maleate*	Meiji Seika (licensed from Solvay)	Selective 5-HT reuptake inhibitor	Prereg. (social phobia)
AP-521	Asahi Kasei	5-HT_{1A} antagonist	Phase II (anxiety)
AR-A000002	AstraZeneca	5-HT_{1B} antagonist	Phase II (anxiety)

*Marketed for another indication(s).

Tachykinin NK_1 antagonists

The neuropeptide compound substance P, which is localized in the amygdala and other brain regions implicated in emotion, acts on tachykinin NK_1 receptors. Many researchers believe that tachykinin antagonists, and especially substance P antagonists, may hold the greatest promise for the treatment of anxiety.

At least three tachykinin NK_1 receptor antagonists are known to be in active clinical development for the treatment of anxiety disorders at this time. **NKP-608** (Novartis) is in phase II testing for social phobia. Two other antagonists – **GW-597599** and **679769** – are in phase II testing at GlaxoSmithKline.

CRF receptor antagonists

Studies have shown that patients with posttraumatic stress disorder have abnormally high levels of corticotropin-releasing factor (CRF, also known as corticotropin-releasing hormone or CRH), a neurotransmitter hormone that switches on the stress response. Corticotropin-releasing factor has additionally been implicated in anxiety and depression. Corticotropin-releasing factor receptor-containing neurons are localized in the central nucleus of the amygdala, the paraventricular nuclei of the hypothalamus and the lateral bed nucleus of the stria terminalis. Several CRF receptor antagonists are in preclinical and early clinical development for the treatment of anxiety.

Neurocrine Biosciences and GlaxoSmithKline signed a worldwide research, development and commercialization agreement in July 2001 for CRF (CRF_1 and CRF_2) receptor antagonists to treat psychiatric, neurological and gastrointestinal diseases including anxiety, depression and irritable bowel syndrome. The companies are currently conducting phase I clinical trials with **NBI-34041** for anxiety and depression. Another CRF_1 antagonist, GlaxoSmithKline's **SB-723620**, is also in phase I testing for anxiety.

Novartis is studying a CRF_1 antagonist designated **AAG-561** for the indications of anxiety and depression. Phase I testing is reportedly in progress.

Miscellaneous anxiolytics

In addition to the major mechanisms of action discussed above, several potential anxiolytic agents are known to be in development. These include compounds with unusual mechanisms of action as well as others for

Table III: Miscellaneous anxiolytic drugs.

Drug Name	Source	Mechanism of Action	Status (indication)
NGI-101	Afecta Pharmaceuticals	Undisclosed	Phase II
Mifepristone*	National Institutes of Health	Glucocorticoid receptor antagonist	Phase II (posttraumatic stress disorder)
PH-94B	Pherin	Vomeropherin compound	Phase II (social phobia)
BTG-1640	BTG/Abiogen	Undisclosed	Phase I
Eglumegad hydrate	Lilly	Metabotropic glutamate ($mglu_2$ and $mglu_3$) agonist	Phase I
Itriglumide	Rotta	CCK_2 antagonist	Phase I
R-1204	Roche	Undisclosed	Phase I
(*S*)-Tofisopam	Vela Pharmaceuticals	Undisclosed	Phase I

*Marketed for another indication(s).

which this information has not yet been revealed by the manufacturer. Table III presents miscellaneous anxiolytic drugs in active clinical development, as well as their mechanisms of action, when known.

Depression

Depression is a common mood disorder characterized by sadness, loss of interest in activities and decreased energy. Some people experience a single depressive episode, while for many others it is a chronic condition. Depression may be a primary condition or may coexist with other mental, psychiatric or physical illnesses or substance abuse disorders. Depression can come on suddenly, triggered by an unhappy or stressful event, or can build slowly over months and years. It is frequently a recurring disease; a person suffering a first episode of depression has a 50% chance of recurrence within 5 years. After 3 episodes, the likelihood of recurrence is 90%.

There are several different classes of depression. The most common is major depressive disorder (also called unipolar major depression). Other common forms include dysthymia, seasonal affective disorder, double depression, minor depression and postpartum depression.

Depressive disorders are extremely common, affecting more than 19 million adult Americans and a total of 121 million people worldwide each year. The yearly incidence of depression is estimated to be 5.8% for men and 9.5% for women. Depressive disorders represent the leading cause of disability worldwide among persons 5 years of age and older in terms of the number of people affected. According to the World Health Organization, depression currently costs the U.S. approximately USD 53 billion annually and is the second biggest cause of disability in developed countries.

Three major classes of drugs are currently used in the treatment of depression. Tricyclic antidepressants (TCAs) alter the balance of neurotransmitters in the brain. Monoamine oxidase (MAO) inhibitors slow the breakdown of norepinephrine and 5-HT in the brain, allowing them to continue sending messages for a longer time. Selective serotonin reuptake inhibitors (SSRIs) enhance the activity of 5-HT but do not affect other chemical messengers, and thus cause fewer side effects than TCAs or MAO inhibitors. Newer generation antidepressants (bupropion, mirtazapine, nefazodone and venlafaxine) have novel mechanisms of action and improved side effect profiles.

Neurotransmitter reuptake inhibitors

Following the popularity of SSRIs, most of the newer antidepressant drugs in the pipeline target the reuptake of two or more of the following neurotransmitters: dopamine (DA), 5-HT and/or norepinephrine (NE).

The SSRI **escitalopram oxalate** (Cipralex®; Lundbeck) was launched for the first time in 2002 in Switzerland. The product is indicated for the treatment of major depressive episodes, as well as for the treatment of panic disorder with or without agoraphobia. It was approved and launched later in the year in the U.S. by licensee Forest, where the trade name Lexapro™ is being used.

In September 2003, the U.S. FDA approved GlaxoSmithKline's Wellbutrin XL™ (**bupropion hydrochloride** extended-release tablets) for the treatment of major depressive disorder in patients 18 years of age and older. The product was rolled out for this new indication in mid-September. Wellbutrin XL™ is a once-daily norepinephrine and dopamine reuptake inhibitor that carries a low risk of sexual side effects and weight gain. The efficacy of bupropion in the treatment of major depressive episodes was established using the immediate-release formulation in two 4-week controlled trials in inpatients and a 6-week controlled trial in outpatients who met criteria for major depression. The efficacy of bupropion in maintaining an antidepressive response for up to 44 weeks was established with the sustained-release formulation in a placebo-controlled trial. Bupropion has also been shown to be effective in preventing relapse of depression.

In May 2002, the FDA approved Pfizer's Zoloft® (**sertraline hydrochloride**) for the new indication of premenstrual dysphoric disorder (PMDD). In randomized, double-blind, placebo-controlled trials involving 532 women

Table IV: Neurotransmitter reuptake inhibitors recently launched or in active clinical development for the treatment of depression.

Drug Name	Source	Mechanism of Action	Status (indication)
Escitalopram oxalate	Lundbeck	5-HT reuptake inhibitor	L-2002 (major depression)
Sertraline hydrochloride*	Pfizer	5-HT reuptake inhibitor	L-2002 (PMDD)
Bupropion hydrochloride*	GlaxoSmithKline	NE and DA reuptake inhibitor	L-2003 (major depression)
Paroxetine hydrochloride*	GlaxoSmithKline	5-HT reuptake inhibitor	R-2003 (PMDD)
Duloxetine hydrochloride	Lilly/Boehringer Ingelheim/Shionogi	5-HT and NE reuptake inhibitor	Prereg.
DOV-216303	DOV Pharmaceutical	5-HT, NE and DA reuptake inhibitor	Phase II (major depression)
DOV-21947	DOV Pharmaceutical	5-HT, NE and DA reuptake inhibitor	Phase I
GW-353162	GlaxoSmithKline	NE and DA reuptake inhibitor	Phase I

*Marketed for another indication(s).

Table V: Drugs acting on 5-HT receptors in development for the treatment of depression.

Drug Name	Source	Mechanism of Action	Status
Gepirone hydrochloride	Organon	5-HT_{1A} agonist	Prereg.*
AR-A000002	AstraZeneca	5-HT_{1B} antagonist	Phase II
Elzasonan hydrochloride	Pfizer	5-HT_{1B} and 5-HT_{1D} antagonist	Phase II
OPC-14523	Otsuka	5-HT_{1A} agonist	Phase II

*Indicated for major depression.

with PMDD, sertraline was significantly more effective than placebo in improving symptoms, including emotional and behavioral symptoms. Improvement was noted after both intermittent use of sertraline through the premenstrual phase of the menstrual cycle, as well as with continuous use. Continuous use was also associated with significant improvements in physical symptoms.

Table IV presents progress in this active area of research.

Drugs acting on 5-HT receptors

Over the past three decades there has been an enormous increase in understanding of the neurotransmitter 5-HT. The identification of receptor subtypes has opened the door to a number of new therapeutic options targeting specific receptor types. Evidence has accumulated to suggest therapeutic roles for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors in depression. Recent experimental data also support a role for 5-HT_7 receptors in the mechanism of antidepressant action. In fact a number of antidepressants demonstrate high affinity for brain 5-HT_7 receptors, which are localized in brain regions thought to be implicated in depression.

Table V presents information on drugs acting on 5-HT receptors in development for the treatment of depression.

CRF receptor antagonists

Several experimental studies have been reported supporting the role of the hypothalamic-pituitary-adrenal (HPA) axis, the system that regulates the body's response to stress, in the development of depression. Upregulation of the HPA axis causes increased production of CRF, which signals the pituitary gland to secrete adrenocorticotropic hormone (ACTH). In the presence of increased ACTH, the adrenal glands release cortisol. In response to these changes, the body prepares itself to fight or flee, and ceases all activities that are not required for self-protection. As early as the 1960s researchers noticed that the HPA axis was chronically activated in depressed individuals, as evidenced by abnormally high cortisol levels in the urine, blood and cerebrospinal fluid. Additional research over the years has provided convincing evidence that abnormalities in CRF-producing neurons of the hypothalamus and other brain regions underlie the hyperactivity of the HPA axis, and suggests that CRF antagonists may be useful in the treatment of depression.

As mentioned before, Neurocrine Biosciences and GlaxoSmithKline are currently conducting phase I clinical trials with the CRF_1 antagonist **NBI-34041** for anxiety and depression, and Novartis is conducting phase I studies with a CRF_1 antagonist designated **AAG-561** for the indications of anxiety and depression.

Tachykinin antagonists

Since the discovery in 1990 of the first selective antagonists of the substance P-preferring NK_1 receptor, the putative role of this neuropeptide in disorders ranging from pain to asthma to depression has been the subject of extensive research activity. Substance P receptors have been located to the locus coeruleus and amygdala, brain regions that coordinate stress responses and relay convergent monoaminergic signals. Activation of the substance P pathway in response to aversive or noxious stimulation has also been observed, with the resulting

suggestion that NK_1 antagonists could be useful in the treatment of depression and other psychological disorders.

Tachykinin receptor antagonists in development for the treatment of depressive disorders are listed in Table VI.

Miscellaneous antidepressants

In the search for effective drugs to treat depressive disorders, other mechanisms of action are also being explored. These include β_3-adrenoceptor agonists, melatonin agonists, adenosine antagonists and others, as shown in Table VII.

Nemifitide ditriflutate, a pentapeptide compound administered by subcutaneous or needleless injection, has emerged as Innapharma's lead product candidate after extensive research and development. Nemifitide is one of a new class of synthetic brain peptide antidepressants that may provide a powerful new strategy for the treatment of depression and that could, according to the company, transform the way this debilitating illness is treated. Several advantages over marketed antidepressants have been observed in ongoing clinical trials, including a more rapid onset of effect and relief of symptoms, a higher percentage of responders and an improved side effect profile. Furthermore, most patients report experiencing complete relief of symptoms.

Bipolar disorder

Bipolar disorder, also known as manic-depressive illness, is defined by the National Institute of Mental Health as "a brain disorder that causes unusual shifts in a person's mood, energy, and ability to function." Bipolar disorder causes dramatic mood swings – from overly euphoric and/or irritable to sad and hopeless, and then back again, often with periods of normal mood in between. Severe changes in energy and behavior accompany these changes in mood. The periods of highs and lows are called episodes of mania and depression, respectively.

According to the National Institute of Mental Health, bipolar disorder affects approximately 2.3 million adult Americans. The lifetime prevalence of bipolar I disorder is in the range of 1.3-1.6%, and the prevalence of bipolar spectrum disorders is 2.5-4%.

A variety of mood-stabilizing medications, generally in combination with psychotherapy or psychosocial intervention, are currently used to treat bipolar disorder. Mood stabilizers are designed to treat the two extremes of bipolar disorder – depression and mania – using a single

Table VI: Tachykinin receptor antagonists in development for the treatment of depression.

Drug Name	Source	Mechanism of Action	Status
GW-597599	GlaxoSmithKline	NK_1 antagonist	Phase II
R-673	Roche	NK_1 antagonist	Phase II
Saredutant	Sanofi-Synthélabo	NK_2 antagonist	Phase II
CJ-17493	Pfizer	NK_1 antagonist	Phase I/II
679769	GlaxoSmithKline	NK_1 antagonist	Phase I
SSR-146977	Sanofi-Synthélabo	NK_3 antagonist	Phase I

Table VII: Miscellaneous compounds in active clinical development as antidepressants.

Drug Name	Source	Mechanism of Action/Description	Status (indication)
Transdermal selegiline*	Somerset	MAO-B inhibitor	Prereg.
Agomelatine	Servier	Melatonin agonist; also 5-HT_{2C} antagonist	Phase III (major depression)
SR-58611A	Sanofi-Synthélabo	β_3-Adrenoceptor agonist	Phase III
Nemifitide ditriflutate	Innapharma	Synthetic brain peptide	Phase II/III (major depression)
NGI-101	Afecta Pharmaceuticals	Undisclosed	Phase II
Org-34167	Organon	Undisclosed	Phase II
Org-34517	Akzo Nobel	Glucocorticoid receptor antagonist	Phase II
PH-80	Pherin	Vomeropherin compound	Phase II (PMDD)
TAU	Repligen	Oral uridine prodrug	Phase I/II (major depression)
AC-5216	Dainippon	$GABA_A$ BZ site receptor agonist	Phase I
E-6006 citrate	Esteve	Undisclosed	Phase I
R-1204	Roche	Undisclosed	Phase I
SA-4503	M's Science (licensed from Santen)	Acetylcholinesterase release enhancer/ sigma receptor agonist	Phase I
SNEC-2	Synaptic (Lundbeck)	Undisclosed	Phase I
Chromium picolinate*	Nutrition 21	Dietary supplement	Clinical

*Marketed for another indication(s).

Table VIII: Anticonvulsant medications in development for bipolar disorder.

Drug Name	Source	Mechanism of Action	Status (indication)
Olanzapine*	Lilly	Dopamine D_2 and 5-HT_{2A} antagonist	L-2003 (combination therapy) R-2003 (long-term maintenance)
Valproic acid sodium salt*	Dainippon		R-2002
Lamotrigine*	GlaxoSmithKline	Sodium channel blocker	Prereg.
Felbamate*	National Institutes of Health		Phase II
DP-VPA	D-Pharm	Prodrug of valproic acid	Phase I
Levetiracetam*	UCB	N-type calcium channel antagonist	Clinical

*Marketed for another indication(s).

medication. Lithium is the gold standard among mood stabilizers, although it is not effective in all patients. Most patients obtain better results through the judicious use of combination drug therapy rather than monotherapy, with treatment modification over the course of evolution of the disorder.

Lithium salts

The Australian psychiatrist John Cade first reported in 1949 that lithium carbonate was effective in the treatment of patients with bipolar disorder. In the last half century, lithium has become established as the first choice in maintenance therapy of patients with bipolar disorder who have a classical course of illness. It has beneficial effects in the control of both acute mania and breakthrough depression.

In 2002, GlaxoSmithKline launched Eskalith CR, a new controlled-release formulation of **lithium carbonate**, for the first time in the U.S. The product is indicated for the treatment of manic episodes of bipolar disorder.

Anticonvulsants

An accumulating body of evidence indicates that bipolar spectrum disorders are a group of neuropsychiatric disorders characterized by neurotransmitter imbalance, disrupted signal transduction pathways and abnormal gene expression; long-term neuronal damage may also occur. In spite of their widely differing chemical structures and mechanisms of action, all anticonvulsant drugs appear to act in some fashion on these processes, which may account for their mood-stabilizing effects.

Table VIII presents anticonvulsant medications in active development for the treatment of bipolar disorder, together with their mechanism of action, if known. Most of these drugs are already marketed for epileptic disorders, as indicated.

Antipsychotic agents

Antipsychotic medications have potent, rapid-onset effects in all manic states and are widely used in both Europe and the U.S. Studies examining prescription rates have determined that up to 90% of bipolar patients receive antipsychotic drugs at some point during their illness.

AstraZeneca has successfully completed the mutual recognition procedure involving 14 European countries to extend the use of the known antipsychotic agent **quetiapine fumarate** (Seroquel™) for the treatment of mania associated with bipolar disorder. Individual licenses in these countries will follow from the completion of the procedure. The approval was based on data from AstraZeneca's clinical trial program in bipolar disorder, involving almost 1,000 patients in 28 countries. Data from two trials confirmed that quetiapine monotherapy is as effective as current treatments for bipolar disorder, with improved tolerability benefits. Another trial examining quetiapine fumarate as an adjunctive therapy to mood stabilizers in the treatment of bipolar mania showed that the study drug is significantly more effective than mood stabilizers alone in the treatment of bipolar mania. Seroquel™ is also under review for bipolar mania in the U.S., where an approvable letter was issued in November, and in the U.K. Approvals have been received in Mexico and New Zealand.

Lilly's atypical antipsychotic **olanzapine** (Zuprexa®), approved as monotherapy for the short-term treatment of acute manic episodes associated with bipolar disorder, was further approved in the U.S. this year for combination therapy with lithium or valproate. The European authorities also recently cleared its use for long-term maintenance of response in bipolar disorder, and this indication is being considered by the FDA.

Table IX lists antipsychotic drugs recently approved and in active development for the treatment of patients with bipolar disorder. Again, many of these products have been marketed for some years for another indication, as noted.

Antidepressants

Antidepressant monotherapy is not indicated in the treatment of bipolar depression, as these agents may trigger episodes of mania or induce a pattern of rapid cycling. However, antidepressant medications may be used in judicious combination with lithium or anticonvulsant mood stabilizers, as per the updated American Psychiatric Association treatment guidelines.

Table IX: Antipsychotic agents recently approved and in active development for the treatment of bipolar disorder.

Drug Name	Source	Mechanism of Action	Status
Quetiapine fumarate*	AstraZeneca	5-HT_{2A} antagonist/dopamine D_2 antagonist	R-2003
Aripiprazole*	Bristol-Myers Squibb/Otsuka	5-HT_{1A} partial agonist/dopamine D_2 partial agonist/ 5-HT_{2A} antagonist	Prereg.
Risperidone*	Janssen	5-HT_{2A} antagonist/ dopamine D_2 antagonist	Prereg.
Ziprasidone hydrochloride*	Pfizer	5-HT_{2A} antagonist/dopamine D_2 antagonist	Prereg.
Asenapine maleate	Organon/Pfizer	5-HT_2 antagonist/dopamine D_1 and D_2 antagonist	Phase III
SLV-314	Solvay	5-HT reuptake inhibitor/dopamine D_2 antagonist	Phase I

*Marketed for another indication(s).

Table X: Antidepressants in active development for the treatment of bipolar disorder.

Drug Name	Source	Mechanism of Action	Status
Pramipexole hydrochloride*	National Institutes of Health	Dopamine D_3 agonist	Phase II
TAU	Repligen	Prodrug of uridine	Phase I/II
GW-353162	GlaxoSmithKline	Dopamine and NE reuptake inhibitor	Phase I

*Marketed for another indication(s).

Preliminary studies suggest that **pramipexole hydrochloride** (Mirapex®), a dopaminergic agent approved by the FDA for Parkinson's disease, may have antidepressant properties in unipolar and bipolar patients as well as neurotrophic properties. An ongoing National Institutes of Health-sponsored study is investigating the potential therapeutic efficacy of pramipexole, which enhances dopaminergic throughput via D_2 and D_3 receptors and exerts robust neurotrophic effects via direct intracellular mechanisms, in acutely depressed bipolar II patients.

Antidepressant medications – as well as drugs exerting an antidepressant effect in the context of bipolar disorder – under active development for the treatment of this illness are described in Table X.

Combination products

Lilly is developing Symbyax, a novel fixed-dose combination product incorporating the 5-HT reuptake inhibitor **fluoxetine hydrochloride** and the atypical antipsychotic agent **olanzapine**, as a potential first-in-class therapeutic for bipolar disorder. Symbyax is undergoing regulatory review in the U.S., where the FDA issued an approvable letter during the second quarter of this year.

Antiglucocorticoid therapies

Hyperactivity of the HPA has been described in bipolar disorder, especially with regard to depression and mixed states. Patients with bipolar disorder also have cognitive difficulties and endocrine disturbances that may contribute to such dysfunction. Antiglucorticoid therapies are being studied as novel treatments for mood disorders. Preliminary data in psychotic depression suggest that **mifepristone** (RU-486), a glucocorticoid receptor antagonist, has antidepressant and salutary cognitive effects within days of initiating treatment. Based on these findings, the National Institute of Mental Health has initiated a double-blind, placebo-controlled phase II trial to evaluate the effects of mifepristone in severe bipolar depression.

Drugs affecting signal transduction pathways

A growing body of evidence supports the role of signal transduction pathways in both the pathophysiology and treatment of bipolar disorder. Some mood-stabilizing drugs, most notably lithium and valproate, with extremely different chemical structures, have been shown to cause considerable inhibition of the protein kinase C (PKC) signaling pathway at therapeutically relevant concentrations, although the significance of this mechanism of action in the context of bipolar disorder is still unclear.

The National Institute of Mental Health is conducting a phase II study to examine how the drug **tamoxifen citrate** affects the brain's PKC signaling pathway in male patients with bipolar I disorder. It will also examine whether the chemical changes that occur in the brain result in improvement of manic symptoms. A potent inhibitor of the PKC pathway, tamoxifen is better known for its use in treating breast and other cancers.

Schizophrenia

Schizophrenia is a common and severe psychiatric illness of unknown etiology that is characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. It is a chronic disorder typified by a life-long pattern of acute psychotic episodes superimposed upon chronically poor psychosocial adjustment. Schizophrenia is characterized by

positive symptoms (auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears) and negative symptoms (social withdrawal, poor motivation, poverty of speech, apathy and lack of energy). All schizophrenic individuals experience positive symptoms, although not continuously. Negative symptoms are present in most, but not all, patients. Many patients also experience cognitive dysfunction ranging from impaired attention to abnormal executive function, as well as depression and/or anxiety.

Schizophrenia affects approximately 1% of the world's population. According to the World Health Organization, approximately 24 million people worldwide suffer from schizophrenia, making this the fourth leading cause of disability worldwide. In the U.S., the financial burden of schizophrenia is greater than that of all cancers, resulting in an annual expenditure of more than USD 65 billion in terms of direct medical costs and lost productivity. Schizophrenia accounts for more hospitalizations in the U.S. than almost any other illness.

Schizophrenia therapy has improved tremendously in recent years. A plethora of treatments has become available to help patients control their symptoms, improve quality of life and lead productive lives. The treatment of schizophrenia involves three main components: drug therapy to relieve symptoms and prevent relapse, education and psychosocial intervention to help patients and their families cope with the illness, and rehabilitation to facilitate reintegration of patients into the community.

Conventional, first-generation antipsychotic drugs are dopamine antagonists, while the newer, atypical, second-generation antipsychotics are dopamine and 5-HT antagonists. These drugs stop the neurotransmitter binding to its receptor, thereby blocking its activity. They are associated with significantly improved side effect profiles.

Dopaminergic agents

Antipsychotic drug development over the past 40 years has been based on the "hyperdopaminergic hypothesis" of schizophrenia, which suggests that excessive production of dopamine and/or increased D_2 receptor density or increased postreceptor action is implicated in the pathogenesis of the disorder. The antipsychotic activity of dopamine antagonists has been observed in several disease states in addition to schizophrenia. Dopamine antagonists alleviate reality distortions and disorganization symptom complexes, but have little effect on cognitive impairment and the negative symptoms of schizophrenia, suggesting that the hyperdopaminergic hypothesis alone is not sufficient to explain this complex disorder.

While early dopaminergic drugs targeted D_2 receptors, investigators have more recently begun to design pharmaceutical agents that act on other G-protein-coupled receptors including D_1, D_3 and D_4 receptors. Dopamine D_4 receptors, in particular, have been the subject of increased attention due to the observation that clozapine has high affinity for this receptor subtype.

The atypical antipsychotic agent **aripiprazole** (Abilify™) was approved and launched last November in the U.S. by partners Otsuka and Bristol-Myers Squibb. The product, which is proposed to act as a partial agonist at dopamine D_2 and 5-HT_{1A} receptors and as an antagonist at 5-HT_{2A} receptors, is indicated for the treatment of schizophrenia. Clinical studies in 1,238 patients with acute relapse of schizophrenia demonstrated that treatment with aripiprazole provided significant improvement in both positive and negative symptoms. Moreover, treatment with aripiprazole was associated with minimal weight change and extrapyramidal symptoms, a modest difference in sedation compared to placebo and no difference in the incidence of Q-Tc interval prolongation compared to placebo.

In September 2003, Solvay and Lundbeck announced plans to advance bifeprunox mesilate (formerly DU-127090) into phase III development with immediate effect, having successfully completed phase II trials. Bifeprunox is a putative full-spectrum atypical antipsychotic compound designed for the treatment of both positive and negative symptoms of schizophrenia. Its mechanism of action couples a highly potent partial agonist effect at dopamine D_2 receptors and an additional partial agonist effect at 5-HT_{1A} receptors.

Dopamine receptor-targeting therapeutics in development for the treatment of schizophrenia are presented in Table XI.

Dual-acting dopamine and 5-HT antagonists

The finding that clozapine, a dual-acting dopamine D_2 and 5-HT_{2A} antagonist, demonstrated enhanced therapeutic efficacy as compared to pure dopamine antagonists such as chlorpromazine led to the exploration of serotonergic pathways and their role in the pathogenesis and treatment of schizophrenia. Atypical antipsychotics such as clozapine, olanzapine and risperidone treat a wider range of schizophrenia symptoms. Several dual-acting antagonists as well as a few compounds acting only on 5-HT receptors have been developed and studied, with variable results, in recent years.

Lundbeck developed the atypical antipsychotic drug **sertindole** (Serdolect®) and launched the product in 1996. However, concerns about safety led to the drug being withdrawn from all E.U. markets in 2000. In 2001 the EMEA decided to allow a limited reintroduction of sertindole for use in postmarketing safety studies, which are currently in progress. Pending favorable completion of the same, Lundbeck hopes to relaunch the agent in 2005.

Several dual-acting dopamine D_2 antagonists/5-HT_{2A} antagonists are in advanced stages of development for the treatment of schizophrenia, as indicated in Table XII.

Table XI: Dopaminergic agents in development for the treatment of schizophrenia.

Drug Name	Source	Mechanism of Action	Status
Aripiprazole	Bristol-Myers Squibb/Otsuka	Dopamine D_2 partial agonist/5-HT_{1A} partial agonist	L-2002
Bifeprunox mesilate	Solvay/Lundbeck	Dopamine D_2 partial agonist/5-HT_{1A} partial agonist	Phase II/III
SLV-310	Solvay	Dopamine D_2 antagonist/5-HT reuptake inhibitor	Phase II
SLV-313	Solvay	Dopamine D_2 antagonist/5-HT_{1A} agonist	Phase II
LU-35-138	Lundbeck	Dopamine D_4 antagonist	Phase I/II
ACR-16	Carlsson Research/Merck & Co.	Dopamine stabilizer	Phase I
AVE-5997	Aventis	Dopamine D_3 antagonist	Phase I
SLV-314	Solvay	Dopamine D_2 antagonist/5-HT reuptake inhibitor	Phase I
SSR-181507	Sanofi-Synthélabo	Dopamine D_2 antagonist/5-HT_{1A} agonist	Phase I

Table XII: Dual-acting dopamine D_2 antagonists/5-HT_{2A} antagonists in development for the treatment of schizophrenia.

Drug Name	Source	Status (indication)
Sertindole	Lundbeck	Clinical testing (postmarketing studies)
Olanzapine*	Lilly	Prereg. (agitation in psychotic patients)
Asenapine maleate	Organon/Pfizer	Phase III
Blonanserin	Dainippon	Phase III
Iloperidone	Titan/Novartis	Phase III
SM-13496	Sumitomo	Phase II
Abaperidone hydrochloride	Ferrer	Phase I

*Marketed for other indication(s).

Other serotonergic agents

Several drugs acting on various receptors within the serotonergic pathway are also under investigation as potential treatments for schizophrenia. Merck KGaA has initiated phase I clinical testing of **EMR-62218**, a 5-HT_{2A} receptor antagonist. Phase I studies are in progress with the potential antipsychotic drug **SB-271046** (GlaxoSmithKline), a 5-HT_6 receptor antagonist that is also being developed for the treatment of Alzheimer's disease.

Tachykinin NK_3 antagonists

Brain regions such as the substantia nigra and the ventral tegmental area with a high concentration of dopamine neurons also have high concentrations of tachykinin NK_3 receptors, and NK_3 receptor agonists are reportedly able to potentiate dopamine release.

At least three tachykinin NK_3 antagonists are in clinical testing at the present time for the treatment of schizophrenia: GlaxoSmithKline's **talnetant** (phase II) and two compounds from Sanofi-Synthélabo – **osanetant** (phase II) and **SSR-146977** (phase I).

Agents affecting glutamatergic transmission

Enhancement of glutamatergic transmission via the administration of agonists or partial agonists of the NMDA receptor glycine modulatory site is considered one of the most promising leads in the development of new antipsychotic agents at this time. Activation of this receptor complex requires simultaneous occupancy of the glycine and glutamate receptor sites, and has the potential to effectively reduce the negative symptoms of schizophrenia. Both NMDA antagonists and AMPA/kainate antagonists also blunt hyperdopaminergic mechanisms in the early stages of the disease, indicating the interrelationship of these two neurochemical systems and suggesting the potential therapeutic efficacy of this class of agents in treating the early stages of schizophrenia.

In collaboration with development partner Organon, Cortex is developing the Ampakine® class of AMPA receptor modulators for the treatment of schizophrenia. Both the first-generation compound **CX-516** and the newer generation agent **Org-24448** are in phase II testing, although the latter is reported to demonstrate a significant advance over the former in terms of potency. CX-516 is also in clinical trials for a variety of other neurological and psychological disorders including Alzheimer's disease, autism, attention deficit hyperactivity disorder and narcolepsy.

Miscellaneous antipsychotic agents

In the continued search for new drugs to treat schizophrenia, new therapeutic targets and compounds directed thereto have been reported in recent years. Other compounds have been reported whose mechanism of action is unclear or has not yet been disclosed. Miscellaneous antipsychotic agents in development include the drugs listed in Table XIII.

Table XIII: Miscellaneous antipsychotic agents in active clinical development.

Drug Name	Source	Mechanism of Action	Status
PH-399733	Pfizer	Nicotinic alpha$_7$ receptor agonist	Phase I/II
Cannabidiol	GW Pharmaceuticals	Cannabinoid receptor agonist	Phase I
SLV-319	Solvay	Cannabinoid CB_1 receptor antagonist	Phase I
RG-1068	Repligen	Synthetic human secretin	Phase I
SSR-125047	Sanofi-Synthélabo	Sigma receptor ligand	Phase I
YKP-1358	SK Bio-pharmaceuticals	Undisclosed	IND Filed

Autism

Autism is a complex developmental disability that typically appears during the first three years of life. The result of a neurological disorder that affects the functioning of the brain, autism impacts the normal development of the brain in the areas of social interaction and communication skills. Children and adults with autism typically have difficulties in verbal and nonverbal communication, social interaction and leisure or play activities.

Autism is a spectrum disorder, meaning that the symptoms and characteristics of autism can present in a wide variety of combinations, from mild to severe. Although autism is defined by a certain set of behaviors, children and adults can exhibit any combination of the behaviors in any degree of severity.

Autism affects an estimated 2-6 per 1,000 individuals, according to figures presented by the Centers for Disease Control and Prevention in 2001. This means that as many as 1.5 million Americans today are believed to have some form of autism. And that number is on the rise. Based on statistics from the U.S. Department of Education and other governmental agencies, autism is growing at a rate of 10-17% per year. At these rates, the Autism Society of America estimates that the prevalence of autism could reach 4 million Americans in the next decade. The overall incidence of autism is consistent around the globe. Autism knows no racial, ethnic or social boundaries, although it is 4 times more prevalent in boys than girls.

There is no cure for autism at the present time. However, treatment and education approaches have been developed that may reduce some of the challenges associated with the disability. Intervention may help to lessen disruptive behaviors, and education can teach self-help skills that permit greater independence. But just as there is no one symptom or behavior that identifies autistic children, there is no single treatment. Treatment approaches currently include behavior modification and communication approaches, dietary and biomedical approaches, and complementary approaches.

Secretin

Secretin is a hormone produced by the small intestine that helps in digestion. It is currently used as a single dose to diagnose gastrointestinal problems. Studies in rats suggest that treatment with secretin activates several regions of the brain including the amygdala. The amygdala is one of several brain regions that have been implicated in autism. Repligen is currently developing synthetic human secretin (**RG-1068**) as a potential new treatment for autism. The FDA has approved an open-label extension of the company's ongoing phase III clinical trial, one of two studies designed to determine the ability of the hormone to positively impact the social and communicative deficits associated with autism.

Drugs acting on glutamate receptors

A growing body of scientific evidence indicates that increasing glutamate receptor transmission may produce benefits in patients with autism. Imaging studies have shown that areas of the brain that are normally rich in glutamatergic transmission are less active in autistic patients, apparently due to an abnormally low density of AMPA-type glutamate receptors. Based on these and other findings indicative of the potential therapeutic benefits that might be obtained by enhancing AMPA receptor activity in autistic patients, a study has been initiated to evaluate the efficacy of the AMPA receptor modulator **CX-516** (Cortex). The company, in collaboration with Rush-Presbyterian-St. Luke's Medical Center and the FRAXA Foundation, is evaluating the Ampakine® compound in 50 patients with autism or fragile X syndrome.

5-HT reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) may be effective in treating symptoms of depression, anxiety and obsessive-compulsive behaviors that are sometimes present in autism. Researchers have consistently found elevated levels of 5-HT in the bloodstream of one-third of individuals with autism, leading to the theory that these drugs could potentially reverse some symptoms of 5-HT dysregulation in autism. Studies have shown that SSRIs may reduce the frequency and intensity of repetitive behaviors, and may decrease irritability, tantrums and aggressive behavior. Some children have shown improvements in eye contact and responsiveness.

The U.S. National Institutes of Health is conducting two clinical studies to evaluate the efficacy of the SSRI **fluoxetine hydrochloride** (Prozac®) in patients with

autism. One study is enrolling adult patients, and the other will study the drug in children and adolescents.

Norepinephrine reuptake inhibitors

Atomoxetine hydrochloride (Lilly), a selective norepinephrine reuptake inhibitor, has been suggested to be potentially effective for treating disruptive behaviors in children with autism spectrum disorders.

Antipsychotic agents

Antipsychotic medications have been the most widely studied of the psychopharmacological agents in autism over the past 35 years. Originally developed for treating schizophrenia, these drugs have been found to decrease hyperactivity, stereotypic behaviors, withdrawal and aggression in individuals with autism. The FDA Office of Orphan Drug Development is conducting a phase II trial to evaluate the atypical antipsychotic agent **olanzapine** for decreasing symptoms of autism in children aged 4-12 years.

Cognition-enhancing agents

Unlike most previous drug therapies developed to treat the symptoms of autism rather than the core features of the disease, the cognition-enhancing agent **donepezil hydrochloride** (Aricept®) has been selected by the National Institute of Mental Health as a promising new treatment for cognitive deficits in this patient group. Patients are currently being enrolled for a phase I study to test this hypothesis. A recent study indicates that donepezil may improve speech production, attention span and the ability to express emotions in autistic children.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD, also known as attention deficit disorder, or ADD) is a highly prevalent and complex neuropsychiatric and behavioral disorder. Children and adults with ADHD exhibit degrees of inattention, hyperactivity and impulsivity that are inappropriate for their ages. They generally have a difficult time maintaining interpersonal relationships and succeeding at school, in the workplace or in other endeavors. Adults with ADHD experience symptoms very similar to those manifested in children: they are restless, easily distracted, have a difficult time sustaining attention, and are impulsive and/or impatient. They are often intolerant of stress, leading to greater expressed emotion.

Although estimates vary widely, ADHD is believed to affect some 2.6 million children. According to the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV), 3-5% of all school-age children in the U.S. have ADHD. Other estimates are in the range of 4-12% of the population, making ADHD one of the most common behavioral and psychological disorders encountered in pediatric medicine. Rates in some other countries are reported to be much lower, although this difference has been attributed to differences in classification and disease definition rather than to true geographical differences.

The direct costs of medical care for ADHD are substantial, and represent a serious burden for many families as they are frequently not covered by health insurance. According to Chase Hambrecht & Quist, the market for this condition in the U.S., which is considered to account for nearly the entire world market, amounted to USD 680 million in the year 1999.

Psychostimulant drugs have been used in the treatment of ADHD for more than 60 years. The most widely used and well studied psychostimulant is methylphenidate (Ritalin™) first introduced by Novartis in 1954.

In 2002, patients with ADHD welcomed the arrival of two new drugs designed to improve ADHD symptomatology and facilitate adherence to therapy. The first of these, **dexmethylphenidate hydrochloride** (Focalin™), is the more pharmacologically active d-*threo*-enantiomer of methylphenidate hydrochloride. Focalin™ was developed by Celgene and is marketed worldwide by Novartis. It was launched in the U.S., its first market, in January 2002.

In November 2002, the U.S. FDA approved Lilly's proprietary drug Strattera™ (**atomoxetine hydrochloride**, formerly tomoxetine hydrochloride) for the once- or twice-daily treatment of ADHD in children, adolescents and adults. Atomoxetine is a selective norepinephrine reuptake inhibitor that works differently from any other approved ADHD treatment and the first FDA-approved treatment for this disorder that is not a stimulant; precisely how the agent reduces ADHD symptoms is not known. The drug does not appear to have the potential for abuse and so is not classified as a controlled substance, although it is a prescription drug. The product was launched in the U.S. in January 2003.

Table XIV presents new drugs that have recently been marketed or are in active clinical development for the treatment of ADHD.

Sleep disorders

A sleep disorder is a physical and psychological condition or disturbance of sleep and wakefulness caused by abnormalities that occur during sleep or by abnormalities of specific sleep mechanisms. Although the sleep disorder exists during sleep, recognizable symptoms manifest themselves during the day. Up to 84 different sleep disorders have been defined, including narcolepsy, insomnia, hypersomnia, parasomnia, snoring and sleep apnea.

It is estimated that some 40 million Americans suffer from chronic, long-term sleep disorders. Another 20-30

Table XIV: New drugs recently launched or in clinical testing for the treatment of ADHD.

Drug Name	Source	Mechanism of Action	Status
Dexmethylphenidate hydrochloride	Celgene/Novartis	Psychostimulant	L-2002
Atomoxetine hydrochloride	Lilly	Antidepressant, NE reuptake inhibitor	L-2003
Methylphenidate hydrochloride**	Shire Laboratories/Noven	Psychostimulant, transdermal patch formulation	Prereg.
SPD-503*	Shire Laboratories	Long-acting form of the α_2-adrenoceptor agonist guanfacine hydrochloride	Phase III
ABT-089	Abbott	Nicotinic acetylcholine receptor modulator	Phase II
Bupropion hydrochloride*,+	National Institutes of Health	DA reuptake inhibitor	Phase II
NGI-221	Afecta Pharmaceuticals	Nonstimulant	Phase II
NS-2359	NeuroSearch	Monoamine reuptake inhibitor	Phase II
BTS-74398 (SPD-473)	Shire Laboratories	5-HT, DA and NE reuptake inhibitor	Phase I
SPD-465	Shire Pharmaceuticals	Undisclosed	Phase I

*Previously marketed for another indication(s).
**New formulation.
+Indicated for adolescents with comorbid ADHD and alcoholism.

Table XV: New drugs in development for the treatment of insomnia.

Drug Name	Source	Mechanism of Action	Status
Eszopiclone+	Sepracor	GABAergic transmission enhancer	Prereg.
Gaboxadol	Lundbeck	$GABA_A$ receptor agonist	Phase III
Indiplon	Neurocrine Biosciences/Pfizer	$GABA_A$ receptor agonist	Phase III
TAK-375	Takeda	Melatonin MT_1 and MT_2 agonist	Phase III
Eplivanserin	Sanofi-Synthélabo	$5\text{-}HT_{2A}$ antagonist	Phase II
Triazolam*	Questcor	$GABA_A$ BZ site receptor agonist (intranasal formulation)	Phase II
CP-730330	Pfizer	Undisclosed	Phase I/II
PD-200390	Pfizer	Undisclosed	Phase I/II
PD-299685	Pfizer	Undisclosed	Phase I/II
LY-156735++	Lilly/Phase 2 Discovery	Melatonin agonist	Phase I
NGD-96-3	Neurogen/Pfizer	GABA-A receptor modulator	Phase I

*New formulation.
+Indicated for transient and chronic insomnia.
++Indicated for sleep-onset insomnia.

million Americans suffer from some kind of sleep disorder on an irregular basis. The annual costs in productivity, healthcare and safety have been estimated in billions of dollars.

Insomnia

Insomnia is the perception or complaint of inadequate or poor-quality sleep because of one or more of the following: difficulty falling asleep, waking up frequently during the night with difficulty returning to sleep, waking up too early in the morning, or unrefreshing sleep. Insomnia is not defined by the number of hours of sleep a person gets or how long it takes to fall asleep, because individuals normally vary in their need for, and their satisfaction with, sleep. Insomnia may cause problems during the day, such as tiredness, a lack of energy, difficulty concentrating and irritability.

Transient and intermittent insomnia, in which episodes last only a few days at a time, may not require treatment. However, for people who experience daytime sleepiness and impaired performance as a result of transient insomnia, the use of short-acting sedative/hypnotic agents may improve sleep and next-day alertness. As with all drugs, there are potential side effects. The use of over-the-counter sleep medicines is not usually recommended for the treatment of insomnia.

Table XV presents new drugs in development for the treatment of insomnia.

Circadian rhythm disorders

Normal circadian rhythm in living organisms is marked by an approximately 24-h cycle, which is generated by the organism and maintained naturally. Deviations to this cycle, such as those caused by jet lag, shift work or chronic disorders cause the organism to suffer abnormal sleep patterns, as well as irregularities in daytime activities such as eating.

Melatonin is a pineal gland hormone that is sometimes administered in order to “reset” the body’s internal clock and enhance natural sleep processes. Melatonin itself is available in the U.S. and some other countries as an over-the-counter preparation. Takeda is developing the melatonin MT_1 and MT_2 receptor agonist **TAK-375** (ramelteon) in phase II trials for the treatment of circadian

rhythm disorders. This product is also in clinical testing for the treatment of insomnia.

Narcolepsy

Narcolepsy affects about 120,000 people in the U.S. This rare condition causes an irresistible tendency to fall asleep even in unlikely circumstances such as in the middle of a conversation or at a meal. Cataplexy, a symptom of this condition, is a sudden loss of muscular control and weakness usually triggered by emotions such as amusement, anger or excitement, and is estimated to affect 20,000-50,000 individuals. The effects of cataplexy range from dropping of the jaw and slumping of the head, to buckling of the legs and even collapse of the whole body. These effects can last for a few seconds or up to many minutes.

Last year, the FDA approved Orphan Medical's Xyrem® (**sodium oxybate** or γ-hydroxybutyrate [GHB]) for the treatment of cataplexy and excessive daytime sleepiness associated with narcolepsy. In the early 1990s, GHB was marketed purporting to be a dietary supplement for enhancing athletic performance and sexual activity and for inducing sleep. It was also abused as a recreational drug and is well known for use in date rape. As a result of a number of serious adverse events, including coma and death, the FDA intervened to prohibit marketing of GHB. As a condition of its approval for the cataplexy indication, Xyrem® has been designated a Schedule III controlled substance for medical use. Unauthorized use of Xyrem® will be subject to penalties under Schedule I of the Controlled Substances Act. The FDA has also worked with the drug's manufacturer Orphan Medical to design a comprehensive risk management program. The program includes limited distribution, physician education, patient education, the creation of a patient and physician registry and detailed patient surveillance.

Alcohol abuse and alcoholism

Alcoholism is a disease that is characterized by four defining symptoms: craving, tolerance, physical dependence and loss of control. Due to a combination of genetic and environmental influences, alcoholics experience a need for alcohol that may be as strong as the need for physical sustenance.

Alcohol abuse differs from alcoholism in that it does not include a strong craving for or physical dependence on alcohol, or a loss of control over drinking. Alcohol abuse is thus defined as the inappropriate use of alcohol that results in a failure to fulfill professional, academic or domestic responsibilities, drinking in situations that are dangerous or risky, suffering recurrent alcohol-related legal problems and continued drinking in spite of relationship problems derived from alcohol abuse. Although alcohol abuse is conceptually different from alcoholism, many alcoholics also suffer the consequences of alcohol abuse.

Currently, nearly 14 million Americans – 1 in every 13 adults – abuse alcohol or are alcoholics. Several million more adults engage in unhealthy drinking patterns, such as binge drinking and heavy drinking on a regular basis, that could lead to alcohol problems. According to the National Institutes of Health, alcohol-related problems cost society approximately USD 185 billion per year.

Although some people are able to recover from alcoholism without help, the majority of alcoholics need assistance. With treatment and support, many individuals are able to stop drinking and rebuild their lives. Treatment strategies may include any of the following: detoxification, prescription drug therapy and individual or group counseling.

Several clinical trials are under way at this time evaluating new drug therapies for alcohol abuse and alcoholism, as indicated in Table XVI. In the U.S., most of these are supported by the National Institute on Alcohol Abuse and Alcoholism.

Alkermes has completed enrollment in its pivotal phase III trial of Vivitrex®, a proprietary formulation of **naltrexone** based on the company's Medisorb® injectable, extended-release technology, designed to provide once-monthly dosing for the treatment of alcohol dependency. The randomized, double-blind, placebo-controlled study is designed to confirm the safety and efficacy of Vivitrex® in alcohol-dependent patients over 6 months. The patients may then enter an extension study that will collect longer term data over 12 months. Over 600 patients have been enrolled in the phase III trial at 24 U.S. centers and more than 180 patients have now entered the extension study.

Drug abuse and addiction

Approximately 19.5 million Americans, or 8.3% of the population 12 years of age and older, used illegal drugs in 2002, according to a new survey for the Substance Abuse and Mental Health Services Administration. The survey estimates that about 14.6 million persons used marijuana, 2 million used cocaine and 1.2 million used hallucinogens (such as Ecstasy) in 2002.

According to the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, the total economic cost of alcohol and drug abuse was USD 245.7 billion in the year 1992. Of this cost, USD 97.7 billion was due to drug abuse. This estimate includes substance abuse treatment and prevention costs as well as other healthcare costs, costs associated with reduced job productivity or lost earnings, and other costs to society such as crime and social welfare.

Addiction is best treated using a combination approach of psychotherapy and medication. Currently available medications include substitutes where a street drug is replaced with a clean drug (like methadone), blockers that prevent the addictive substance from having

Table XVI: New treatment strategies under evaluation for the treatment of alcohol abuse and alcoholism.

Drug Name	Source	Mechanism of Action	Status
Nalmefene*	BioTie Therapies	Opioid antagonist	Phase III
Naltrexone hydrochloride**	Alkermes	Opioid antagonist (once-monthly injectable formulation)	Phase III
Naltrexone hydrochloride depot**	DrugAbuse Sciences	Opioid antagonist (once-monthly injectable formulation)	Phase III
Bupropion hydrochloride*,+	National Institute on Alcohol Abuse and Alcoholism	DA reuptake inhibitor	Phase II
CEE-03-310	Addex Pharmaceuticals (licensed from CeNeS)	Dopamine D_1 antagonist	Phase II
Gabapentin*	National Institute on Alcohol Abuse and Alcoholism		Phase II
NPI-028	National Center for Complementary and Alternative Medicine	Chinese herbal medicine	Phase II
Ondansetron hydrochloride*	National Institute on Alcohol Abuse and Alcoholism	5-HT_3 antagonist	Phase II

*Marketed for other indication(s).
**New formulation.
+Indicated for adolescents with comorbid ADHD and alcoholism.

Table XVII: New treatment strategies under evaluation for the treatment of drug abuse and addiction.

Drug Name	Organization	Mechanism of Action	Status (indication)
Adrogolide hydrochloride	DrugAbuse Sciences	Dopamine D_1 agonist	Phase II (cocaine dependence)
BP-897	Bioprojet	Dopamine D_3 partial agonist	Phase II (cocaine dependence)
Bupropion hydrochloride*	National Institute on Drug Abuse	DA reuptake inhibitor	Phase II (methamphetamine dependence)
Cabergoline*	National Institute on Drug Abuse	Dopamine D_2 agonist/prolactin secretion inhibitor	Phase II (cocaine dependence)
Naltrexone hydrochloride**	DrugAbuse Sciences	Opioid antagonist (once-monthly injectable formulation)	Phase II (opiate dependence)
NGI-909	Afecta Pharmaceuticals	Undisclosed	Phase II (drug addiction, unspecified)
TA-CD	Xenova	Cocaine-BSA conjugate vaccine	Phase II (cocaine dependence)
Tetrodotoxin	Esteve/Int. Wex Technologies	Sodium channel blocker	Phase II (withdrawal from opiate addiction)
CP-601927	Pfizer	Undisclosed	Phase I/II (drug addiction, unspecified)
SA-4503	M's Science (licensed from Santen)	Sigma receptor agonist	Phase I (drug dependence, unspecified)
Vanoxerine hydrochloride	National Institute on Drug Abuse	DA reuptake inhibitor	Phase I (cocaine dependence)

*Marketed for another indication(s).
**New formulation.

any reinforcing effect (like naltrexone), or aversive therapies (like disulfiram) that cause a negative reaction to the addictive substance. However, because it is extremely difficult for addicted patients to remain compliant with medications, there is a strong need for improved medications that have less frequent dosing schedules to facilitate compliance. There is also a critical need for effective treatments for cocaine and methamphetamine overdoses, as none are currently available. A more long-term goal is to develop medications that help keep abusive substances out of the brain to help prevent their addictive effects and consequences.

Several clinical trials are under way at this time evaluating new drug therapies for drug abuse and addiction, as indicated in Table XVII. In the U.S., most of these are supported by the National Institute on Drug Abuse.

Table XVIII: Smoking cessation therapies in active clinical development.

Drug Name	Source	Mechanism of Action/Description	Status
Bupropion hydrochloride*	Biovail	DA reuptake inhibitor (controlled-release, once-daily formulation)	Phase III
Rimonabant hydrochloride	Sanofi-Synthélabo	Cannabinoid CB_1 receptor antagonist	Phase III
Varenicline	Pfizer	Nicotine receptor partial agonist	Phase III
NicVAX	Nabi National Institute on Drug Abuse	Nicotine conjugate vaccine	Phase II
The Straw™*	Recovery Pharmaceuticals	Nicotine replacement therapy (single-use plastic straw containing small beads of nicotine)	Phase I/II
GW-468816	GlaxoSmithKline	Glycine antagonist	Phase I
SSR-591813	Sanofi-Synthélabo	Nicotinic $\alpha_4\beta_2$ partial agonist	Phase I
TA-NIC	Xenova	Nicotine conjugate vaccine	Phase I

*New formulation

Smoking cessation

Nicotine is an addictive drug, which when inhaled in cigarette smoke reaches the brain faster than drugs that enter the body intravenously. Smokers become not only physically addicted to nicotine, but also link smoking with many social activities, making smoking a difficult habit to break.

In 1999, an estimated 46.5 million Americans were current cigarette smokers and another 45.7 million adults were former smokers. Of the current smokers, more than 32 million persons expressed a desire to quit smoking completely.

Cigarette smoking has been identified as the most important source of preventable morbidity and premature mortality in the U.S. Smoking-related diseases claimed an estimated 440,000 American lives each year during the period from 1995-1999, according to the American Lung Association. This figure includes those affected indirectly, such as babies born prematurely due to prenatal maternal smoking and some of the victims of second-hand exposure to tobacco's carcinogens. Smoking costs the U.S. approximately USD 150 billion each year in healthcare costs and lost productivity.

Smoking cessation aids include nicotine replacement products (patches, gum, nasal spray and inhalers), as well as the non-nicotine pill bupropion hydrochloride (Zyban®). All help relieve withdrawal symptoms people experience when they quit smoking. Nicotine replacement therapies are helpful in quitting when combined with a behavioral modification program that addresses psychological and behavioral addictions to smoking and strategies for coping with the urge to smoke.

Table XVIII presents information on new drugs in development as aids to smoking cessation, together with their status of development for this indication.

Varenicline (Pfizer), a nicotine partial agonist for smoking cessation, is currently in phase III studies in the U.S., Canada and Europe. Data show that almost half of smokers given this oral medicine were able to quit smoking. This represents a significant improvement over results achieved with bupropion. Varenicline works by partially activating nicotine receptors in the brain, altering the normal response to the addictive substance. It satisfies the craving for nicotine without causing addiction itself. If the drug does reach the market, varenicline will be the first non-nicotine substance developed specifically as a smoking cessation therapy.

Information sources on the internet

American Psychiatric Association
www.psych.org

Anxiety Disorders Association of America
www.adaa.org

Autism Society of America
www.autism-society.org

National Alliance for Research on Schizophrenia and Depression
www.narsad.org

National Institute on Alcohol Abuse and Alcoholism
www.niaaa.nih.gov

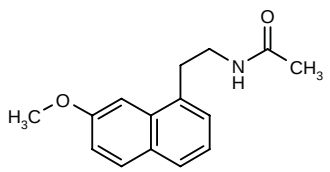
National Institute on Drug Abuse
www.nida.nih.gov

National Institute of Mental Health
www.nimh.nih.gov

Monograph Updates of Drugs for Psychiatric Disorders and Substance Abuse

N.E. Mealy and M. Bayés
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

Agomelatine



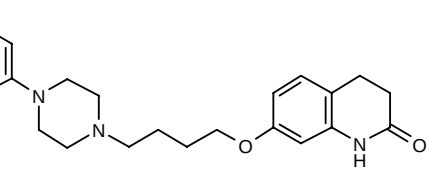
Agomelatine (S-20098, Valdoxan) is in late-stage clinical development at Servier as an antidepressant based on its dual melatonin-agonist and 5-HT_{2C} receptor-antagonist properties.

The potential appearance of symptoms after sudden discontinuation of treatment with agomelatine was evaluated in a multicenter, double-blind, randomized clinical trial in 192 patients with major depressive disorder who had shown stable remission after receiving agomelatine (25 mg/day) or paroxetine (20 mg/day) for 12 weeks and were subsequently randomized to switch to placebo or continue receiving antidepressant for another 2 weeks. At 1 week, switching from agomelatine to placebo was not associated with an increase in the rate of discontinuation symptoms compared to those who continued on agomelatine, whereas switching from paroxetine to placebo significantly increased the rate of discontinuation symptoms compared to patients who remained on paroxetine (1).

1. Montgomery, S.A. *Safety of agomelatine in the treatment of depression: Absence of discontinuation symptoms.* Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S210.

Original monograph - Drugs Fut 2003, 28(1): 7.

Aripiprazole



Aripiprazole (Abilify™) was approved by the FDA in November 2002 for the acute treatment of schizophrenia, and its label was subsequently expanded to include the long-term treatment of schizophrenia; it is also available in Australia and several South and Central American countries. Codeveloped by Bristol-Myers Squibb and Otsuka, the drug is now under review at the FDA for the treatment of acute mania in patients with bipolar disorder. Aripiprazole has been proposed to act through a combination of partial agonist activity at dopamine D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Otsuka and BMS are collaborating on the development and marketing of aripiprazole in the U.S. and major European countries.

The initial NDA included data from clinical studies in 1,238 patients with acute relapse of schizophrenia, demonstrating that treatment with aripiprazole provided significant improvement in both positive and negative symptoms. Moreover, treatment with aripiprazole was associated with minimal weight change and extrapyramidal symptoms, a modest difference in sedation compared to placebo and no difference in the incidence of Q-Tc interval prolongation compared to placebo. The sNDA for the long-term treatment of schizophrenia included results from a placebo-controlled trial in 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were symptomatically stable on other antipsychotic medications for at least 3 months. Patients who were switched to receive aripiprazole 15 mg/day experienced a significantly longer time to relapse over the 26 weeks compared to those receiving placebo. The relative risk of relapse for aripiprazole-treated patients was half that of placebo-treated patients. There were no medically important differences in metabolic profiles between patients receiving aripiprazole and placebo in terms of the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL and total cholesterol measurements. The overall mean weight change in patients receiving aripiprazole over the course of the study was –1.3 kg compared to –0.9 kg in placebo-treated patients (1-4).

Two open-label clinical trials that included a total of 71 healthy volunteers established that neither the time of dosing nor the ingestion of a high-fat breakfast had any significant effects on the pharmacokinetics of aripiprazole. A single aripiprazole dose of 20 mg given in the evening instead of the morning reduced the drug's peak concentration and delayed the time to peak concentration, but did not change total exposure or the clearance rate. The peak plasma levels and AUC values measured for a single aripiprazole dose of 15 mg were similar when the drug was given under fasting conditions or after a high-fat breakfast (5).

Compared with healthy volunteers, the AUC of a single dose of 15 mg of aripiprazole increased by 31% and 8%, respectively, in cirrhotic patients with mild and moderate hepatic impairment and decreased by 20% in patients with severe hepatic impairment. This single dose also showed a C_{max} 36% higher and an AUC 15% lower in patients with severe renal impairment compared with healthy volunteers. These differences were not considered to be clinically significant, and the authors concluded that no dose adjustment should be necessary in these populations (6).

A multicenter, double-blind clinical trial randomized 347 patients with acute mania or mixed bipolar episodes to receive aripiprazole (15 mg/day) or haloperidol (10 mg/day) for 12 weeks. Response, which was defined as an improvement of at least 50% compared to baseline in the Young Mania Rating Scale [Y-MRS]), was more frequent with aripiprazole than with haloperidol (50% *vs.* 28%). Aripiprazole was also associated with a higher percentage of patients who continued receiving treatment after the end of the 12-week period (50.9% *vs.* 29.1%) and with a lower incidence of extrapyramidal symptoms (9% *vs.* 36%) than the haloperidol group (7). The results of this study and some that follow are summarized in Table I.

A total of 208 outpatients with a mean age of 81.5 years and psychotic symptoms associated with Alzheimer's disease were randomized to receive either placebo or flexible daily doses of 2-15 mg of aripiprazole for 10 weeks. At the end of the study, patients treated with the active drug showed significant improvements in the Brief Psychiatric Rating Scale subscores for psychotic symptoms (hallucinations and delusions) compared to placebo (–1.93 *vs.* –1.27, respectively), as well as in the Neuropsychiatric Inventory Psychosis subscale. The percentage of patients who discontinued the treatment due to adverse effects was low (8% with aripiprazole and 7% with placebo). The most frequent adverse events were urinary tract infections, accidental injury and somnolence, and no potentially clinically significant ECG anomalies were reported in either study group (8, 9).

A 4-week double-blind study investigated the efficacy, safety and tolerability of aripiprazole 20 and 30 mg for the treatment of acute psychosis in patients with schizophrenia or schizoaffective disorders and compared it with risperidone and placebo. Results showed that both doses of aripiprazole were effective, safe and well tolerated in patients with acute relapse of schizophrenia or schizoaffective disorder and superior to placebo in treating both positive and negative symptoms of the disease. Both doses showed a rapid onset and the improvement in symptoms was comparable to that produced by risperidone (10).

A group of 300 patients with schizophrenia who did not respond to 4-6 weeks of open-label treatment with olanzapine or risperidone were randomized to receive daily doses of aripiprazole (15 or 30 mg) or the typical neuroleptic perphenazine (864 mg). Both drugs significantly improved the Positive And Negative Syndrome Scale scores and response was obtained in 27% of aripiprazole patients and 25% of perphenazine patients. Aripiprazole was more effective in improving quality of life and was associated with a lower incidence of extrapyramidal symptoms, ECG abnormalities or increases in plasma prolactin levels compared to perphenazine (11).

Twenty-three children and adolescents with a conduct disorder and mild to moderate aggressive behavior, as measured by the Rating of Aggression Against People and/or Property scale, were included in a clinical trial that assessed the pharmacokinetics and safety of aripiprazole in this population. The drug was administered for 14 days at doses ranging from 1 to 10 mg/kg/day depending on the patient's weight. Aripiprazole was well tolerated and effectively reduced the aggressive behavior of the patients. The pharmacokinetic profile of aripiprazole in this population was similar to in adult patients (12).

In a multicenter, double-blind clinical trial, 1,294 patients with schizophrenia were randomized to receive 30 mg/day of aripiprazole or 10 mg/day of haloperidol for 52 weeks. The severity of the negative symptoms

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

Indication	Design	Treatments	n	Conclusions	Ref.
Bipolar disorder	Randomized, double-blind, multicenter	Aripiprazole, 15 mg od x 12 wk Haloperidol, 10 mg od x 12 wk	347	Aripiprazole was well tolerated and significantly more effective than haloperidol in improving the Young Mania Rating Scale scores in patients with acute mania. The percentage of patients who continued receiving treatment at the end of the study was also higher with aripiprazole	7
Dementia, Alzheimer's type	Randomized, single-blind, multicenter	Aripiprazole, 2 mg/d [starting dose] x 2 wk → up to 15 mg/d x 8 wk Placebo	208	Aripiprazole was well tolerated and significantly more effective than placebo in improving the Neuropsychiatric Inventory Psychosis subscale and the Brief Psychiatric Rating Scale scores in elderly patients with psychosis and Alzheimer's disease	8, 9
Schizophrenia	Randomized, double-blind, multicenter	Aripiprazole, 15 mg od (n=154) Aripiprazole, 30 mg od Perphenazine, 864 mg od (n=146)	300	Both aripiprazole and perphenazine were effective in improving the Positive and Negative Symptom Scale scores and quality of life in patients with schizophrenia. Aripiprazole was better tolerated, as it was associated with a lower incidence of extrapyramidal symptoms	11
Behavioral disorder	Open	Aripiprazole, 1-10 mg od x 15 d	23	Aripiprazole at daily doses ranging from 1-10 mg was well tolerated and associated with mild to moderate adverse events in children and adolescents with behavioral disorder	12
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	13
Schizophrenia	Randomized, double-blind	Aripiprazole x 26 wk Placebo		The administration of aripiprazole for 26 weeks did not induce significant changes in glycemic control or lipid profile in patients with chronic stable schizophrenia	14

associated with schizophrenia was reduced more markedly with aripiprazole than with haloperidol, even after stabilization of acute symptoms (13).

In a randomized, placebo-controlled clinical trial of the potential use of aripiprazole to prevent relapse in patients with chronic stable schizophrenia, neither the active drug nor placebo induced significant changes in mean fasting plasma glucose levels, glycosylated hemoglobin or lipid profiles of the patients compared to baseline. No evidence of adverse metabolic changes was found after long-term treatment of schizophrenia with aripiprazole (14).

1. *BMS and Otsuka submit sNDA for Abilify*. DailyDrugNews.com (Daily Essentials) July 18, 2003.

2. *Abilify sNDA approved for maintaining stability in patients with schizophrenia*. DailyDrugNews.com (Daily Essentials) Sept 12, 2003.

3. *First approval for new antipsychotic drug granted by FDA*. DailyDrugNews.com (Daily Essentials) Nov 19, 2002.

4. *Abilify sNDA submitted for long-term treatment of schizophrenia*. DailyDrugNews.com (Daily Essentials) Feb 27, 2003.

5. Mallikaarjun, S., Riesgo, Y., Salazar, D., Bramer, S., Xie, J., Weston, I. *Time of dosing and food effect on aripiprazole pharmacokinetics*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S332.

6. Bramer, S., Shoaf, S., Salazar, D., Mallikaarjun, S. *Lack of effect of renal and hepatic impairment on the pharmacokinetics of aripiprazole*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S333.

7. Bourin, M., Auby, P., Swanik, S., Marcus, R., McQuade, R., Iwamoto, T., Sanchez, R. *Aripiprazole vs. haloperidol for maintained treatment effect in acute mania*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S333.

8. Jeste, D.V., De Deyn, P., Carson, W., Marcus, R., McQuade, R.D., Schneider, L., Mintzer, J. *Aripiprazole in dementia of the Alzheimer's type*. J Am Geriatr Soc 2003, 51(4, Suppl.): Abst P543.

9. De Deyn, P.P., Jeste, D., Aubrey, P., Goyvaerts, H., Breder, C., Schneider, L., Mintzer, J. *Aripiprazole treatment for psychosis in patients with Alzheimer's disease.* Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S324.

10. Potkin, S.G., Saha, A.R., Kujawa, M.J. et al. *Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder*. Arch Gen Psychiatry 2003, 60(7): 681.

11. McQuade, R., Jody, D., Kane, J. et al. *Efficacy and safety of aripiprazole versus perphenazine in treatment-resistant schizophrenia*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S326.

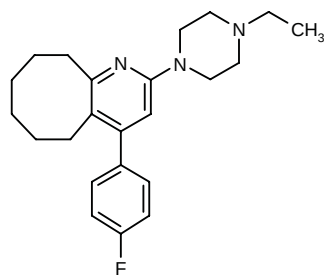
12. Findling, R.L., Blumer, J.L., Kauffman, R., Batterson, J.R., Gilbert, D.L., Bramer, S., Marcus, R. *Aripiprazole in pediatric conduct disorder: A pilot study*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S335.

13. Kostic, D., Manos, G., Stock, E., Jody, D., Archibald, D., Tourkodimitris, S., Marcus, R. *Long-term effects of aripirazole on the negative symptoms of schizophrenia*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S328.

14. Stock, E., Marder, S.R., Jody, D., Kaplita, S., Saha, A., Carson, W., Torbeyns, A. *Plasma lipids levels and glycemic control in long-term treatment with aripiprazole*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S327.

Original monograph - Drugs Fut 1995, 20(9): 884.

Blonanserin



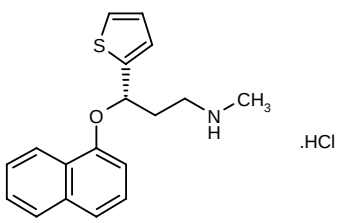
A 5-HT_2/dopamine D_2 receptor antagonist, blonanserin (AD-5423, Lonasen®) is being evaluated in phase III clinical trials by Dainippon as a potential new antipsychotic agent.

The antipsychotic efficacy of blonanserin was demonstrated in murine models of schizophrenia. Both blonanserin and haloperidol (0.1 mg/kg p.o.) significantly blocked sensitization to phencyclidine (PCP)-induced hyperlocomotion in mice, a positive symptom of schizophrenia. However, only blonanserin (1 mg/kg p.o.) attenuated PCP-induced enhancement of immobility in the forced swimming test, a negative symptom of schizophrenia. Blonanserin-induced effects in this model were suggested to be via the 5-HT_2 receptor since the 5-HT_2 receptor agonist DOI blocked the agent's effects. Results suggest that blonanserin may have clinical efficacy against both the positive and negative symptoms of schizophrenia (1).

1. Nagai, T., Noda, Y., Une, T., Furukawa, K., Furukawa, H., Kan, Q.M., Nabeshima, T. *Effect of AD-5423 on animal models of schizophrenia: Phencyclidine-induced behavioral changes in mice*. NeuroReport 2003, 14(2): 269.

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

Duloxetine Hydrochloride



Lilly has received approvable letters from the FDA for duloxetine hydrochloride, the company's dual 5-HT and norepinephrine reuptake inhibitor, for the treatment of both depression (Cymbalta™) and stress urinary incontinence. This is the second approvable letter issued for duloxetine in depression. The company has a long-term agreement with Boehringer Ingelheim for the joint development and commercialization of duloxetine covering most countries worldwide with few exceptions. In the U.S., the collaboration is for incontinence only. In Japan, duloxetine is in clinical trials for depression by licensee Shionogi (1-3).

Results from a randomized, double-blind, crossover study in 12 healthy male volunteers indicated that duloxetine inhibits platelet 5-HT and norepinephrine reuptake. In the study, subjects received duloxetine 80 mg once daily or 60 mg b.i.d., desipramine 50 mg b.i.d. or placebo. Duloxetine appeared to have no effect on an intravenous tyramine pressor test (4). The results of this study and some that follow are summarized in Table II.

A multicenter, randomized, double-blind study compared duloxetine 60 mg once daily to placebo in 267 patients with major depressive disorder (MDD). Treatment with duloxetine for 9 weeks was safe and significantly reduced physical symptoms, as well as measures of MDD severity, compared with placebo (5).

The efficacy of duloxetine in the treatment of physical pain associated with major depression was evaluated in a placebo-controlled clinical trial. A total of 495 patients with major depressive disorder were randomized to receive either duloxetine (60 mg) or placebo once daily for 9 weeks. The drug was significantly better than

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	Desipramine, 50 mg bid x 7 d Duloxetine, 60 mg bid x 7 d Duloxetine, 80 mg/d x 7 d Placebo	12	Duloxetine inhibited platelet serotonin and norepinephrine reuptake in healthy volunteers	4
Depression	Randomized, double-blind, multicenter	Duloxetine, 60 mg od x 9 wk (n=128) Placebo (n=139)	267	Duloxetine was safe and effective in patients with major depressive disorder	5
Depression	Randomized, double-blind	Duloxetine, 60 mg od x 9 wk (n=244) Placebo (n=251)	495	Duloxetine once daily was significantly better than placebo in improving the symptoms of physical pain associated with major depression	6
Depression	Open	Duloxetine, 80-120 mg/d x 52 wk	1279	Duloxetine was effective and safe in older and younger patients with major depression	7
Fibromyalgia	Randomized, double-blind, multicenter	Duloxetine, 60 mg b.i.d. x 12 wks (n=104) Placebo (n=103)	207	Duloxetine was significantly more effective than placebo in improving the total Fibromyalgia Impact Questionnaire score and other secondary endpoints (including pain severity scores, the tender point count, the stiffness scores and the quality of life scores) in patients with fibromyalgia. The drug was well tolerated and effective regardless of the baseline depression score, but only induced significant symptom improvements in female patients	8
Depression	Randomized, double-blind, multicenter	Duloxetine, 60 mg od x 12 wk Placebo	276	Duloxetine was more effective than placebo in preventing relapse of major depression. The drug was also well tolerated with a safety profile similar to that of placebo and most adverse events resolving without requiring discontinuation	9
Depression	Open	Duloxetine, 80-120 mg/d x 52 wk	101	Duloxetine was safe and significantly effective in elderly patients with major depression	10
Depression	Randomized, double-blind, multicenter, pooled/meta-analysis	Duloxetine, 20 mg bidx 8 wk (n=86) Duloxetine, 40 mg bidx 8 wk (n=91) Duloxetine, 60 mg bid x 8 wk (n=68) Duloxetine, 60 mg od x 9 wk (n=249) Fluoxetine, 20 mg od x 8 wk (n=33) Paroxetine, 20 mg od x 8 wk (n=87) Placebo (n=408)	1022	The Hamilton Rating Scale for Depression scores measured at the end of treatment revealed that duloxetine improved depression-related symptoms such as mood, anxiety and painful physical symptoms in patients with major depressive disorder	11

placebo in improving most pain outcomes, with mean improvement rates of 22-41% compared with 5-18% on placebo. Pain relief was partially independent of improvement in the Hamilton Depression Rating Scale (HAMD-17) total score (6).

In an open-label study, 1,279 patients with major depressive disorder were treated for 1 year with duloxetine 80-120 mg/day. The treatment led to significant and sustained improvements according to both clinicians and patients, and efficacy and adverse events were similar in younger and elderly patients (7).

A multicenter, double-blind clinical trial evaluated the efficacy and safety of duloxetine in 207 patients with primary fibromyalgia with or without major depressive disorder. The patients were randomized to receive placebo or 60 mg of duloxetine twice daily for 12 weeks. The active drug was significantly more effective than placebo in improving the Fibromyalgia Impact Questionnaire (FIQ) total scores of the patients, but had no significant effects on their FIQ pain scores. Duloxetine was also associated with significant improvements in several secondary outcome measurements, including the pain severity scores, tender point number, stiffness score and quality-of-life scores. The drug was well tolerated and effective regardless of the baseline depression score of the patients, but only induced significant symptom improvement in female patients (8).

The long-term effects and safety of duloxetine hydrochloride in the management of major depressive disorder were assessed in a double-blind, placebo-

controlled clinical trial. In a preliminary open-label phase, 533 patients were treated with a daily dose of 60 mg of duloxetine for 12 weeks. At the end of this period, 276 patients had responded to the treatment and were randomized to either switch to placebo or continue receiving duloxetine 60 mg/day for another 26 weeks. The percentage of patients who relapsed at the end of the study was 17.4% with duloxetine and 28.5% with placebo. The analysis of the HAMD-17 scores and the Visual Analogue Scale (VAS) pain scores showed that duloxetine was better than placebo in preventing the relapse of both depression and associated pain. Duloxetine was safe and well tolerated; the most frequent adverse events were nausea and headache, and most drug-related adverse effects were transient and resolved without requiring discontinuation of the treatment (9).

Duloxetine 80 or 120 mg/day was administered to 101 patients at least 65 years of age with major depression in a 52-week open study. Significant improvements and high response rates were achieved with treatment, which was safe over the long term. Adverse events included dizziness, nausea, constipation and somnolence (10).

Four multicenter, double-blind, randomized, placebo-controlled clinical trials assessed the effects of duloxetine on anxiety symptoms related to depression in a total of 1,022 adult patients with major depressive disorder, a moderate Clinical Global Impression (CGI) of Severity score and a clinician-rated HAMD-17 score of at least 15. The patients were randomized to receive placebo, duloxetine (40-120 mg/day for 8 or 9 weeks) or comparator drugs (fluoxetine or paroxetine, 20 mg/day for 8 weeks). The comparison of the changes induced by the study treatments on the HAMD-17 scores of the patients revealed that duloxetine improved depression-related symptoms such as mood, anxiety and painful physical symptoms. The authors suggested that the high probability of remission associated with duloxetine may be related to its efficacy in the management of these symptoms (11).

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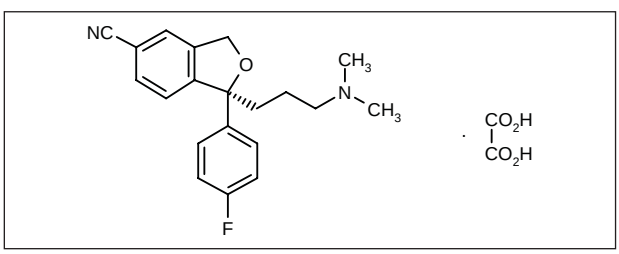
Escitalopram Oxalate



Escitalopram oxalate (Lexapro™, Cipralex® in Europe) is a selective serotonin reuptake inhibitor (SSRI) developed at Lundbeck by isolating the therapeutically active portion of the antidepressant Celexa™ (citalopram hydrobromide). Available in the form of tablets and oral solution, it is indicated for the initial and maintenance treatment of major depressive disorder and for the treatment of panic disorder (1).

Lundbeck also plans to seek expansion of its label to include social anxiety disorder (SAD). Earlier this year, licensee Forest submitted a supplemental NDA to the FDA seeking to expand the labeling of escitalopram to include the treatment of panic disorder, and the FDA just recently issued an approvable letter for its use in the treatment of generalized anxiety disorder (GAD). Lundbeck also has a licensing agreement with Janssen-Cilag (Xian-Janssen, both members of the Johnson & Johnson group) for the drug in China. Escitalopram is approved in more than 26 countries and awaiting approval in others (2-4).

The efficacy of escitalopram, citalopram, (*R*)-citalopram and a combination of (*R*)-citalopram plus escitalopram was compared using a rat model of depression. The sequential exposure of rats to mild stressors for a prolonged period of time resulted in depression that was

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

Indication	Design	Treatments	n	Conclusions	Ref.
Anxiety	Randomized, double-blind, multicenter	Escitalopram, 10-20 mg od x 8 wk (n=158) Placebo (n=157)	315	Escitalopram was well tolerated and significantly improved the Hamilton Rating Scale for Anxiety scores of outpatients with generalized anxiety disorder	7
Anxiety	Randomized, double-blind, pooled/meta-analysis	Escitalopram, 10 [later increased to 20] mg od x 8 wk (n=421) Placebo (n=419)	830	Escitalopram was well tolerated and significantly better than placebo in improving the Hamilton Rating Scale for Anxiety scores in patients with generalized anxiety disorder. The beneficial effects of escitalopram were evident after 1 week of treatment and were maintained throughout the study	9
Anxiety	Randomized, double-blind	Escitalopram Placebo		Compared to placebo, escitalopram was associated with better quality of life in patients with social anxiety disorder. The drug improved all the mental health-related parameters, was effective in preventing relapse and was more cost-effective	13
Depression	Randomized, double-blind, multicenter	Escitalopram, 20 [max] mg od x 8 wk (n=97) Venlafaxine XR, 225 [max] mg od x 8 wk (n=98)	195	Escitalopram was better tolerated and more effective than venlafaxine in inducing response and remission of symptoms in patients with major depressive disorder	15
Depression	Randomized, double-blind	Escitalopram, 10-20 mg/d x 8 wk (n=147) Placebo (n=153)	300	Escitalopram significantly improved the Montgomery-Asberg Depression Rating Scale and Hamilton Rating Scale for Depression scores in patients with major depression after 2 and 4 weeks of treatment, respectively. These improvements were maintained throughout the study. The response rate was greater with escitalopram than with placebo, and few patients discontinued the study due to adverse events	16

measured as a reduction in the consumption of a 1% sucrose solution. Both escitalopram (3.9 mg/kg i.p. once daily) and citalopram (8.0 mg/kg i.p. once daily) increased sucrose intake in depressed animals after 1 and 2 weeks of treatment, respectively, although greater effects were found for escitalopram. (*R*)-Citalopram (7.8 mg/kg i.p. once daily) alone or combined with escitalopram was not better than vehicle in improving sucrose intake. The authors concluded that the antidepressant effect of escitalopram was attenuated by (*R*)-citalopram in this model of depression (5).

Escitalopram 10-20 mg/day was studied in 315 patients with GAD enrolled in a randomized, double-blind, placebo-controlled trial. Significantly greater improvement in all endpoints was seen with escitalopram as compared to placebo, with mean changes in the Hamilton Anxiety Scale (HAMA) total score after 8 weeks of treatment of –11.3 and –7.4 for escitalopram and placebo, respectively. Escitalopram was safe and well tolerated (6, 7). These results and those from some of the following studies are summarized in Table III.

The efficacy and safety of escitalopram in the treatment of GAD were confirmed by the results of a meta-analysis that combined data from 3 double-blind, randomized, placebo-controlled clinical trials. A total of 840 patients with moderate to severe GAD (defined by a mean baseline HAMA score of about 23) received placebo or escitalopram (10 mg/day for 4 weeks, later increased to 20 mg/day if necessary) for a total of 8 weeks. The benefits induced by the drug on the depression scores of the patients were significantly higher than placebo after 1 week of treatment and remained so throughout the study (8, 9).

In 3 randomized, double-blind, placebo-controlled phase III trials, 128 patients with panic disorder (PD) 124 patients with GAD and 181 patients with SAD were treated with escitalopram for 8-12 weeks. The active treatment was well tolerated and significantly more effective than placebo in primary and secondary efficacy parameters (CGI and quality of life) in all studies and study-specific measures, including panic and agoraphobia in the

PD study, HAMA psychic anxiety in the GAD study and LSAS avoidance and fear/anxiety in the SAD study (10).

Patients with SAD were given open-label escitalopram 10-20 mg/day for 12 weeks and responders entered a 24-week, randomized, placebo-controlled trial to evaluate the incidence of relapse. Relapses occurred significantly later and in significantly fewer patients with escitalopram treatment *versus* placebo. Withdrawals due to adverse events were noted in 4% of patients in the escitalopram group (11, 12).

The cost-effectiveness and effect on quality of life of escitalopram treatment in SAD patients were assessed as part of a 6-month, randomized, double-blind, placebo-controlled trial. Health-related quality of life was found to be higher in patients given escitalopram, for whom total costs were also 22.5% lower (13, 14).

A comparative clinical trial assessed the efficacy and safety of escitalopram and extended-release venlafaxine (venlafaxine XR) in the management of major depressive disorder. In this trial, 195 patients with mean baseline MADRS (Montgomery-Asberg Depression Rating Scale) scores suggestive of moderate to severe illness were randomized to receive up to 20 mg/day of escitalopram or 225 mg/day of venlafaxine XR for 8 weeks. The remission and response rates at the end of the study were, respectively, 41.2% and 58.8% for escitalopram and 36.7% and 48.0% for venlafaxine XR. Escitalopram was also associated with a lower incidence of drug-related adverse events (68.4% vs. 85.0%) and a lower number of patients discontinuing the trial due to adverse events (4.1% *vs.* 16.0%). The authors concluded that the poor tolerability of venlafaxine XR might be related to its nonselective activity (15).

A double-blind, randomized, placebo-controlled clinical trial determined the effects induced by escitalopram in 300 patients with severe major depression. The drug significantly improved the MADRS scores and the total HAMD scores of the patients after 2 and 4 weeks of treatment, respectively; these improvements were maintained throughout the study. The response rate was greater among escitalopram-treated patients compared to placebo, and few patients discontinued the study due to adverse events (6% *vs.* 0% with placebo) (16).

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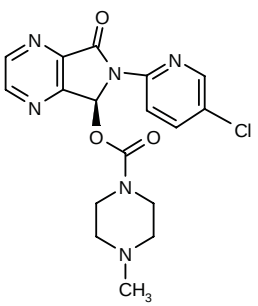
Original monograph - Drugs Fut 2001, 26(2): 115.

Eszopiclone



Eszopiclone, the (*S*)- or (+)-isomer of zopiclone, is a nonbenzodiazepine agent for insomnia. Sepracor submitted an NDA for eszopiclone (Estorra™, tablets of 2 and 3 mg) for the treatment of transient and chronic insomnia to the FDA on January 31, 2003, and it was accepted for filing by the agency in April. The product was studied in the higher dose strength for adults and in the lower dose strength for the elderly population (1-3).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized, double-blind, multicenter	Eszopiclone, 2 mg od x 44 d Eszopiclone, 3 mg od x 44 d Placebo	308	Eszopiclone administered once daily at nighttime significantly improved the onset, maintenance, duration, quality and depth of sleep in patients with chronic insomnia. The drug also improved sleep latency, sleep efficiency and total sleep time, and was associated with a beneficial learning effect. No evidence of pharmacological tolerance or next day residual effects was found	5
Insomnia	Randomized, double-blind, multicenter	Eszopiclone, 3 mg od x 6 mo (n=593) Placebo (n=195)	788	Eszopiclone was more effective than placebo in improving sleep maintenance, sleep latency, total sleep time and sleep quality in patients with chronic insomnia. The drug was well tolerated and no pharmacological tolerance was found	6, 7

The NDA contains data from 24 clinical trials, which included more than 2,700 adult and elderly subjects, and more than 60 preclinical studies. Six randomized, placebo-controlled phase III studies, including one with a positive control, for the treatment of chronic or transient insomnia formed part of the NDA package. Sepracor recently reported data from a 231-patient, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study of eszopiclone in elderly patients with chronic insomnia. Patients were randomized to receive nightly treatment with eszopiclone 2 mg or placebo for 2 weeks. Eszopiclone 2 mg significantly improved sleep onset, wake time after sleep onset, total sleep time, sleep quality and depth of sleep compared to placebo. The drug also significantly reduced the number of naps and reduced the duration of daytime naps over the entire treatment period. Patients treated with eszopiclone 2 mg reported significant improvements in daytime alertness and sense of physical well-being. There was also a trend toward significance in improved daytime ability to function and reduced morning sleepiness (4).

The efficacy and safety of eszopiclone were assessed in a double-blind, randomized, placebo-controlled clinical trial that enrolled 308 patients aged 21-64 years with chronic insomnia. Compared with placebo, a dose of 2 or 3 mg of eszopiclone given every night for 44 consecutive days significantly improved sleep onset, sleep duration, sleep maintenance and the quality and depth of sleep of the patients. No pharmacological tolerance or next-day residual effects were found, and the most frequent adverse effect was unpleasant taste (5). The results of this study and the one that follows are summarized in Table IV.

A multicenter, double-blind, randomized phase III clinical trial assessed the efficacy and safety of eszopiclone in the treatment of insomnia. A total of 788 chronic insomniacs aged 21-69 years with a history of less than 6.5 h of sleep per night and sleep onset of more than 30 min were treated with placebo or 3 mg of eszopiclone every night for 6 months. Compared with placebo, eszopiclone was significantly more effective in improving sleep maintenance, number of awakenings, sleep latency and sleep quality of the patients. The most frequent adverse event was unpleasant taste, which was reported by 5.6% of placebo-treated patients and 26.1% of eszopiclone-treated patients. No evidence of pharmacological tolerance was found (6, 7).

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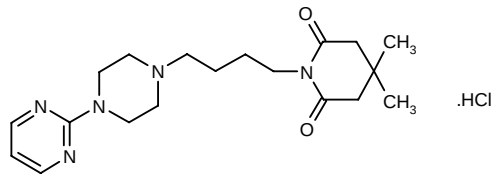
Original monograph - Drugs Fut 2003, 28(7): 640.

Gepirone Hydrochloride



Organon's extended-release formulation of gepirone hydrochloride (formerly known as Ariza®), a 5-HT_{1A} agonist, is being developed for use in major depressive disorder. Last year the company reported plans to submit additional data to the FDA in response to issues raised by the agency in its initial review of the NDA, and launch is now anticipated for 2004.

A total of 115 healthy volunteers were administered between 10 and 120 mg/day gepirone as solution or extended-release (ER) tablets for up to 7 days in 3 randomized, single- and multiple-dose, placebo-controlled studies to investigate the pharmacokinetics and tolerability of gepirone ER. Gepirone and its major metabolite demonstrated linear pharmacokinetics. Steady-state plasma concentrations were obtained at 4-5 h and on day 2 following single and multiple doses of gepirone ER, respectively, with fluctuations in plasma concentrations reduced with the ER tablet as compared with the solution, without affecting total exposure. The drug was generally well tolerated except for at the highest dose; adverse events included headache, dizziness and nausea (1).

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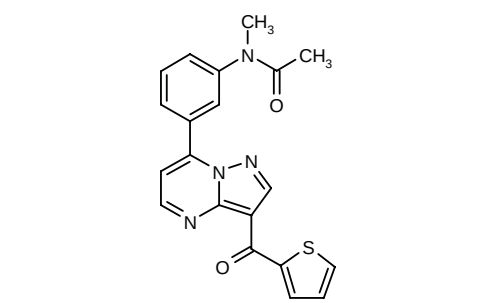
Indiplon



Indiplon (NBI-34060) is a unique nonbenzodiazepine sedative/hypnotic that acts on a specific site of the $GABA_A$ receptor in the brain thought to be responsible for promoting sleep.

Indiplon is being evaluated by Neurocrine Biosciences under a global collaboration with Pfizer in phase III trials for the treatment of multiple types of insomnia, as both immediate- and modified-release formulations. The phase III program involves over 6,000 adult, elderly, male and female subjects and will include subjects treated for up to 1 year. These trials are being conducted to support an NDA filing, expected early next year. Under their agreement, the companies will collaborate on clinical development and copromotion in the U.S., while Pfizer will be responsible for development and marketing outside the U.S. Neurocrine Biosciences licensed indiplon from DOV Pharmaceutical (1, 2).

Results from the second phase III trial of an immediate-release formulation of indiplon demonstrated statistically significant results in both primary and secondary endpoints of sleep initiation, with no evidence of next-day residual effects in 200 adult patients with chronic primary insomnia. The immediate-release formulation of indiplon was found to be safe, well tolerated and effective in these patients throughout the 35-day treatment period. The multicenter, randomized, double-blind, placebo-controlled, parallel-group trial assessed 2 dose levels of immediate-release indiplon capsules (10 or 20 mg) in adult patients with chronic primary insomnia enrolled at 19 U.S. centers. The primary endpoint was latency to persistent sleep (LPS), as measured objectively by polysomnography. Patients received treatment on an inpatient and outpatient basis over 35 days. The immediate-release formulation of indiplon demonstrated a statistically significant improvement in the primary endpoint of LPS at both dose levels compared to placebo on the first 2 nights after dosing, as well as on nights 15 and 16 and nights 29 and 30. There were no statistically significant differences in next-day residual sedation as compared with placebo (3).

Preliminary topline results from the first phase III trial of modified-release indiplon also showed statistically significant results, demonstrating that patients with chronic insomnia taking indiplon 30 mg fell asleep more rapidly and stayed asleep longer. The multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III trial enrolled 211 adult patients with chronic primary insomnia at 32 U.S. centers. Nightly administration of 30 mg modified-release indiplon over a 2-week period produced a statistically significant improvement in the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized, double-blind, multicenter	Indiplon, 10 mg od x 2 d Indiplon, 20 mg od x 2 d Indiplon, 30 mg od x 2 d Indiplon, 35 mg od x 2 d Placebo	79	Indiplon administered once daily for 2 consecutive nights improved sleep maintenance and dose-dependently reduced sleep latency and wake time after sleep onset in patients with chronic sleep maintenance insomnia	5
Insomnia	Randomized, double-blind	Indiplon, 40 mg po Placebo	36	Indiplon was significantly more effective than placebo in improving both sleep initiation and sleep duration in healthy subjects suffering from insomnia caused by venipuncture	8
Insomnia	Randomized, double-blind, multicenter	Indiplon, 15 mg Indiplon, 30 mg Placebo	228	Indiplon significantly improved the latency to persistent sleep and subjective sleep latency in a model of transient insomnia, but had no effects on total sleep time or sleep architecture. The drug was well tolerated and no residual effects were found 9 h after dosing	10, 11
Insomnia	Randomized, double-blind, crossover, multicenter	Indiplon, 5 mg po Indiplon, 10 mg po Indiplon, 20 mg po Placebo	42	The nonbenzodiazepine GABA-A receptor modulator indiplon dose-dependently improved the mean latency to persistent sleep, the mean total sleep time and the latency to sleep onset in elderly patients with insomnia. The drug was well tolerated, and no serious adverse events were reported	12

primary endpoint of patient-reported total sleep time relative to placebo at 1 and 2 weeks. Patients on indiplon slept significantly longer than those taking placebo and the effect was sustained over the 2-week treatment period. Modified-release indiplon also demonstrated statistically significant efficacy results in sleep maintenance as compared to placebo on multiple secondary endpoints, including patient-reported wake after sleep onset, total wake time and number of awakenings after sleep onset. Statistically significant improvements were also seen in a key secondary efficacy endpoint of patient-reported latency to sleep onset in the indiplon group. Indiplon patients reported a statistically significant improvement in the quality of their sleep compared to the placebo group. Patient-reported global impression (PGI) assessed for overall effect on sleep, time to sleep, amount of sleep, sleep quality and strength of medication also showed significant improvement over placebo. Investigator-reported Global Rating for Severity of insomnia and Change as a result of treatment were both in favor of indiplon (4).

A multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the effects of indiplon on chronic sleep maintenance insomnia. Seventy-nine patients with primary insomnia (wake after sleep onset greater than 40 min, total sleep time of 240-390 min on at least 2 nights, and total wake time greater than 60 min on all nights) for at least 3 months were randomized to receive placebo or modified-release indiplon at doses of 10, 20, 30 or 35 mg on 2 consecutive nights. The polysomnography results revealed that the drug dose-dependently reduced the latency to persistent sleep and the wake after sleep onset of the patients, therefore improving their mean sleep efficiency. Six patients discontinued the treatment due to adverse events, but none of these were serious (5). The results of this study and some that follow are summarized in Table V.

The potential interaction between indiplon and alcohol was studied in a randomized, double-blind, placebo-controlled, crossover trial in 10 healthy subjects. The subjects received indiplon (10 mg), ethanol (0.7 mg/ml) and a combination of the two. The pharmacokinetics of indiplon were not changed by alcohol. Similar reductions in performance at maximal effects were seen on indiplon and alcohol alone, and a slight additive effect was observed when the two were given together. Indiplon was associated with a greater increase in sedation and reaction time than alcohol, but this was not potentiated by the addition of alcohol (6, 7).

Researchers used a venipuncture model of insomnia in healthy volunteers to further determine the benefits of indiplon in the treatment of insomnia. Thirty-six male volunteers 19-42 years old were included in a double-blind clinical trial and randomized to receive modified-release indiplon (40 mg) or placebo orally at bedtime. A total of 16 blood samples were withdrawn during the night. Placebo-treated patients showed a significantly disrupted

sleep pattern, whereas indiplon reduced the venipuncture effects on sleep initiation and duration. The drug was rapidly absorbed and reached therapeutic levels of 5 ng/ml in plasma at 30 min after administration. Indiplon was well tolerated, and no evidence of next-day residual effects was found (8).

Thirty young healthy male subjects were included in a randomized clinical trial that established that no tolerance to indiplon develops after repeated administration. The subjects received oral doses of placebo or indiplon (10, 30 or 45 mg) once daily in the morning for 14 days. No significant differences were found between the pharmacokinetic parameters and the changes in quantitative electroencephalogram tests conducted at baseline and at the end of the treatment. The drug was well tolerated at doses up to 45 mg/day, as no serious adverse events were reported (9).

A total of 228 subjects without a history of insomnia had transient insomnia induced in the laboratory and were randomized to indiplon solution 15 or 30 mg, or placebo, 30 min before bedtime in a multicenter, double-blind trial. Indiplon significantly shortened the latency to persistent sleep and subjective latency to sleep onset compared to placebo, while being devoid of next-day residual effects, as assessed on several different tests (10. 11).

A double-blind, randomized, placebo-controlled, crossover clinical trial established the efficacy and safety of indiplon in elderly patients with chronic insomnia. Forty-two patients with a mean age of 70 years received a sequence of four 2-day treatments with placebo or indiplon at daily doses of 5, 10 and 20 mg. The drug significantly shortened the mean latency to persistent sleep from 25.2 min with placebo to 9.8 min with 20 mg/day indiplon. Significant improvements were also found for the mean total sleep time (385.6 min with 20 mg indiplon *vs*. 354.4 min with placebo) and the latency to sleep onset (20.2 min with 20 mg indiplon *vs*. 41.8 min with placebo). The drug was also well tolerated, and no patients withdrew from the study due to adverse events (12).

1. *Neurocrine Biosciences and Pfizer enter global agreement for indiplon*. DailyDrugNews.com (Daily Essentials) Dec 30, 2002.

2. *DOV Pharmaceutical reports on past four months*. DailyDrugNews.com (Daily Essentials) April 1, 2003.

3. *Positive results from second phase III trial of immediate-release indiplon*. DailyDrugNews.com (Daily Essentials) April 24, 2003.

4. *Preliminary phase III results for modified-release indiplon*. DailyDrugNews.com (Daily Essentials) Sept 30, 2003.

5. Walsh, J.K., Lankford, D.D., Krystal, A., Roth, T., Jochelson, P., Garber, M., Alexander, T., Burke, J. *Efficacy and tolerability of four doses of indiplon (NBI-34060) modified-release in elderly patients with sleep maintenance insomnia*. Sleep 2003, 26(Suppl.): Abst 0190.C.

6. Berkowitz, D.V., Scharf, M.B., Jochelson, P., Oliva, J., Boyd, M., Kean, Y., Campbell, B. *The co-administration of indiplon (NBI-34060) and alcohol lacks pharmacokinetic and pharmacodynamic interactions*. Sleep 2003, 26(Suppl.): Abst 0199.C.

7. Scharf, M., Berkowitz, D.V., Boyd, M., Jochelson, P., Kean, Y., Olivia, J., Campbell, B. *Lack of interactions with indiplon (NBI-34060) and EtOH in healthy adults*. 156th Annu Meet Am Psychiatr Assoc (May 17-22, San Francisco) 2003, Abst NR173.

8. Jochelson, P., Bozigian, H., Garber, M., Baron, C., Boyd, M., Burke, J., Roth, T., Campbell, B. *The activity of modified release indiplon (NBI-34060) in a transient nighttime venipuncture model*. Sleep 2003, 26(Suppl.): Abst 0206.C.

9. Jochelson, P., Chen, T.K., Farber, R., Campbell, B. *Lack of pharmacological and pharmacokinetic tolerance following repeat dosing of indiplon (NBI-34060)*. Sleep 2003, 26(Suppl.): Abst 0210.C.

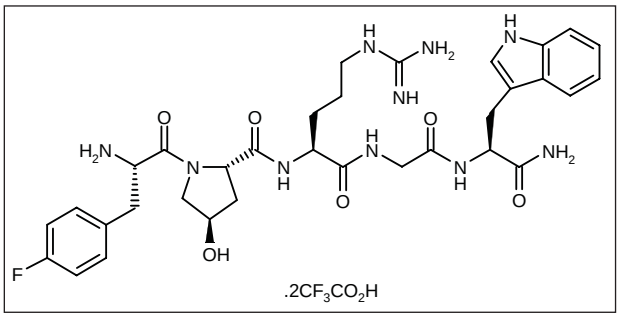
10. Roth, T., Walsh, J.K., Burke, J., Rogowski, R., Campbell, B., Jochelson, P. *Efficacy of indiplon solution in a model of transient insomnia*. 156th Annu Meet Am Psychiatr Assoc (May 17-22, San Francisco) 2003, Abst NR846.

11. Roth, T., Walsh, J.K., Rogowski, R., Farber, R., Burke, J., Jochelson, P. *Efficacy and tolerability of indiplon (NBI-34060) solution in healthy adults in a model of transient insomnia*. Sleep 2003, 26(Suppl.): Abst 0214.C.

12. Scharf, M.B., Rosenberg, R., Cohn, M., Zammit, G., Rogowski, R., Jochelson, P., Farber, R., Burke, J., Campbell, B. *Safety and efficacy of immediate release indiplon (NBI-34060) in elderly patients with insomnia*. Sleep 2003, 26(Suppl.): Abst 0209.C.

Original monograph - Drugs Fut 2003, 28(8): 739.

INN-00835



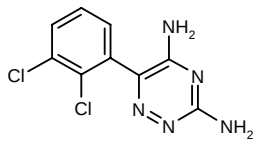
A low-molecular-weight pentapeptide compound, INN-00835 (nemifitide ditriflutate, netamiftide trifluoroacetate) is undergoing phase II/III clinical evaluation at Innapharma for the treatment of depression.

A meta-analysis of data from 2 double-blind, randomized, placebo-controlled phase II clinical trials evaluating the efficacy and safety of nemifitide ditriflutate in the treatment of major depression has been reported. A total of 52 hospitalized patients and 55 outpatients received once-daily doses of 0.2 mg/kg s.c. for 5 days and 18 mg s.c. for 10 days, respectively. Patients whose peak plasma drug concentrations were equal to or higher than the minimum projected therapeutic concentration established in a previous pharmacokinetic analysis were more likely to respond to the treatment. No statistically significant differences were found between the results reported in the clinical trials. Nemifitide was well tolerated and no serious drug-related adverse events were observed (1).

1. Montgomery, S.A., Feighner, J.P., Sverdlov, L., Abajian, H., Hlavka, J., Nicolau, G., Freed, J. *Meta-analysis of efficacy of two pilot clinical studies with a novel pentapeptide antidepressant, nemifitide, in the treatment of depression*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S179.

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

Lamotrigine



GlaxoSmithKline's Lamictal® (lamotrigine) is a sodium channel blocker currently used as an antiepileptic and under review in the U.S. and the E.U. for the long-term treatment of biopolar disorder to delay the relapse/recurrence of depressive episodes.

A double-blind clinical trial compared the effects of lithium, lamotrigine and placebo for the prevention of relapse or recurrence of mood episodes in recently manic or hypomanic patients with bipolar I disorder. A total of 349 patients at least 18 years of age with bipolar I disorder and manic or hypomanic symptoms first received an open-label treatment with lamotrigine (100-200 mg/day) for 8-16 weeks. At the end of this phase, 175 patients who had responded to the open-label treatment were randomized to receive either lithium (titrated to serum levels of 0.8-1.1 mEq/l), lamotrigine (100-400 mg/day, depending on clinical response) or placebo for up to 76 weeks. Both lamotrigine and lithium were significantly better than placebo in prolonging the time to intervention for mood episodes; lamotrigine was more effective in delaying depressive episodes and lithium was more effective in delaying manic, hypomanic or mixed episodes. Most mood episodes reported by patients treated with lamotrigine or placebo consisted of mood elevation (*i.e.*, mania, hypomania and mixed), whereas lithium was mostly associated with depressive episodes. All study treatments were well tolerated; the most common adverse event reported throughout the clinical trial was headache, which was found in 20.3%, 4.3% and 15.9% of patients treated with lamotrigine, lithium and placebo, respectively. Other common adverse events were rash, infection, somnolence, nausea and diarrhea, but most were mild or moderate and resolved without any sequelae (1).

A total of 638 patients with bipolar I disorder were enrolled in 2 double-blind, randomized clinical trials that compared the prophylactic effects and tolerability of lithium, lamotrigine (50-400 mg/day as fixed or flexible doses) and placebo over 52 weeks. Both active drugs were more effective than placebo in stabilizing mood and prolonging the time to intervention. The incidence of relapsed/recurrent depression was lower with lamotrigine than with lithium or placebo in recently manic patients (14% *vs*. 22% and 30%, respectively) and in recently depressed patients (34% *vs*. 38% and 39%, respectively), suggesting that lamotrigine would be especially effective when administered during or shortly after stabilization of mania and before the appearance of depression. The results also indicated that the response to treatment with lithium or lamotrigine was associated with a later onset of bipolar disorder, shorter time to stabilization on lamotrigine alone and no previous psychiatric hospitalization. The response to lamotrigine was associated with less than 3 depressive episodes in 3 years, response to placebo with less than 3 manic episodes in 3 years, and response to lithium with a late onset of illness. Lamotrigine was associated with less increase in body weight than placebo or lithium. These differences were especially evident in obese patients with a baseline body mass index > 30. The authors concluded that, contrary to with other mood stabilizers, body weight increase may not be a complication of long-term treatment of bipolar I disorder with lamotrigine (2-5). These results and those from some of the following studies are summarized in Table VI.

The pooled data from 8 double-blind, randomized, placebo-controlled clinical trials were used to evaluate the safety of lamotrigine at doses of 50-500 mg/day for up to 18 months in adult patients with bipolar I disorder. The most common adverse event was headache (25% on lamotrigine and 21% on placebo). Both serious adverse events and withdrawals due to adverse events were uncommon (8% and 12%, respectively, on lamotrigine and 7% and 10%, respectively, on placebo). No association was found between lamotrigine administration and mood destabilization, sexual changes, weight increase or withdrawal symptoms. The data also revealed that lamotrigine did not increase the risk of manic/hypomanic/mixed episodes in patients with bipolar disorder. In double-blind studies, the percentage of patients who developed mania or required intervention for mania was 21% on lamotrigine and 26% on placebo, and the mean Mania Rating Scale of the patients was similar in both study groups. These results suggested that lamotrigine stabilized mood by preventing depression without promoting mania (6, 7).

The data from 2 large clinical trials of lamotrigine monotherapy or combination therapy for maintenance in patients with bipolar I disorder showed that lamotrigine significantly improved the cognitive function (measured using the Medical Outcomes Study Cognitive scale and the AB-Neurological Assessment Scale) of the patients. Additionally, lamotrigine significantly improved the quality

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

Indication	Design	Treatments	n	Conclusions	Ref.
Bipolar disorder I	Randomized, double-blind, pooled/meta-analysis	Lamotrigine, 50-400 mg/d x 52 wk (n=280) Lithium, 0.81.1 mEq/d x 52 wk (n=167) Placebo (n=191)	638	Lamotrigine administered for 52 weeks induced a lower body weight increase than placebo or lithium. These differences were especially evident in obese patients with a baseline body mass index >30	2
Bipolar disorder I	Randomized, double-blind, pooled/meta-analysis	Lamotrigine, 50-400 mg/d x 18 mo (n=280) Lithium, 0.81.1 mEq/d x 18 mo (n=167) Placebo (n=191)	638	Both lamotrigine and lithium were effective in the treatment of patients with bipolar I disorder. The effects of the drugs were unrelated to previous episode burden, although the risk of intervention tended to be higher in patients with more previous depressive episodes	3-5
Bipolar disorder	Randomized, double-blind, pooled/meta-analysis	Lamotrigine, 50-500 mg/d x 18 [max] mo (n=827) Placebo (n=685)	1512	Lamotrigine was well tolerated and effective in stabilizing mood and preventing depression without increasing mania in patients with bipolar disorder	6, 7
Bipolar disorder I	Open	Lamotrigine x 8-16 wk (n=1105) Lamotrigine + Valproate semisodium x 8-16 wk (n=200)	1305	The combination of half-dose lamotrigine plus valproate semisodium was well tolerated and as effective as full-dose lamotrigine alone in the treatment of patients with bipolar I disorder	10

of life (measured using the Medical Outcomes Study Short-Form 36) of the patients. The benefits of lamotrigine on these endpoints were not affected by either mood polarity or the fact that lamotrigine was administered alone or combined with other drugs (8, 9).

In order to determine the tolerability of a combination of both drugs, a total of 1,305 patients received either lamotrigine alone or a reduced lamotrigine dose combined with valproate for 8-16 weeks. The adverse events most frequently reported during this study were headache, infection, nausea and rash. The addition of valproate to the treatment did not increase the incidence of rash significantly. The combination was thus confirmed to be well tolerated, despite previous fears that valproate might reduce lamotrigine clearance and thus increase serum lamotrigine concentrations to unsafe levels (10).

1. Bowden, C.L., Calabrese, J.R., Sachs, G. et al. *A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.* Arch Gen Psychiatry 2003, 60(4): 392.

2. Calabrese, J., Young, A.H., Bowden, C., Antonijevic, Z., Evoniuk, G. *Effects of lithium and lamotrigine on body weight after 18 months in bipolar I disorder.* Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S265.

3. Frye, M., Vieta, E., Ketter, T., Goldberg, J.F., Antonijevic, Z., Calabrese, J. *Previous episode burden and response to lithium and lamotrigine in bipolar I disorder.* Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S267.

4. Yatham, L., Goodwin, G., Bowden, C., Calabrese, J., White, R., Leadbetter, R. *Lamotrigine but not lithium prevents or delays depressive episodes in bipolar I disorder*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S266.

5. Ketter, T., Bowden, C., Vieta, E., Goldberg, J.F., Antonijevic, Z. , Leadbetter, R. *Predictors of response to lithium and lamotrigine prophylaxis in bipolar I disorder*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S267.

6. Vieta, E., Young, A., Berk, M., Asnis, G., Calabrese, J., Sachs, G., Bowden, C. *Safety and tolerability of lamotrigine in bipolar I disorder*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S265.

7. Grunze, H., Calabrese, J., Yatham, L., Suppes, T., McElroy, S., Goldberg, J.F., Bowden, C. *Lamotrigine controls bipolar depression without destabilising mood: An analysis of data from 8 placebo-controlled trials*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S265.

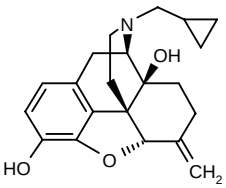
8. Yatham, L.N., Davis, K.H., Khan, A., Ginsberg, L.D., Asnis, G.M., Goodwin, F.K. *Effects of lamotrigine on neurocognitive measures in bipolar I patients*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S227.

9. Rapaport, M., Kennedy, S., Davis, K. *Effects of lamotrigine on quality of life in patients with bipolar I disorder*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S457.

10. Bowden, C., Calabrese, J., Sachs, G., Evoniuk, G. *Concomitant use of lamotrigine and valproate in bipolar I disorder.* Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S264.

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

Nalmefene



Nalmefene is a specific opioid receptor antagonist that inhibits the effects of endorphins in the central nervous system.

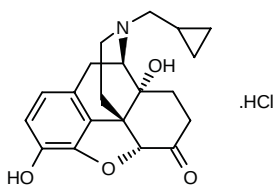
BioTie Therapies is developing two nalmefene-based products: Soberal® for the treatment of alcoholism and alcohol abuse, currently in phase III evaluation, and Cessal® in phase II trials for impulse control disorders. Soberal® is expected to offer a new alternative to traditional treatments for alcoholism, which aim at total abstinence and usually include intensive psychosocial therapy. Nalmefene was developed by Baker Norton (Ivax) and launched in the U.S. as Revex™ in 1995 by licensee Baxter as a narcotic antagonist for reversing opioid drug effects and managing known or suspected opioid overdose. It is also licensed to SSP for Japan.

Earlier this year, BioTie completed the first phase III studies of nalmefene for the treatment of alcoholism. The multicenter, placebo-controlled studies were conducted in Finland and the U.K. and evaluated the safety and efficacy of nalmefene in the treatment of alcoholism and alcohol abuse without supporting psychosocial therapy in patients who considered themselves to be incapable of controlling their drinking. Drug therapy lasted 28 weeks in both studies. Patients took the study drug before drinking alcohol. In the Finnish study, the number of heavy drinking days decreased almost by half in nalmefene users. In the placebo group, the number of heavy drinking days decreased by about one-third and the difference between the nalmefene and placebo groups was statistically significant. In the British study, the number of heavy drinking days was also reduced by half in the nalmefene group, and the difference between the groups was in the same range as in the Finnish study. However, owing to a higher than expected proportion of patient withdrawal, the results were not statistically significant. In both studies, patients receiving nalmefene felt that the treatment was beneficial more often than the patients receiving placebo. BioTie plans to outlicense the project for further development and marketing. As regards the company's other nalmefene product for impulse control disorder, approximately 200 patients with addictive pathological gambling were enrolled in a multicenter study begun in the U.S. during the first half of the year (1).

1. *BioTie Therapies updates progress*. DailyDrugNews.com (Daily Essentials) May 28, 2003.

Original monograph - Drugs Fut 1984, 9(7): 518.

Naltrexone Hydrochloride



Naltrexone hydrochloride, another opioid antagonist, is currently available in the U.S. in an oral formulation for the treatment of alcohol and opiate dependence in combination with a comprehensive treatment program.

DrugAbuse Sciences is conducting phase III clinical trials with naltrexone depot, an extended-release injectable form of the drug, for the once-monthly treatment of alcohol dependence. The company is also evaluating Naltrel™ (naltrexone depot for injectable suspension) as a once-a-month treatment of opiate dependence. Alkermes is developing its own naltrexone product for alcohol dependence: Vivitrex™, a proprietary, injectable formulation based on its Medisorb® extended-release delivery technology releasing the drug over 1 month. This product is also in phase III clinical evaluation.

Alkermes recently completed enrollment in the pivotal phase III trial of Vivitrex™, a randomized, double-blind, placebo-controlled study designed to confirm the safety and efficacy of Vivitrex™ in alcohol-dependent patients over 6 months. The patients may then enter an extension study which will collect longer term data over 12 months. Over 600 patients have been enrolled in the phase III trial at 24 U.S. centers and more than 180 patients have now entered the extension study (1).

In comparison to saline, naltrexone (0.005-0.25 mg/kg s.c. b.i.d. x 5 days), alone or in combination with acamprosate (25 or 100 mg/kg i.p. b.i.d. x 5 days), abrogated ethanol self-administration in rats trained to respond to ethanol, without altering the responses to water. The combination also increased the efficacy of low-dose naltrexone on day 2. Thus, chronic administration of

naltrexone and acamprosate modulated alcohol-seeking behavior in this rodent model (2).

A treatment for alcohol and drug dependence has been claimed comprising a pharmaceutical composition which combines an opioid antagonist, such as naloxone or naltrexone, with an NMDA receptor complex modulator, such as acamprosate (3).

Stabilized pharmaceutical compositions containing 20 mg or less of the opioid antagonist naltrexone hydrochloride have been claimed. The claim embodies the inclusion of a pharmaceutically compatible stabilizing agent, such as ascorbic acid, in order to prevent deterioration and ensure prolonged stability throughout the preparation, storage and use of the drug (4).

1. *Enrollment complete in phase III trial of Vivitrex in alcohol dependence*. DailyDrugNews.com (Daily Essentials) April 3, 2003.

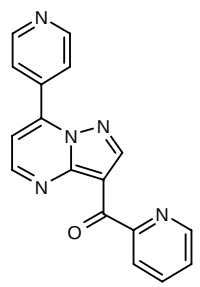
2. Heyser, C.J., Moc, K., Koob, G.F. *Effects of naltrexone alone and in combination with acamprosate on the alcohol deprivation effect in rats*. Neuropsychopharmacology 2003, 28(8): 1463.

3. Daoust, M. et al. (Lipha Santé). *Combination for the treatment of alcohol and drug dependence containing an opioid antagonist and a NMDA receptor complex modulator*. US 6512009, WO 9948500, EP 0945133, EP 1063995.

4. Oshlack, B. et al. (Euroceltique SA). *Naltrexone hydrochloride compsns.* WO 0377867.

Original monograph - Drugs Fut 1977, 2(1): 45.

Ocinaplon



The FDA has placed on hold the start of a pivotal phase III trial of DOV Pharmaceutical's novel antianxiety product candidate ocinaplon, a $GABA_A$ receptor modulator.

The FDA has requested additional safety information before removing the hold and allowing commencement of the trial. The nonbenzodiazepine product has demonstrated antianxiety effects without sedation, muscle relaxation or amnesia, and is being developed for the treatment of generalized anxiety disorder (GAD). The company recently agreed with Elan to purchase 100% ownership of the parties' joint venture operating company established in 1999 to develop controlled-release formulations of bicifadine and ocinaplon (1-3).

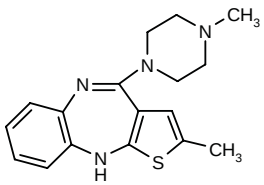
1. *Pivotal ocinaplon trial on hold pending additional safety information*. DailyDrugNews.com (Daily Essentials) Oct 7, 2003.

2. *DOV to purchase Elan's stake in joint venture*. DailyDrugNews.com (Daily Essentials) Oct 24, 2003.

3. *DOV Pharmaceutical reports on past four months*. DailyDrugNews.com (Daily Essentials) April 1, 2003.

Original monograph - Drugs Fut 2003, 28(2): 118.

Olanzapine



The indications for the atypical antipsychotic agent olanzapine (Zyprexa®; Lilly) continue to be expanded. The agent was recently approved by the FDA for use in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar I disorder.

Olanzapine is the first agent to be approved for use in combination with other mood stabilizers to treat acute bipolar mania. The agent was approved by the FDA in 2000 as monotherapy for the short-term treatment of acute manic episodes associated with bipolar disorder and is the only atypical antipsychotic approved by the FDA to treat this patient population. It is also available in the E.U. for this indication. The new approval was based on data from 2 double-blind, randomized, placebo-controlled trials which showed that bipolar patients in manic or mixed episodes treated with olanzapine in combination therapy demonstrated improved manic and depressive symptoms compared to patients treated with lithium or valproate alone. Olanzapine was also recently approved in the E.U. and is under review at the FDA for long-term maintenance of response in the treatment of bipolar disorder. Additionally, Symbyax™, which combines

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

Indication	Design	Treatments	n	Conclusions	Ref.
Mania	Randomized, double-blind	Olanzapine, 5-20 mg od x 47 wk (n=125) Valproate semisodium, 500-2500 mg od x 47 wk (n=126)	251	Compared with valproate semisodium, olanzapine was more effective in the treatment of mania, as it was associated with greater symptom improvement and a shorter time to remission. No significant differences between drugs were found for the rate of bipolar disorder relapse	4
Schizophrenia	Open	Olanzapine, 10-20 mg/d po x 8 wk	85	The orally disinterating tablet formulation of olanzapine was effective in previously noncompliant patients with schizophrenia or schizoaffective disorder	6
Dementia	Randomized	Olanzapine, 2.5 mg/d x 1 y Olanzapine, 5 mg/d x 1 y Olanzapine, 7.5 mg/d x 1 y	18	Olanzapine was well tolerated and showed activity in patients with dementia with Lewy bodies	7

olanzapine with Prozac® (fluoxetine), is under FDA review for the treatment of bipolar depression (1, 2).

A 12-month randomized, double-blind, controlled trial compared the efficacy and safety of olanzapine (5-20 mg/day) and lithium (300-1800 mg/day) in relapse prevention in 431 patients with bipolar disorder. The relapse rate to an affective manic episode and the incidence rate of relapse into a manic episode were lower in olanzapine-treated patients than lithium-treated patients (30.0% *vs*. 38.8% and 14.3% *vs*. 28.0%, respectively). More patients in the lithium group withdrew because of adverse events, but weight gain was greater in the olanzapine group. Both olanzapine and lithium were effective in prolonging remission, with more patients remaining on olanzapine due to its efficacy in preventing relapse to mania (3).

A multicenter, double-blind clinical trial compared the efficacy and safety of divalproex sodium and olanzapine in the long-term treatment of bipolar disorder. A population of 251 patients suffering from manic or mixed episodes of bipolar disorder were randomized to receive olanzapine 15 mg/day or divalproex sodium 750 mg/day for 47 weeks; both doses were adjusted during the trial according to serum drug concentrations, adverse events and clinical response. Both drugs were effective in reducing the severity of the acute mania symptoms, assessed using the Young Mania Rating Scale, but patients treated with olanzapine showed a greater mean improvement in symptom scores and a shorter time to symptomatic remission compared to divalproex sodium. No significant differences between treatments were found for the remission rate, the relapse rate or the time to relapse of bipolar symptoms. A similar percentage of patients withdrew from the study due to adverse events in each study group: 24.8% with olanzapine and 19.8% with divalproex sodium. The most common adverse events reported were somnolence, dry mouth, increased appetite, weight gain, akathisia and increased alanine aminotransferase (for olanzapine), and nausea, nervousness, rectal disorder and manic reaction (for divalproex sodium) (4). The results of this study and some that follow are summarized in Table VII.

A multicenter, double-blind study compared the efficacy, safety and tolerability of the mood stabilizer divalproex sodium and the antipsychotic agent olanzapine in 120 patients with bipolar disorder type I who had been hospitalized for an episode of acute mania. The patients were randomized to receive either divalproex sodium (maximum daily dose of 10 mg/kg b.i.d. + 1000 mg/day) or olanzapine (maximum daily dose of 5 mg/kg b.i.d. + 20 mg/day) for 21 days, after which they were either discharged and followed as outpatients for another 63 days or withdrawn from the study due to lack of efficacy. After 21 days of treatment, both therapies were found to produce similar changes from baseline in several efficacy scores, although olanzapine was associated with a higher incidence of weight gain, somnolence, edema, rhinitis and speech disorder (5).

Compliance and psychopathology were significantly improved among patients with schizophrenia or schizoaffective disorder (n=85) who were given the orally disintegrating tablet formulation of olanzapine 10-20 mg/day. The patients were previously found to be noncompliant with their treatment and were given the new medication for up to 6 weeks (6).

Patients with dementia and Lewy bodies were treated with olanzapine 2.5, 5 or 7.5 mg in a randomized, 1-year study. Cognitive impairment did not increase in the 16 patients who completed the study, and improvements in measures of psychosis were seen. The 5-mg dose appeared to be the best dose for efficacy and tolerability (7).

Pharmaceutical compositions capable of stimulating nerve cell growth to a predetermined level in at least one region of the brain have been claimed for the treatment of conditions characterized by an impairment of brain function, including memory loss, schizophrenia, Alzheimer's disease, Parkinson's disease, attention deficit disorder

and stroke. The claim embodies compositions comprising one or more antipsychotic agents, such as the atypical neuroleptic dopamine D_2 receptor antagonists haloperidol, risperidone and olanzapine (8).

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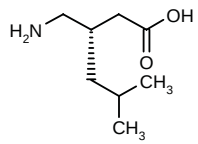
Original monograph - Drugs Fut 1994, 19(2): 114.

Pregabalin



Pfizer's pregabalin reached several milestones this past year. The drug was recently submitted to the FDA seeking approval for use in the management of neuropathic pain associated with diabetic peripheral neuropathy and herpes zoster (postherpetic neuralgia), GAD – the indication discussed here – and as adjunctive therapy for partial seizures in patients with epilepsy.

Earlier in the year, Pfizer filed with regulatory authorities in Europe for the use of pregabalin in the treatment of neuropathic pain and as an adjunctive therapy for partial seizures. Pregabalin has a unique mechanism of action for the treatment of certain neurological and psychiatric disorders. It inhibits excitatory neurotransmitters such as glutamate through binding selectively to the alpha2-delta subunit of voltage-dependent calcium channels. This in turn reduces the entry of calcium into the nerve terminals and may trigger mechanisms responsible for the analgesic, anxiolytic and anticonvulsant effects of the drug. It is rapidly absorbed, does not bind to plasma proteins and is excreted through the urine. No evidence of abstinence syndrome has been found at doses up to 900 mg administered for 24 weeks to healthy volunteers. The drug also has a favorable safety profile, with mild to moderate dizziness and somnolence being the most common adverse events (1, 2).

Five clinical trials enrolled a total of 111 healthy subjects to receive single doses ranging from 1 to 300 mg, or multiple doses of 25-300 mg t.i.d. or 300 mg b.i.d. The pooled results from these trials revealed that the drug was rapidly absorbed and reached peak plasma levels between 0.7 and 1.4 h after administration. Pregabalin levels in plasma increased with dose and its oral bioavailability was 90% regardless of dose and dosing frequency. Two clinical trials that determined the effects of food on single doses of 100 or 150 mg of pregabalin established that food reduced the drug's absorption rate and peak plasma concentrations, but these effects were not considered to be clinically significant. Pregabalin showed a half-life of about 6 h and was mainly excreted through the urine. Steady state was achieved after 1-2 days of repeated dosing (3).

A randomized, crossover trial compared the cognitive and psychomotor effects of pregabalin, placebo and alprazolam (used as a negative control) in 24 healthy volunteers. A series of tests revealed that pregabalin had similar effects to placebo on short-term memory, rapid visual information processing, the ability to perform one task while responding to a second stimulus, and the ability to attend and respond to a critical stimulus; all these abilities were significantly impaired by alprazolam. The authors concluded that pregabalin had a positive cognitive and psychomotor profile in healthy volunteers (4, 5). These results and those from some of the following studies are summarized in Table VIII.

Data from 5 double-blind, placebo-controlled trials of pegabalin treatment (150-600 mg) for GAD in 970 patients showed that all doses of the drug tested significantly improved psychic and somatic symptoms (6).

Over 270 patients with GAD received pregabalin 150 or 600 mg/day, lorazepam 6 mg/day or placebo in a 4-week, multicenter, randomized, double-blind trial. All of the active treatments significantly lowered the Hamilton Anxiety Scale (HAMA) scores compared to placebo. The higher dose of pregabalin had a significant effect at week 1 and all active treatments were superior to placebo after 4 weeks. Pregabalin was not associated with serious adverse events and the withdrawal syndrome was not seen in patients given the drug (7, 8).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	Pregabalin Alprazolam Placebo	24	Pregabalin had the same effects as placebo on short-term memory, rapid visual information processing, the ability to perform one task while responding to a second stimulus, and the ability to attend and respond to a critical stimulus in healthy volunteers. These results suggested that pregabalin had clinically irrelevant effects on cognitive and psychomotor abilities. Alprazolam, which was used as a negative control, significantly impaired these abilities. Although both drugs significantly decreased the time to sleep onset and improved sleep efficiency compared with placebo, pregabalin appeared to have an effect on sleep architecture that distinguished it from benzodiazepines	4, 5
Anxiety	Randomized, double-blind	Pregabalin, 150 mg/d x 4 wk (n=69) Pregabalin, 600 mg/d x 4 wk (n=70) Lorazepam, 6 mg/d x 4 wk (n=68) Placebo (n=69)	276	Pregabalin was safe, effective and without withdrawal effects in patients with generalized anxiety disorder	7
Anxiety	Randomized, double-blind, multicenter	Pregabalin, 50 mg tid x 4 wk (n=70) Pregabalin, 200 mg tid x 4 wk (n=66) Lorazepam, 2 mg tid x 4 wk (n=68) Placebo (n=67)	271	Pregabalin was well tolerated and improved anxiety in patients with generalized anxiety disorder	8
Anxiety	Randomized, double-blind, pooled/meta-analysis	Pregabalin, 150-200 mg od x 4-6 wk (n=212) Pregabalin, 300-450 mg od x 4-6 wk (n=440) Pregabalin, 600 mg od x 4-6 wk (n=317) Placebo (n=398)	1367	The percentage of patients with generalized anxiety disorder who showed at least a 30% improvement in HAMA total score after 1 week of treatment was higher with pregabalin than with placebo, regardless of the severity of depressive symptoms shown at baseline. The higher pregabalin doses were associated with a greater percentage of improvement	9-11
Anxiety	Randomized, double-blind, pooled/meta-analysis	Pregabalin, 200 mg x 46 wk (n=78) Pregabalin, 300 mg x 46 wk (n=91) Pregabalin, 400-450 mg x 46 wk (n=364) Pregabalin, 600 mg x 46 wk (n=335) Placebo (n=414)	1282	Pregabalin was significantly more effective than placebo in improving Bech-melancholia scores and Bech-melancholia scores and Hamilton Rating Scale for Anxiety scores in patients with generalized anxiety disorder regardless of depression scores. The mean time to response was 22 days in patients with Hamilton Rating Scale for Depression scores >15 and 17 days in those with a Hamilton Rating Scale for Depression scores <15	12-14
Anxiety	Randomized, double-blind	Pregabalin, 100 mg tid x 4 wk Pregabalin, 150 mg tid x 4 wk Pregabalin, 200 mg tid x 4 wk Alprazolam, 0.5 mg tid x 4 wk Placebo	455	Pregabalin 600 mg o.d. for 4 weeks was significantly more effective than other pregabalin dose levels, alprazolam 1.5 mg/day or placebo in improving work productivity in patients with generalized anxiety disorder, as evaluated using the Endicott Work Productivity Scale	16

The pooled results from 5 double-blind, randomized, placebo-controlled trials were analyzed to better assess the efficacy and safety of pregabalin in the management of patients with GAD. A total of 1,367 patients with DSM-IV GAD were randomized to receive placebo or pregabalin at daily doses of 150-600 mg for 4-6 weeks. The efficacy of pregabalin as an anxiolytic in patients with comorbid depressive symptoms was significantly higher than placebo and was not affected by the baseline HAMD total score of the patients (9). The onset of efficacy of the

drug showed a slight dose-dependence, as the higher dose levels were associated with higher percentages of patients with at least a 30% improvement in their GAD symptoms after 1 week of treatment (44% with 150-200 mg, 51% with 300-450 mg, 54% with 600 mg and 30% with placebo) (10). The mean HAMA score of the patients, which ranged from 24.3 to 26.0 at baseline, improved in all patients treated with pregabalin. The drug showed similar efficacy in improving the psychic and somatic symptoms of GAD at all dose levels (11-13). Pregabalin was significantly more effective than placebo in improving the Bech-melancholia scores and the HAMA scale scores of the patients, regardless of the baseline depression score. Response to the treatment, which was defined as the percentage of patients who achieved at least a 50% reduction of their baseline HAMA scores, was more frequent with pregabalin than with placebo. The mean time to response was established at 22 days in patients with a high level of depression and 17 days in those with a low level of depression (14).

The efficacy of pregabalin in GAD with subsyndromic depression was investigated using data from 337 patients treated with the drug in these studies. All pregabalin doses (200/300, 400/450, 600 mg) except the lowest (150 mg) were found to produce significant changes in anxiety over placebo (15).

A double-blind, randomized, placebo-controlled clinical trial used the Endicott Work Productivity Scale (EWPS) to determine the effects of pregabalin on the work productivity of patients with GAD. A total of 455 patients were included in the trial and randomized to receive pregabalin (150-600 mg/day), alprazolam (1.5 mg/day) or placebo for 4 weeks. The EWPS scores of the patients were significantly higher with a daily dose of 600 mg of pregabalin compared to placebo or alprazolam. The lower pregabalin doses also improved work productivity, but the differences did not reach statistical significance (16).

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6. Bezkorovainy, G. *Efficacy of pregabalin in treating psychic and somatic symptoms in generalized anxiety disorder*. 23rd Annu Conf Anxiety Disord Assoc Am (March 27-30, Toronto) 2003, Abst 10.

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12. Lydiard, B. *Efficacy of pregabalin in treating psychic and somatic symptoms in generalized anxiety disorder (GAD)*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S377.

13. Montgomery, S.A. *Pregabalin in generalized anxiety disorder: Speed of onset*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S376.

14. Pollack, M. *Pregabalin in generalized anxiety disorder: Influence of subsyndromic depression*. Eur Neuropsychopharmacol 2003, 13(Suppl. 4): S377.

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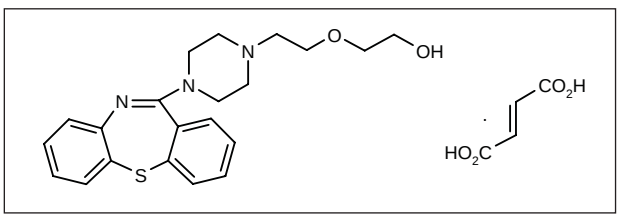
Original monograph - Drugs Fut 1999, 24(8): 862.

Quetiapine Fumarate



The known antipsychotic agent Seroquel™ (quetiapine fumarate) has successfully completed the mutual recognition procedure involving 14 European countries to extend its use, both as monotherapy and as an adjunct, to the treatment of mania associated with bipolar disorder.

The approval was based on data from AstraZeneca's clinical trial program in bipolar disorder, involving almost 1,000 patients in 28 countries. Data from 2 trials confirmed that quetiapine monotherapy is as effective as current treatments for bipolar disorder, with improved tolerability benefits. Another trial examining quetiapine as an

adjunctive therapy to mood stabilizers in the treatment of bipolar mania showed that the combination is significantly more effective than mood stabilizers alone in the treatment of bipolar mania. Quetiapine is also under review for bipolar mania in the U.S., where an approvable letter was recently issued by the FDA, and the U.K. Health authority approvals have already been received in Mexico and New Zealand (1-3).

Hospitalized adolescents (12-18 years old; n=30) with acute mania and bipolar disorder were given a dose of divalproex 20 mg/kg and were then randomized to combination treatment with placebo or quetiapine titrated to 450 mg/day. Quetiapine was well tolerated when administered with divalproex and the combination was more effective than divalproex alone in reducing manic symptoms in this population (4).

A retrospective investigation identified 106 patients with Parkinson's disease who were treated with quetiapine for psychosis. Partial or complete resolution of psychosis was seen in 82%. The risk of non-response was higher in demented patients. Quetiapine was generally well tolerated although motor worsening was seen in 32% of patients (5).

Pharmaceutical formulations have been claimed for use in the treatment of diseases commonly treated with 5-HT_{1D} agonists and/or atypical antipsychotics, such as migraine and associated conditions, and for the prevention of their reappearance. The formulations comprise a combination of the antipsychotic dopamine D_2/5-HT_{2A} antagonist quetiapine and the 5-$HT_{1B/1D}$ agonist zolmitriptan, or pharmaceutically acceptable salts thereof (6).

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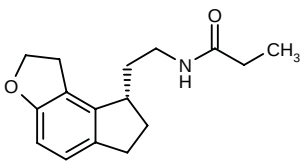
TAK-375



TAK-375 (ramelteon) is a new melatonin ML_1 receptor agonist in development at Takeda for the treatment of sleep disorders. It is in phase III clinical evaluation for the treatment of insomnia and phase II trials for circadian rhythm disorders.

TAK-375 specifically targets brain ML_1 receptors located in the suprachiasmatic nucleus (SCN), a part of the hypothalamus. The SCN is known as the body's "master clock" because it regulates circadian (sleep-wake) cycles, playing an important role in the sleep cycle. Preclinical trials have demonstrated significantly higher selectivity, affinity and potency for the ML1 receptor than melatonin.

The high selectivity of TAK-375 for the melatonin ML_1 receptor was demonstrated in an *in vitro* study using conventional binding assays. TAK-375 had no affinity for several ligand binding sites, including benzodiazepine, dopamine and opiate receptors, and had no effects on various enzyme activities. Similar results were obtained for the principal metabolite of TAK-375, with the exception that the metabolite also showed low affinity (K_i = 1.75 mM) for the 5-HT_{2B} receptor (1).

A randomized, double-blind, placebo-controlled, single-dose, crossover trial involving 48 healthy young (18-34 years) and elderly (63-79 years) male and female subjects examined the influence of age on the pharmacokinetic and pharmacodynamic profiles of TAK-375 (16 mg in the morning). Elderly subjects were found to have significantly greater C_{max} (11.6 ± 13.8 ng/ml *vs.* 6.9 ± 7.6 ng/ml), AUC (18.7 ± 19.4 ng·ml/h *vs.* 10.5 ± 12.8 ng.ml/h) and $t_{1/2}$ (2.6 ± 1.1 h *vs.* 1.57 ± 0.78 h) values and increased systemic exposure as compared to younger subjects; similar findings were obtained for the major metabolite of TAK-375. Age had no effect on urinary excretion of the agent or its metabolite, which was only about 5% of the total dose. No significant differences were observed between young women and men and elderly men in observer- or self-rated sedation, memory or digit-symbol substitution test (DSST) scores. Elderly women had significantly higher self-rated sedation and DSST scores, although these differences were quantitatively small as compared to placebo (2-4).

A total of 60 healthy volunteers were included in a randomized, placebo-controlled clinical trial that assessed the pharmacokinetics of single doses of 4, 8, 16, 32 and 64 mg of TAK-375, administered in the morning after a 10-h fast. Both the AUC and the peak plasma concentration increased with dose. TAK-375 was extensively metabolized, and urinary excretion accounted for less

than 2% of the unchanged drug. All adverse events were mild or moderate, the most common being somnolence and nausea (5).

A double-blind, randomized, placebo-controlled, crossover clinical trial randomized 107 patients with primary chronic insomnia to receive oral doses of placebo or TAK-375 (4, 8, 16 or 32 mg) once daily on 2 consecutive nights. Compared with placebo, all TAK-375 doses significantly reduced the latency to persistent sleep and increased the mean total sleep time and the sleep efficiency of the patients. The drug was well tolerated and had no adverse effects on memory recall or on post-sleep alertness and ability to concentrate (6).

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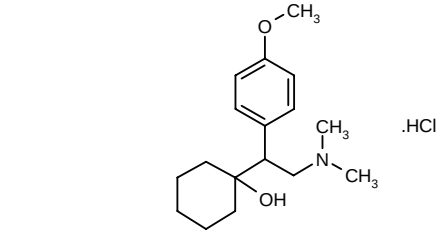
Venlafaxine Hydrochloride



Wyeth's Effexor® XR (venlafaxine hydrochloride, Efexor®), a serotonin norepinephrine reuptake inhibitor, has now been approved by the FDA for the treatment of patients with social anxiety disorder (SAD). The FDA approval was based on two 12-week studies in which Effexor® XR significantly reduced SAD symptoms compared to placebo as early as 4-6 weeks, with improvements through week 12. Effexor® XR is already approved for the treatment of depression and GAD. It was discovered and developed and is marketed by Wyeth Pharmaceuticals. The immediate-release formulation was approved by the FDA in 1993, and the extended-release (XR) formulation in 1997. The company also intends to expand its indications to include panic disorder (1).

Extended-release venlafaxine was compared to placebo and paroxetine in 2 multicenter, randomized, double-blind trials in 434 and 429 patients, respectively, with SAD. Flexible doses of venlafaxine (75-225 mg/day) and paroxetine (20-50 mg/day) were administered for up to 12 weeks. Liebowitz Social Anxiety Scale total scores, CGI-Severity scores, CGI-Improvement scores and Social Phobia Inventory scores were signficantly better with the active treatments compared to placebo. Adverse events in both studies included nausea, insomnia, somnolence, asthenia, dry mouth and dizziness (2).

Outpatients with SAD (n=395) were treated with extended-release venlafaxine in a fixed 75 mg/day dose or a flexible dose of 150-225 mg/day as part of a multicenter, randomized, double-blind, placebo-controlled trial. Treatment was administered for up to 28 weeks. Improvements on the CGI-Improvement, CGI-Severity, Liebowitz Social Anxiety Scale and Social Phobia Inventory scales were significantly greater with venlafaxine than with placebo. From weeks 4 to 28, 58% and 33% of patients given venlafaxine and placebo, respectively, responded. Adverse events in the venlafaxine treatment groups were headache, nausea, nervousness and somnolence (3).

In a 12-week, multicenter, randomized study in 664 outpatients with panic disorder, venlafaxine XR 75 or 150 mg/day, paroxetine 40 mg/day and placebo were compared. Both active treatments were significantly superior to placebo in terms of the proportion of panic-free patients, the PDSS and the response rate. In addition to similar efficacy, adverse events incidence and severity were similar with the active agents (4).

Data from 5 placebo-controlled trials of venlafaxine XR 37.5-225 mg/day in patients with GAD were pooled to assess the effect of the treatment on the physical symptoms of anxiety. Hamilton Rating Scale for Anxiety scores (psychic and somatic) were significantly reduced with venlafaxine over placebo and more venlafaxine-treated patients were responders for both psychic and somatic factors. In addition, venlafaxine was superior to placebo in patients with all levels of gastrointestinal symptom severity (5).

A comparative clinical trial assessed the efficacy and safety of escitalopram and venlafaxine XR in the management of major depressive disorder. In this trial, 195 patients with mean baseline MADRS (Montgomery-

Asberg Depression Rating Scale) scores suggestive of moderate to severe illness were randomized to receive up to 20 mg/day of escitalopram or 225 mg/day of venlafaxine XR for 8 weeks. The remission and response rates at the end of the study were, respectively, 41.2% and 58.8% for escitalopram and 36.7% and 48.0% for venlafaxine. Escitalopram was also associated with a lower incidence of drug-related adverse events (68.4% *vs*. 85.0%) and fewer patients discontinuing the trial due to adverse events (4.1% *vs*. 16.0%). The authors concluded that the poor tolerability of venlafaxine XR might be related to its nonselective activity (6).

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