NbNomenclature

NEUROSCIENCE-BASED NOMENCLATURE

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PREFACE

Research into disorders of the brain is moving quickly, and new insights are being gained rapidly. In particular, we are learning more and more about how psychotropic interventions interact and affect brain function. For the busy clinician though, keeping up with these discoveries is understandably a challenge.

The Neuroscience-based Nomenclature project was launched with exactly this challenge in mind: To help clinicians incorporate updated neuroscience insights into their clinical decision making and link contemporary advances in psychopharmacology to prescribing.

The project is a unique collaboration between the world's five major independent scientific societies dedicated to research into brain treatments:

- European College of Neuropsychopharmacology – ECNP
- American College of Neuropsychopharmacology – ACNP
- Asian College of Neuropsychopharmacology – AcCNP
- International College of Neuropsychopharmacology – CINP
- The International Union of Basic and Clinical Pharmacology – IUPHAR

Its goal is to give clinicians a practical tool that equips them with the latest insights in neuroscience, in a way that can applied on day-to-day basis in their treatment of patients.

The system has been designed to combine the very best science with optimum usability. It remains an ongoing project, and we rely on your input to continuously improve it. If you have suggestions or comments, do please let us know at nbn@ecnp.eu.

Joseph Zohar, MD

Taskforce chair

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CONTENTS

MISSION AND SCOPE

It has become clear that the current pharmacological nomenclature of psychotropic medications does not reflect our contemporary knowledge, nor does it properly inform the clinician about how to make neuroscience-based prescriptions. Very often we prescribe antidepressants for anxiety disorders or "second-generation anti-psychotics" to depressed patients.

This practice is confusing. To address this problem, five international independent, non-profit, scientific associations; ECNP, ACNP, AsCNP, CINP and IUPHAR, decided in 2008 to establish a taskforce and gave it the mission to embed our current neuroscience advances in the nomenclature.

The scope is to include all the medications with CNS indications and to harness this new nomenclature to help clinicians when they are trying to determine what would be the next rational "neuropsychopharmacology step".

In the NbN-2R 2019, new information on doses was added. Another change in NbN2R 2019 is related to nomenclature; it was simplified, (e.g., instead of talking about “serotonin reuptake inhibitor” we now use “serotonin inhibitor”), yet the full terminology is brought as the first line in the neurobiology layer.

In parallel, with additional members with expertise in Child and Adolescent Psychiatry, we produced in 2018 an additional book: NbN Child and Adolescent NbN-C&A.

This proposed nomenclature aims to reflect the current pharmacological knowledge base and cannot necessarily represent the ultimate scientific consensus.

The taskforce that assembled this book could have taken the stand that our current knowledge is not enough to define the pharmacology domain or the correct mechanisms of action. But as a taskforce, we feel that it is better to present a cutting-edge scientific interpretation than to wait for the definitive conclusion.

We need to treat our patients now, and we cannot postpone treatment until the last word is known.

Therefore this nomenclature is based upon:

1. The need to treat now.
2. Updated neuroscience insights.
3. The judgment of the members of the taskforce.

Along these lines, we have come up with the following proposal:

The Nomenclature

Pharmacology and Mode of Action reflects the current knowledge and understanding about the neurotransmitter/molecule/system being modified and the mode/mechanism of action.

We have also added five additional dimensions:

Approved Indications – Based on the recommendations of major regulatory bodies (e.g. FDA, EMA , etc.).

Efficacy and Side Effects – Driven from positive single, large, RCT and/or "heavy weight " clinical data. Only prevalent or life-threatening side effects were included.

Practical Note – Summarizes the clinical knowledge that has been "filtered" through the taskforce's "sieve".

Neurobiology – This dimension is focused on biology. It is divided into preclinical and clinical sections, with the emphasis on the latter.

Pregnancy – Highlight relevant knowledge about using psychotropic during pregnancy.

For those who would like to know more about the pharmacology there is a **direct** link to the relevant site of IUPHAR, our collaborator in this endeavor.

As this is an ongoing process, we recognize that the product is imperfect. Based on your feedback (and taking into account the feedback of other colleges) new reports and findings, appropriate updates (e.g., later editions) will be undertaken.

This book and the NbN-C&A book have been designed as a bridge to NbN-2 and NbN-C&A Apps which can be downloaded free of charge from Google Play and the iOS App Store.

EIGHT IMPORTANT NOTES

1. Medication included

In principle, medications with CNS indications are included. In this book you will find the medications that we were aware of. The taskforce welcomes proposals to include medications that for one reason or another have been omitted. Please check our website: **www.ecnp.eu/nomenclature**.

1a. Fixed combinations of medications

The taskforce decided not to include them. This decision reflects the taskforce's generally negative view regarding this type of prescribing practice.

2. Inclusion criteria for the efficacy section

Positive single, large, RCT, "heavyweight" clinical data, and/or well-supported expert guidelines.

3. Inclusion criteria for the side effects section

Only serious life-threatening or prevalent side effects were included.

4. The practical note

Summarizes the clinical knowledge that has been "filtered" through the taskforce's "sieve".

5. Neurobiology

Focused on biology. It is divided into preclinical and clinical sections, with the emphasis on the latter.

6. Affinity

Included only where it is clinically relevant and if human data is available. Please note that further work is needed, which we intend to do.

7. Uptake Inhibitors

Figures for SERT/ NET or NET/ SERT uptake inhibition have been taken from studies of uptake inhibition which use human transporters. If there is more than one study, we have taken a mean. If there are only rat transporter studies, we have used these in the same way but added (rat) to the description.

8. Pregnancy layer

The information is taken from the "quick take" of Reprotox (copyright Reproduction Toxicology Center, used with permission). For more detailed information please refer to the official website: **www.reprotox.com.**

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MEDICATION ALPHABETICALLY

Z

Medications

ACAMPROSATE

Brand Names: Campral

Pharmacology
Glutamate

Mode of Action
unclear

Approved Indications
Maintenance of abstinence in alcohol dependence

Efficacy
Anti-craving in alcohol abstinence after detoxification

Side Effects
Nausea, diarrhoea; caution in pregnancy

Practical Notes
Not efficacious in reducing heavy drinking; possibly more effective in anxious alcoholics; increases plasma calcium which has been reported to account for some of its effects. Can be used before or after alcohol withdrawal completed. Half-life is about 24 hours; it is excreted exclusively by the kidneys, and must not be used in severe renal impairment. There are no drug-drug interactions and it is not plasma protein bound.
Recommended doses: 666 mg/day in 3 divided doses

Pregnancy
Acamprosate interferes with embryofetal development in experimental animals. Anecdotal human experience might be influenced by co-exposures to ethanol and other drugs.

Neurobiology

Pharmacology and mode of action

unclear

Neurotransmitter Effects

Preclinical

Reduces ethanol-induced dopamine response in N. Acc.; promotes the release of taurine

Human

Glutamate level in anterior cingulate reduced (^{1}H-MRS)

Physiological

Preclinical

Reduces ethanol consumption and ethanol withdrawal in dependent animals

Human

Attenuates post-alcohol withdrawal hyperexcitability

Brain Circuits

Preclinical

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Human

Reduces cue-related cognitive interference in posterior cingulate cortex (fMRI)

AGOMELATINE

Brand Names: Valdoxan, Melitor, Thymanax, Alodil

Pharmacology
melatonin, serotonin

Mode of Action
agonist and antagonist

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety

Side Effects
Rare cases of transient elevation of hepatic enzymes

Practical Notes
No sexual dysfunction; may have a preferential action in decreasing anhedonia. Metabolized by CYP1A2 and levels are increased by some fluoroquinolones, like ciprofloxacine but not levofloxacin, whereas smoking by inducing CYP1A2 decreases agomelatine levels.
Recommended doses: 25 mg/day at bedtime; can be titrated to 50 mg after 2 weeks

Pregnancy
We did not locate adequate details on possible pregnancy effects of agomelatine.

Pharmacology and mode of action

receptor agonist (Mel1,Mel2), receptor antagonist (5-HT2B, 5-HT2C)

Neurotransmitter Effects

Preclinical

Antagonist at Mel1 and Mel2 receptors and 5-HT2B and 5-HT2C receptors.
increases extracellular dopamine

DA and norepinephrine NE in the rat prefrontal cortex and hippocampus;
no effect on DA in the N.Acc.

Human

—

Physiological

Preclinical

Increases DA transmission to dorsal raphe 5-HT neurons; increases 5-HT neuronal firing and 5-HT1A transmission in hippocampus; reverses the decrease of neurogenesis produced by prenatal stress; resynchronisation of circadian rhythms; increases neuroplasticity; increases in BDNF, Arc, FGF-2; clock gene modulation

Human

Phase advance of circadian rhythms; no change in sleep architecture, in particular no increase in slow wave sleep as expected with 5-HT2 antagonists

Brain Circuits

Preclinical

Modifies suprachiasmatic nucleus function; increases DA activity in the mesolimbic and mesocortical pathways

Human

Prefrontal cortex, hippocampus, amygdala (fMRI)

A ALPRAZOLAM

Brand Names: Xanax, Alprazolam Intensol, Niravam

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Generalized anxiety disorder; Panic disorder; Short-term treatment of anxiety; Alcohol withdrawal (France)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only a few. They all act in the same way and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 8-15 hours and it is metabolized by the cytochrome 3A4. Inhibitors of 3A4, like fluoxetine, erythromycin, ketoconazole, but also oral contraceptives, reduce its clearance. The herb kava will robustly reduce its clearance, whereas St John's Wort will increase it. Synergistic effects with alcohol can produce severe sedation, behavioural changes, and intoxication, and with opiates fatal respiratory depression may occur.
Recommended doses: 0.75-1.5 mg/day in 2-3 divided doses up to a dose of 4 mg/day. Must not be discontinued abruptly.

Pregnancy
Experimental animal studies did not show an increase in birth defects except with very high dose level exposure. Human studies have given mixed results. Withdrawal symptoms may occur after pregnancy or lactation exposure to benzodiazepines

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; myorelaxant; anxiolytic; sedating; slows eye saccades; promotes sleep;

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

AMISULPRIDE

Brand Names: Amazeo, Amipride, Amival, Solian, Soltus, Sulpitac, Sulprix, Sulamid Paxiprid

Pharmacology
dopamine

Mode of Action
antagonist

Approved Indications
Schizophrenia (UK; France)

Efficacy
Improves of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Some evidence of beneficial effects of low-dose for dysthymia; excreted by kidney and does not alter lithium levels ; QTc increased at high doses; does not inhibit any cytochrome P450 enzymes. Half-life is about 12 hours.

Recommended doses: 400-800 mg/day in 2 doses with a maximum of 1,200 mg/day. In dysthymia, doses of 25-100 mg/day have been shown to be effective.

Pregnancy
Based on experimental animal studies, amisulpride therapy is not anticipated to increase the risk of congenital anomalies. There are no human pregnancy data.

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

antagonist at D2 and D3, 5-HT7 receptors

Human

Blocks central dopamine D2 receptors. no significant binding of amisulpride to 5-HT2A receptors (PET)

Physiological

Preclinical

—

Human

Acute dose in healthy subjects led to sedation, cognitive slowing, decreased salivation, akathisia, headache.

Brain Circuits

Preclinical

—

Human

Moderate levels of D2/D3 receptor occupancy in striatum and significantly higher levels in thalamus and temporal cortex.

AMITRIPTYLINE

Brand Names: Elavil,Vanatrip

Pharmacology
serotonin, norepinephrine

Mode of Action
multimodal

Approved Indications
Major depressive disorder; chronic pain

Efficacy
Improves symptoms of depression and anxiety; Reduces chronic pain in low dose

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
At low doses (<50mg) is primarily an antagonist at H1 and 5-HT2 receptors. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine) , and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.
Recommended doses: 50 mg or less at bedtime for chronic pain, 150 mg for depression up to a dose of 300 mg/day, unless otherwise indicated by a plasma level determination.

Pregnancy
Amitriptyline can interfere with embryo development in experimental animals. Human studies have not confirmed an increase in birth defects at exposure levels used for treatment of depression.

Pharmacology and mode of action

reuptake inhibitor (SERT and NET), receptor antagonist (5-HT2)

Neurotransmitter Effects

Preclinical

Receptor antagonist at H1, 5-HT2, ACh M1-4, alpha-1 norepinephrine receptors

Human

—

Physiological

Preclinical

Increase in hippocampus Bcl-2

Human

Anti-muscarinic effects in healthy volunteers; suppresses REM sleep

Brain Circuits

Preclinical

Increases extracellular NE in frontal cortex and hypothalamus; increases extracellular dopamine in the N.Acc., hypothalamus, and frontal cortex; increases extracellular 5-HT levels in hypothalamus

Human

Reduces pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome (fMRI)

AMOXAPINE

Brand Names: Asendin, Asendis, Defanyl, Demolox, Moxadil

Pharmacology
norepinephrine, serotonin

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms in major depressive disorder and major depressive disorder with psychotic features or agitation

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; possibility of EPS; toxic (potentially lethal) in overdosage

Practical Notes
Metabolite of the antipsychotic loxapine, and is a D2 and 5-HT2 antagonist; there have been reports of risk of tardive dyskinesia and NMS. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine) , and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.
Recommended doses: 50 mg at bedtime and can be titrated gradually to 400 mg/day, up to a dose of 600 mg/day.

Pregnancy
Amoxapine did not increase congenital anomalies in experimental animal studies. There are no human data.

Pharmacology and mode of action

reuptake inhibitor (NET, SERT)

Neurotransmitter Effects

Preclinical

Also antagonist of D2, 5-HT2A, NE alpha-1, H1 receptors

Human

PET data shows :- occupies majority of 5-HT2A receptors at doses of 100 mg/day and above; D2 receptor occupancies show dose-dependent increase up to 80%; at all doses 5-HT2A occupancy exceeds D2 occupancy.

Physiological

Preclinical

—

Human

Increases prolactin; increases slow wave sleep

Brain Circuits

Preclinical

—

Human

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AMPHETAMINE (D) AND (D.L)

Brand Names: Adderall, Dexamfetamine, Evekeo, Dyanavel XR

Pharmacology
dopamine, norepinephrine

Mode of Action
multimodal

Approved Indications
Attention deficit hyperactivity disorder; Narcolepsy

Efficacy
Improves symptoms of attention deficit hyperactivity disorder and narcolepsy (reduces sleepiness and cataplectic attacks)

Side Effects
Weight loss, insomnia

Practical Notes
The (d) enantiomer alone is used more often; the (l) enantiomer has less effect on DAT and about equal effect on NET. Amphetamine is abusable because of its rapid effect and high site occupancy. It is metabolized by three pathways and has minimal pharmacokinetic drug-drug interactions. Drugs that reduce gastric acidity, proton pump inhibitors and H2 blockers, may increase the effects of amphetamine.
Recommended doses: immediate release preparation can be initiated at 10-20 mg given twice a day, with the second dose in the early afternoon so as not interfere with sleep, and titrated according to response and cardiovascular parameters. Slow release preparations can be given once daily in the morning.

Pregnancy
Studies in rats showed decreases in pup weight and litter size following prenatal amphetamine and methamphetamine exposure. Limited human data showed adverse effects on intrauterine growth, neonatal behavior, and central nervous system development, with possible effects on long-term neurodevelopment. These effects were associated with amphetamine abuse and might not apply to therapeutic use of these agents.

Pharmacology and mode of action

reuptake inhibitor (DAT, NET), releaser (DA, NE)

Neurotransmitter Effects

Preclinical

Increases brain DA and NE. Crosses cell membrane by mechanism independent of the transporter, interacts with vesicular monoamine transporter 2 (VMAT2), thereby displacing vesicular dopamine and causing the release of newly synthesized intraneuronal monoamine

Human

Occupies DAT (SPECT) and causes increase in dopamine in ventral striatum correlated with euphoria (PET)

Physiological

Preclinical

Increased locomotion, reduced sleep and appetite, sterotypy

Human

Increased BP and HR, elevated mood, reduced sleep (SWS and REM), reduced appetite

Brain Circuits

Preclinical

—

Human

Improves function of DLPFC in executive tasks

A ARIPIPRAZOLE

Brand Names: Abilify, Aristada

Pharmacology
Dopamine, serotonin

Mode of Action
partial agonist and antagonist

Approved Indications
Schizophrenia in adults and adolescents; Acute mania; Agitation in bipolar disorder and schizophrenia; Recurrence prevention in bipolar disorder; Irritability in autism (USA); Adjunctive in major depressive disorder (USA, Japan)

Efficacy
Improvement of psychotic symptoms and depressive symptoms

Side Effects
Agitation, anxiety, insomnia, akathisia. Weight gain and risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Used as adjunct in treatment resistant depression; depot available in many countries. Metabolized by CYP 2D6, but also 3A4 to a lesser extent. When used with full CYP 2D6 inhibitors (fluoxetine and paroxetine), dose should be decreased by about 50%. Half life is about 3 days.
Recommended doses: initial dose is 15 mg/day in the morning for schizophrenia and mania and titrated up to a dose of 30 mg/day. As adjunctive in depression, 2 mg/day is the starting dose with increases as needed to 5 and 10 mg/day at no less than 2-week intervals; in OCD 10-15 mg/day has been shown effective at fixed doses; lower doses may be used in tic disorder. Long-acting monthly dose is 400 mg/month with a 14-day overlap of an orally active dose of aripiprazole. Dose may be decreased to 300 mg/month in particular in slow metabolizers.

Pregnancy
In rats, aripiprazole caused diaphragmatic hernia at maternal dose levels 10 times the recommended human dose. There are case reports of use in human pregnancy without adverse consequences. There is limited information on breastfeeding. Aripiprazole, like other antipsychotics, might cause hyperprolactinemia, which is associated with galactorrhea, menstrual irregularities, and infertility, but it has also been reported to reverse antipsychotic-induced hyperprolactinemia.

Pharmacology and mode of action

receptor partial agonist (D2, 5-HT1A) receptor antagonist (5-HT2A)

Neurotransmitter Effects

Preclinical

Partial agonist at D2, D3 and 5-HT1A receptors; weak 5-HT2A receptor antagonist

Human

Occupies central D2 receptors (PET)

Physiological

Preclinical

—

Human

Nausea, akathisia

Brain Circuits

Preclinical

Decreased activation of entorhinal piriform cortex, perirhinal cortex, N.Acc. shell, and basolateral amygdala in rodent (MRI ASL)

Human

Increases striatal rCBF, decreases frontal rCBF as haloperidol, opposite effects to haloperiodol in temporal cortex and posterior cingulate (MRI, ASL)

ASENAPINE

Brand Names: Saphris, Sycrest

Pharmacology
serotonin, dopamine norepinephrine

Mode of Action
antagonist

Approved Indications
Mania, schizophrenia (USA, Canada, Australia)

Efficacy
Improvement of psychotic symptoms

Side Effects
Sedation, dizziness, weight gain, EPS, galactorrhea. Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Must be given sublingually and patient should not eat for 10 minutes after administration as it will decrease absorption. Only fluvoxamine can increase exposure (by 30%) to asenapine through inhibition of CYP 1A2 inhibition, whereas smoking will not induce asenapine elimination.
Recommended doses: 10-20 mg/day in one or two divided doses.

Pregnancy
Therapy with asenapine did not increase congenital malformations in rats and rabbits. Dose levels, limited by maternal toxicity, were lower than human doses in rats. There are no human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (5-HT2, D2, NE alpha-2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, 5-HT6, 5-HT7, NE alpha and alpha-2 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

—

Human

—

Brain Circuits

Preclinical

—

Human

Striatum, PFC, pituitary

A ATOMOXETINE

Brand Names: Strattera

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor

Approved Indications
Attention deficit hyperactivity disorder in children >6y and adults

Efficacy
Reduces signs and symptoms of attention deficit hyperactivity disorder in adults and children

Side Effects
Headache, abdominal pain, decreased appetite, sedation

Practical Notes
As a potent norepinephrine reuptake inhibitor, atomoxetine may increase heart rate, much less so blood pressure, and these should be monitored. It is metabolized by cytochrome 2D6 and its level will be at least doubled by 2D6 inhibitors such as fluoxetine, paroxetine, and bupropion. Slow 2D6 metabolizers may have increased side effects and dose may be reduced accordingly. Atomoxetine may increase the effects of sympathomimetic drugs, like α- and β-adrenergic agonists.
Recommended doses: starting dose is 25-40 mg/day in the morning and increased to 60 and 80 mg/day, up to a dose of 100 mg/day, according to response and side effects, especially cardiovascular parameters.

Pregnancy
Based on experimental animal data, atomoxetine is not expected to cause birth defects at human therapeutic doses; however, in slow-metabolizers exposure to the fetus can be higher than in fast-metabolizers.

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Increases NE and DA in PFC

Human

—

Physiological

Preclinical

—

Human

Increase in BP and HR

Brain Circuits

Preclinical

Increases Fos-positive cells in rat PFC but not in N.Acc. or striatum

Human

Decreases rCBF in midbrain, substantia nigra, thalamus; increases rCBF in cerebellum

BACLOFEN

Brand Names: Lioresal, Lioresal Intrathecal, Kemstro, Gablofen

Pharmacology
GABA

Mode of Action
agonist

Approved Indications
Spasticity

Efficacy
Decreases alcohol craving in alcohol-dependent patients

Side Effects
Sedation, nausea

Practical Notes
High doses often required in alcohol dependence. Some evidence of effect in maintaining alcohol abstinence in particular in alcohol-dependent patients with liver cirrhosis. Baclofen has a 3-hour half-life and should be given frequently throughout the day. It is excreted unchanged by the kidneys, and therefore should be used with caution when there is severe renal impairment.
Recommended doses: 15 mg/day in 3 divided doses and can be titrated at intervals of several days generally up to a dose of 60 mg/day every several days according to side effects and response.

Pregnancy
Studies in rats showed an increase in congenital anomalies at baclofen dose levels considerably higher than those used in therapy. There are no controlled human data, although there are anecdotal reports of normal pregnancy outcome and of a withdrawal syndrome. Intrathecal baclofen might be preferred during pregnancy due to lower systemic exposures.

Pharmacology and mode of action

receptor agonist (GABA-B)

Neurotransmitter Effects

Preclinical

GABA-B receptor agonist. In rat, by inhibiting multivesicular release from the presynaptic terminal, decreases synaptic Glu signaling and inhibits Ca2+ permeability of NMDA receptors; suppresses alcohol-stimulated dopamine release in the shell of the nucleus accumbens

Human

Increases growth hormone

Physiological

Preclinical

Induces suppression of alcohol drinking (including relapse and binge-like drinking) and alcohol rewarding properties in rodents and monkeys. High dose reverses cognitive deficits produced by acute cocaine intoxication in primates; locally applied in dorsal hippocampus reverses ketamine-induced spatial memory deficits in mice

Human

May inhibit drug cue-induced motivational processing in cocaine addiction

Brain Circuits

Preclinical

—

Human

Alters drug cue reactivity in ventral striatum, ventral pallidum, amygdala, midbrain, and orbitofrontal cortex (fMRI)

B

BLONANSERIN

Brand Names: Lonasen

Pharmacology
dopamine, serotonin

Mode of Action
antagonist

Approved Indications
Schizophrenia (Japan)

Efficacy
Blonanserin has a half-life of 8 to 12 hours, food will decrease its absorption, and is produces little weight gain, possibly to its lack of H1 receptor affinity.

Side Effects
Sedation, dizziness, EPS, galactorrhea (low), weight gain (low). Risk of tardive dyskinesia, NMS

Practical Notes
Blonanserin has a half-life of 8 to 12 hours, food will decrease its absorption, and is produces little weight gain, possibly due to its lack of H1 receptor affinity. Can be titrated to 24 mg/day.
Recommended doses: 8-16 mg/day in two divided doses.

Pregnancy
No information

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D2, D3, 5-HT2A receptors

Human

Striatal D2 receptor occupancy by blonanserin ~ 60% at 8 mg, ~70% at 16 mg, and ~80% at 24 mg after ≥ 4 weeks' dosing in schizophrenia patients (11C raclopride PET)

Physiological

Preclinical

Ameliorates PCP-induced impairment of visual-recognition memory in mice

Human

—

Brain Circuits

Preclinical

Increases extracellular dopamine levels in the medial prefrontal cortex in mice

Human

—

BREXPIPRAZOLE

Brand Names: Rexulti

Pharmacology
dopamine, serotonin

Mode of Action
partial agonist and antagonist

Approved Indications
Schizophrenia; Treatment resistant depression as adjunct

Efficacy
—

Side Effects
Akathisia (less than aripiprazole) weight gain and risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Metabolized by CYP 2D6, but also 3A4 to a lesser extent. When used with full CYP 2D6 inhibitors (fluoxetine and paroxetine), dose should be decreased by about 25%. Half life is about 4 days.
Recommended doses: in schizophrenia, the starting dose is 1 mg/day in the morning for 4 days, then 2 mg/day for the next 2 days, up to 3-4 mg thereafter. In treatment-resistant depression, it can be initiated at 0.5-1 mg/day and titrated to 2 mg after 2-3 weeks according to response, up to a dose of 3 mg/day.

Pregnancy
Based on experimental animal studies, brexpiprazole therapy during pregnancy is not expected to increase congenital malformations.

Pharmacology and mode of action

receptor partial agonist (D2, 5-HT1A) receptor antagonist (5-HT2A)

Neurotransmitter Effects

Preclinical

Partial agonist at D2, 5HT1A receptors, antagonist at 5-HT2A receptors, alpha-1B/2C-adrenoceptors, D3, 5-HT7, 5-HT2B, alpha-1A and -1D adrenoceptors, H1 receptors. Low affinity for muscarinic acetylcholine receptors. Compared with aripiprazole, brexpiprazole has lower intrinsic activity at the D2 receptor

Human

—

Physiological

Preclinical

Acute administration of brexpiprazole does not alter the firing activity of ventral tegmental area dopamine neurons, unlike other partial dopamine receptor agonists. Prolonged administration attenuates the responsiveness of D2 autoreceptors in the ventral tegmental area. Acute administration inhibits the firing rate of 5-HT neurons by activating 5-HT1A autoreceptors. Sustained administration enhances the firing rate of norepinephrine neurons. Can ameliorate PCP-induced cognitive deficits in mice via 5-HT1A receptors

Human

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Brain Circuits

Preclinical

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Human

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BUPRENORPHINE

Brand Names: Cizdol, Subutex, Suboxone, Zubsolv, Bunavail, Temgesic, Buprenex, Norspan, Butrans, Belbuca

Pharmacology
opioid

Mode of Action
partial agonist

Approved Indications
opiate dependence (substitution therapy), pain management

Efficacy
—

Side Effects
Lethargy, insomnia, nausea, vomiting

Practical Notes
Not orally active, sublingual and patch preparations available. Buprenorphine/naloxone combination sublingual tablets approved for opioid dependence by FDA and EMA, buprenorphine alone in most countries. Doses for pain are much lower than those for substitution therapy. It is metabolized mainly by cytochrome 3A4 then glucuronidated and eliminated by the liver. Benzodiazepines and alcohol must be used with extreme caution with buprenorphine because of their potentially synergistic action in depressing the central nervous system.
Recommended doses: 8 mg for day 1, 12 or 16 mg on day 2, then increased daily by 4 mg/day increments up to a dose of 32 mg/day

Pregnancy
Based on experimental animal studies, buprenorphine exposure during pregnancy is not expected to increase the risk of adverse outcomes at birth but might produce later behavioral changes. As with other opioids, a neonatal abstinence syndrome can occur.

Pharmacology and mode of action

receptor partial agonist (μ), receptor antagonist (κ,d)

Neurotransmitter Effects

Preclinical

Partial agonist at μ opioid receptor, antagonist at κ, d.

Human

In buprenorphine-maintained heroin addicts, BUP significantly decreased whole-brain μ opioid receptor availability to 42, 81, and 85% at 2, 16, and 32 mg, respectively (measured with PET and [11C]carfentanil)

Physiological

Preclinical

—

Human

Blunts subjective and physiological (cortisol) responses to psychosocial stress in healthy volunteers.

Brain Circuits

Preclinical

Activates thalamus, striatum, frontal and cingulate cortices in monkey (fMRI)

Human

Buprenorphine-elicited BOLD responses in humans correspond to brain regions with abundant μ–opioid receptors and modulate brain functional connectivity ascribed to pain-processing circuitry

BUPROPION

Brand Names: Wellbutrin, Xyban, Buproban

Pharmacology
norepinephrine, dopamine

Mode of Action
multimodal

Approved Indications
Smoking cessation; Major depressive disorder (USA and Canada); Seasonal affective disorder (Canada)

Efficacy
improves symptoms of depression; smoking cessation; prevention of seasonal major depressive disorder

Side Effects
Agitation, dry mouth, constipation, insomnia; seizure risk at doses >450 mg/day

Practical Notes
Weight neutral; no sexual dysfunction; slow release formulations reduce the risk of seizures. Moderate inhibitor of CYP2D6. Metabolized by CYP2B6 and levels will be higher in such slow metabolizers (more frequent in Asian population, about 20%).
Recommended doses: initial dose can be 100 or 150 mg/day in the morning in slow (SR) or extended formulation (XL) and can be increased at no less than a one-week interval to 300 mg/day. The maximal dose is 450 mg/day, which can be given in one dose in its extended formulation and in no more than 300 mg in a single dose as SR.

Pregnancy
Bupropion has not been associated with an increase in congenital defects in experimental animal studies. Human studies have been inconsistent with respect to heart defects.

Pharmacology and mode of action

reuptake inhibitor (NET, DAT), releaser (NE, DA)

Neurotransmitter Effects

Preclinical

Occupies DAT in primate brain (PET); increases extracellular DA, NE, and 5-HT in rat hippocampus; increases extracellular DA and NE in frontal cortex, N.Acc., hypothalamus; repeated administration increases DA level in N.Acc. but not striatum

Human

Does not increase extracellular dopamine levels in striatum (PET); in vitro, moderate to low affinity for human DAT (520 nM); negligible affinity for human NET (52,000 nM)

Physiological

Preclinical

Desensitizes cell body NE alpha-2 and 5-HT1A autoreceptors and NE alpha-2 receptors on NE and 5-HT terminals; increases NE alpha-1 and alpha-2 transmission and 5-HT1A transmission in rat hippocampus

Human

After 2 wks administration in healthy volunteers, decreases subjective fatigue, delays sleep onset, increases resting diastolic BP and body temperature, and decreases body weight. No change in cognitive functions, appetite. Equivocal effects on REM sleep.

Brain Circuits

Preclinical

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Human

Increases BOLD signal in hippocampus, amygdala, and prefrontal cortex

BUSPIRONE

Brand Names: Buspar, Vanspar

Pharmacology
serotonin

Mode of Action
partial agonist

Approved Indications
Generalized anxiety disorder; Short-term relief of anxiety

Efficacy
Reduces anxiety and tension

Side Effects
Dizziness, headache, somnolence

Practical Notes
Used as augmentation in treatment resistant depression, may partially offset SSRI-induced sexual dysfunction. Buspirone is absorbed within an hour and has a half-life of about 3 hours. It is metabolized by cytochrome 3A4 and inhibitors of the isoenzyme like erythromycin, ketoconazole, fluoxetine and grapefruit juice will increase plasma levels, whereas inducers like carbamazepine will decrease its levels.
Recommended doses: initial dose is 10-15 mg/day in 2-3 divided doses which can be increased by 5 mg increments every few days up to a dose of 60 mg/day, according to response and side effects.

Pregnancy
Based on experimental animal studies, buspirone is not anticipated to increase the risk of congenital anomalies. There are no controlled human data.

Pharmacology and mode of action

receptor partial agonist (5-HT1A)

Neurotransmitter Effects

Preclinical

Binds to 5-HT1A, D2 and D3 receptors, increases DA and NE release in rat FC, decreases 5-HT turnover in striatum

Human

Binds to 5-HT1A receptors in post-mortem human brain; has downstream effects on DA

Physiological

Preclinical

Lowers temperature, decreases physiological reactivity to aversive stimuli; reduces conflict behaviour in rat.

Human

Lowers body temperature, antagonises L-dopa-induced dyskinesia and SSRI-induced bruxism, delays REM sleep

Brain Circuits

Preclinical

After microinjection into DRN, hippocampus and amygdala, inhibits shock-induced vocalization in rats

Human

—

CARBAMAZEPINE, OXCARBAZEPINE

C

Brand Names: Tegretol,Carbatrol, Epitol

Pharmacology
glutamate

Mode of Action
channel blocker

Approved Indications
Bipolar disorder (not USA); Epilepsy

Efficacy
Anti-manic; Anti-epilepsy; Reduces neuropathic pain

Side Effects
Dizziness, somnolence

Practical Notes
Acts on subtypes of ion channels, specific relevance as yet unclear. Stevens-Johnson Syndrome and toxic epidermal necrolysis are dangerous cutaneous reactions occasionally associated with carbamazepine. Benign skin rashes relatively common. Inducer of wide range of cytochrome P450 enzymes so can change levels of co-medications. Oxcarbazepine is a derivative of carbamazepine with less impact on liver enzymes, otherwise same actions and risks as carbamazepine. Despite concern about its use in women of child bearing potential, less risky than valproate (foetal malformations).
Recommended doses: initial dose is 200 mg twice daily titrated weekly by 200 mg/day increments up to a dose of 1,200 mg/day. Oxcarbazepine can be initiated at 300 mg twice a day and increased by 150-300 mg/day increments up to a dose of 1,200 mg/day.

Pregnancy
Carbamazepine use during early pregnancy has been associated with an increased risk of neural tube defects. Craniofacial abnormalities and developmental delay have been associated in some but not all studies with use of carbamazepine in pregnancy. In spite of these risks, optimum seizure control is important in pregnancy. Treatment of pregnant women near term with vitamin K has been recommended to prevent a carbamazepine-associated bleeding disorder in the neonate, although evidence for this recommendation has been characterized as limited. Breastfeeding is not contraindicated during carbamazepine therapy. Enrollment of pregnant women in an anticonvulsant registry is encouraged (information listed below).

Neurobiology

Pharmacology and mode of action

voltage-gated sodium and calcium channel blocker

Neurotransmitter Effects

Preclinical

Blockade of sodiumchannels by stabilizing fast-inactivated state, modulator of intracellular signalling cascades (multiple); inhibits adenylyl-cyclase

Human

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Physiological

Preclinical

Anti-epilepsy; inositol depletion; decreased brain cAMP; binding site known (central part of alpha section of sodium channel)

Human

Reduces neuropathic pain, increases slow wave sleep

Brain Circuits

Preclinical

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Human

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CARIPRAZINE

Brand Names: Vraylar

Pharmacology
dopamine, serotonin

Mode of Action
partial agonist and antagonist

Approved Indications
Schizophrenia; Bipolar disorder

Efficacy
In clinical trials for bipolar depression and for treatment-resistant unipolar depression

Side Effects
EPS, akathisia, insomnia. Risk of tardive dyskinesia, NMS

Practical Notes
D3 partial agonist properties show higher affinity than D2 partial agonist properties, and may be physiologically relevant because cariprazine is the only marketed D2 antagonist or partial agonist with D3 affinity lower than that of dopamine itself, so may lead to unique partial agonist actions at D3 receptors, but the clinical effects of this are unknown. An equally active metabolite has a one-week half-life. Metabolized by CYP 3A4, therefore precautions are required with CYP 3A4 inhibitors and inducers.

Recommended doses: In both schizophrenia and bipolar I mania, 1.5 mg on day 1, can be increased to 3 mg on day 2, and by 1.5 to 3 mg steps according to response up to a dose of 6 mg/day.

Pregnancy
Cariprazine interfered with embryo development and viability in rats. We did not locate human data.

Pharmacology and mode of action

receptor partial agonist (D2, 5-HT1A), receptor antagonist (5-HT2B)

Neurotransmitter Effects

Preclinical

In primates, occupies D2/D3 receptors in a dose-dependent and saturable manner, with 1–5 µg/kg occupying ~5% of receptors and 30–300 µg/kg showing more than 90% occupancy. 5-HT1A receptor occupancy was lower, with a maximal value of ~30% for the raphe nuclei. ([11C]MNPA, [11C] raclopride, 11C] WAY-100635 PET)

Human

Demonstrates approximately 10-fold higher affinity for human D3 versus human D2L and human D2S receptors, high affinity at human 5-HT type 2B receptors (pKi 9.24) with pure antagonism, lower affinity at human 5-HT1A and 5-HT2A receptors

Physiological

Preclinical

No catalepsy in rodent models. Overcomes PCP-induced deficits in cognition and social behavior in a thoroughly validated rat model in tests representing specific symptom domains in schizophrenia patients.

Human

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Brain Circuits

Preclinical

—

Human

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CHLORAL HYDRATE, CHLORAL BETAINE

C

Brand Names: Welldorm, Somnote

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Not approved by EMA or FDA but used widely worldwide for night sedation

Efficacy
Intractable status epilepticus

Side Effects
Sedation, gastric irritation. Toxic in overdose

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life of parent compound 6-28 hours Half-life of active metabolite desmethyldiazepam 36-96 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 3-4 doses/day of 5-25 mg as required.

Pregnancy
Based on experimental animal studies and human experience, chloral hydrate is not anticipated to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

positive allosteric modulator (GABA-A receptor, alcohol site)

Neurotransmitter Effects

Preclinical

Potentiates GABAergic transmission. Effects not reversed by flumazenil

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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CHLORDIAZEPOXIDE

Brand Names: Librium, Libritabs, Poxi, Mitran

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Anxiety; Alcohol withdrawal (UK); Anxiety in GI disorders (Canada; France)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life of parent compound 6-28 hours Half-life of active metabolite desmethyldiazepam 36-96 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: 3-4 doses/day of 5-25 mg as required.

Pregnancy
Chlordiazepoxide use during pregnancy has been associated in experimental animal and human reports with an increased risk of congenital malformations, but the lack of consistency of the malformations in the human reports detracts from the credibility of a causal association. This and other benzodiazepines have been associated with transient neonatal complications. There is more experience during pregnancy with lorazepam, alprazolam, clonazepam and diazepam.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; myorelaxant; anxiolytic; slows eye saccades; promotes sleep;

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

CHLORPROMAZINE

Brand Names: Largactil, Thorazine

Pharmacology
dopamine, serotonin

Mode of Action
antagonist

Approved Indications
Schizophrenia; Mania; Acute agitation. Also porphyria; tetanus; nausea and vomiting; hiccups; behavioural problems in children.

Efficacy
Improvement of psychotic symptoms; mania

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Metabolized by cytochromes 2D6 and 1A2 and is a moderate inhibitor of the 2D6. Therefore, its levels will be increased by 1A2 inhibitors like fluvoxamine and ciprofloxacine, but not markedly altered by smoking. Also chlorpromazine will increase levels of 2D6 substrates, like propranolol, and will decrease the production of the active metabolites of codeine and tamoxifen, through 2D6 inhibition.
Recommended doses: for nausea, vomiting or hiccups 12.5-25 mg every 4-6 hours with a maximum of 150 mg/day; for acute psychosis 300-1,000 mg in 2-4 divided doses according to response with an usual maintenance dose of 300-600 mg/day in one or two divided doses. If used intra-muscularly, it should be initiated at 25 mg and 25-50 mg repeated every hour until patient is controlled.

Pregnancy
Chlorpromazine can cause abnormal embryo development in rodents. Human experience has not shown an increase in malformation risk, although transient neonatal complications including extrapyramidal symptoms might occur following 3rd trimester exposure to this agent.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha-1, H1, ACh M1-4 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

—

Human

Sedative and anticholinergic effects. Increases slow wave sleep

Brain Circuits

Preclinical

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Human

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CITALOPRAM

Brand Names: Celexa, Cipramil

Pharmacology
serotonin

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder; Panic disorder; Generalized anxiety disorder; Social anxiety disorder; Obsessive compulsive disorder

Efficacy
Improves symptoms of depression

Side Effects
GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation

Practical Notes
Possibility of dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be done when using high doses. Metabolized by CYP2C19. Should not be used with tamoxifen because of small inhibitory effect on CYP2D6, which transforms tamoxifen into its active metabolite (endoxifen). Dose of 40 mg/day will approximately double CYP2D6 substrate levels (desipramine, metoprolol).

Recommended doses: 20 mg with food is the starting dose with doubling of the dose after one or more weeks. Doses above 40 mg should be monitored with an EKG.

Pregnancy
Based on experimental animal studies and human reports, therapeutic use of citalopram or escitalopram is not expected to increase the risk of congenital anomalies. Use of serotonin reuptake inhibitors late in pregnancy can be associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, and gastrointestinal signs.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas; reduces 5-HT1A mRNA in the raphe of stressed rats, decreases tryptophan hydroxylase 2 in the raphe; increase in hippocampus Bcl-2

Human

Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Physiological

Preclinical

—

Human

Decreased REM sleep, increased REM latency; decrease of task-negative reactivity; decreased reactivity to hedonic stimulus (fMRI)

Brain Circuits

Preclinical

Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)

Human

Decreased activity in anterior cingulate cortex, most frontal and parietal areas

CLOMETHIAZOLE

Brand Names: Heminevrin, Nevrin, Distraneurin

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
(UK, Germany) Restlessness and agitation in elderly patients; Insomnia; alcohol withdrawal

Efficacy

Side Effects
Sedation, nasal congestion and irritation. Toxicity in overdose similar to barbiturates

Practical Notes
Liquid form commonly used. Abuse liability, fast tolerance to effects.
Recommended doses: 192 or 384 mg of the base at bedtime for sedation; 9-12 capsules of 192 mg per day in divided doses or alcohol withdrawal on the first day to be reduced in the next 5 days, and not to be used for more than 9 days.

Pregnancy
There is no evidence of safety in human pregnancy, nor is there evidence from animal studies that it is entirely free from hazard.

Pharmacology and mode of action

positive allosteric modulator (GABA-A receptor, barbiturate site)

Neurotransmitter Effects

Preclinical

Positive allosteric modulator at GABA-A receptor; directly activates GABA-A currents in alpha1/beta1/gamma2- and alpha1/beta2/gamma2-containing cells. Low concentration potentiates the action of GABA in both cell types, equivalent to a 3-fold increase in potency and up to 1.8-fold increase in maximal current; actions similar to barbiturates

Human

—

Physiological

Preclinical

—

Human

Suppresses REM sleep with long-duration rebound after withdrawal.

Brain Circuits

Preclinical

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Human

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CLOMIPRAMINE

Brand Names: Anafranil

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder; Obsessive compulsive disorder; Panic disorder; Cataplexy in narcolepsy

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts.

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers. Demethylated to a potent NET inhibitor by CYP1A2. Plasma levels will be increased by inhibitors like fluvoxamine, especially in favour of the serotonin inhibiting potency of clomipramine. Half-life is 24 hours, 96 hours for norclomipramine, which is a preferential norepinephrine reuptake inhibitor.

Recommended doses: Initial dose is 25 mg at bedtime and increased by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects, response, or plasma level determination when available. Higher doses may be required in OCD than in depression.

Pregnancy
A single study group associated clomipramine use during pregnancy with an increase in congenital heart defects, mostly septal defects. Clomipramine, like other tricyclic and serotonergic antidepressants, has been associated with transient neonatal complications.

Pharmacology and mode of action

reuptake inhibitor (SERT, NET (metabolite))

Neurotransmitter Effects

Preclinical

Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in N.Acc.; antagonist at H1, ACh M1-M4, NE alpha-1 receptors

Human

Reduced platelet 5-HT content; attenuated tyramine pressor response (NE reuptake inhibition)

Physiological

Preclinical

Prevents stress-induced decreased expression of membrane glycoprotein 6a, CDC-like kinase 1, G protein alpha q in the hippocampus

Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

Reduced rat brain activity in brain regions innervated by 5-HT; reverses inhibition of cell proliferation produced by chronic unpredictable stress in hippocampus

Human

Decreased blood flow in some regions of the thalamus; decreased activity in amygdala to negative valence stimuli; decreased activity to negative and positive valence in anterior cingulate and insula

CLONAZEPAM

Brand Names: Rivotril, Klonopin

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Epilepsy; Panic disorder (USA)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 19-60 hours. It is mainly metabolized by the 3A4 cytochrome and its inhibitors, like erythromycin, clarithromycin, and grapefruit juice will increase the action of clonazepam, as well as alcohol as is the case with all benzodiazepine receptor agonists.
Recommended doses: 0.25-0.5 mg twice a day and increase by 0.5 mg every 3 days as necessary, up to a dose of 4 mg/day.

Pregnancy
Based on experimental animal studies and human pregnancy experience, clonazepam therapy is not anticipated to increase the risk of congenital malformations. The risk of mild transient neonatal complications might be increased when this drug is used in combination with serotonin reuptake inhibitors.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; anxiolytic; slows eye saccades; promotes sleep

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

CLONIDINE

Brand Names: Catapres, Kapvay

Pharmacology
norepinephrine

Mode of Action
agonist

Approved Indications
Attention deficit hyperactivity disorder in children >6y (US only); Hypertension; Cancer pain; Migraine (though at different doses)

Efficacy
Reduces signs and symptoms of attention deficit hyperactivity disorder in adults and children. Menopausal flushing

Side Effects
Hypotension, somnolence, fatigue

Practical Notes
May be useful in REM behaviour disorder. It can be used to treat menopausal flushing at a low dose of 0.05 mg twice daily, which will not lower blood pressure extensively. Skin patch available.
Recommended doses: for menopausal flushing 0.05 twice a day and 0.075 to 0.1 mg daily for migraine prophylaxis; in ADHD 0.1 mg at bedtime initially followed by 0.1 mg twice a day with a usual target dose of 0.4 mg/day with monitoring blood pressure. In opiate withdrawal, 0.1 mg up to three times a day while monitoring blood pressure. It must be discontinued gradually to avoid rebound hypertension.

Pregnancy
Based on experimental animal studies, clonidine use during pregnancy is not expected to increase the risk of structural malformations. Effects of pregnancy exposure on offspring behavior have been suspected based on human experience and experimental animal studies. Alternative anti-hypertensive agents may be preferred during

Neurobiology

Pharmacology and mode of action

receptor agonist (alpha-2 NE)

Neurotransmitter Effects

Preclinical

Decreases brain norepinephrine release by agonism of alpha-2 norepinephrine autoreceptors

Human

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Physiological

Preclinical

Improves attention, working memory performance and premature responding in rats and monkeys (post-synaptic effects)

Human

Sedation, decreased BP, hypothermia, inconsistent effects on attention, suppresses REM sleep

Brain Circuits

Preclinical

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Human

Thalamic actions noted on fMRI

CLORAZEPATE

Brand Names: Tranxene

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Short-term symptomatic relief of anxiety (Canada, France, Japan); Alcohol withdrawal (Canada, France)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only a few. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 36-96 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: 7.5-15 mg twice to four times a day and increased gradually according to response up to a dose of 90 mg/day; a single bedtime dose of up to 30 mg may be useful given the long half-life.

Pregnancy
Based on experimental animal studies, clorazepate is not anticipated to increase the risk of congenital anomalies. There are no controlled human data. Clorazepate and diazepam have a common metabolite and pregnancy effects of diazepam might be relevant to clorazepate.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; myorelaxant; anxiolytic; slows eye saccades; promotes sleep. Immediately metabolised to oxazepam and desmethyldiazepam

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

CLOZAPINE

Brand Names: Clozaril, Fazaclo, Leponex

Pharmacology
dopamine, serotonin, norepinephrine

Mode of Action
antagonist

Approved Indications
Treatment resistant schizophrenia (USA, Europe); Reduction of suicide risk in psychosis (USA); Treatment of psychosis in Parkinson's disease (Europe)

Efficacy
Improvement of psychotic symptoms

Side Effects
Sedation, dizziness, weight gain, EPS (low), galactorrhea (low). Risk of tardive dyskinesia (low), NMS. Risk of agranulocytosis, monitoring required. Risk of diabetes, monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients.

Practical Notes
Clozapine has a half-life of 14 hours. It is metabolized by the 1A2 cytochrome. Inhibitors of this isoenzyme, like ciprofloxacine and fluvoxamine, will increase its plasma levels about three fold, whereas smoking will decrease its levels approximately by half (by only 20% in women), therefore requiring proportional dose adjustment. Carbamazepine will decrease clozapine levels but increase the risk of agranulocytosis.

Recommended doses: 12.5 mg once or twice on day 1 and increased by 25 or 50 mg each day reaching a dose of 300-450 mg/day by the end of week 2. Doses above 300 mg should be divided. Increments of no more than 100 mg/day per week can be implemented up to a dose of 900 mg/day.

Pregnancy
Based on experimental animal studies, clozapine is not expected to increase the risk of congenital anomalies. Reports on use during human pregnancy have not suggested an increase in the risk of birth defects.

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2, NE alpha-2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha1 and alpha-2, H1, ACh M1-4 receptors

Human

Blocks central dopamine D2 receptors (PET). NE alpha-2 receptor action may be relevant. Possible ion channel action via 5-HT3 receptor antagonism.

Physiological

Preclinical

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Human

Sedative and anticholinergic effects

Brain Circuits

Preclinical

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Human

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CYAMEMAZINE

Brand Names: Tercian

Pharmacology
dopamine, serotonin

Mode of Action
antagonist

Approved Indications
schizophrenia, anxiety, adjunct in depression (France, Portugal)

Efficacy

Side Effects
EPS, dyskinesia, raised prolactin, sedation. Risk of tardive kinesia, risk of NMS.

Practical Notes
Low doses useful for anxiety symptoms. It is metabolized by several P450 enzymes and not susceptible to drug-drug interactions. Half-life is 10 hours.

Recommended doses: for anxiety usual dose is 25-100 mg at bedtime; for psychosis, 50-300 mg in 2 or 3 doses up to a daily dose of 600 mg.

Pregnancy
No information

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at these receptors in order of affinity: 5-HT2A, NE alpha-1, D4, D2, H1, 5-HT2C, M1, 5-HT7, 5-HT3 . Anxiolytic in models of anxiety in rodents, blocked by 5-HT2C receptor antagonists. Active metabolite desmethylcyamemazine antagonises these receptors in order of affinity

Human

PET in human brain: Much higher affinity for 5-HT2A receptors compared with dopamine D2 receptors (PET) Metabolite N-desmethyl cyamemazine blocks D2 > 5-HT2A receptors

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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DESIPRAMINE

Brand Names: Norpramin

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
Is an active metabolite of imipramine. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 25-50 mg at bedtime and increase by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects, response, or plasma level determination when available, up to a dose of 300 mg/day.

Pregnancy
Based on experimental animal studies and human experience with imipramine (#1108), desipramine is not expected to increase the risk of congenital malformations.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Enhances extracellular levels of NE; weak antagonist at H1, ACh M1-4, alpha-1 norepinephrine receptors

Human

Inhibits the tyramine pressor response (NE reuptake inhibition)

Physiological

Preclinical

Increases mRNA of BDNF, calcium calmodulin-dependent protein kinases; decreases TNF

Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

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Human

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DESVENLAFAXINE

Brand Names: Pristiq, Khedezla

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder (USA, Canada, Australia)

Efficacy
Improves symptoms of depression

Side Effects
GI symptoms, headache, dizziness, insomnia, fatigue, sexual dysfunction. May increase BP at higher doses. Must be gradually decreased on discontinuation

Practical Notes
Doses of 100mg/day are needed to inhibit NET. Active metabolite of venlafaxine. Excreted by kidney. Does not inhibit any CYP enzymes. **Recommended doses:** 50 mg in the morning with food and can be increased to 100 mg after two weeks. Dose may be increased at two-week intervals according to therapeutic effects and cardiovascular parameters. The maximal dose studied is 400 mg/day.

Pregnancy
Based on experimental animal studies and limited human reports, venlafaxine and its active metabolite desmethylvenlafaxine are not anticipated to increase the risk of congenital anomalies. Transient and usually mild neonatal complications have been reported for venlafaxine and other serotonergic antidepressants.

Pharmacology and mode of action

reuptake inhibitor (SERT and NET)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in hypothalamus
Pharmacology and mode of action: reuptake inhibitor (SERT and NET)

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

Alters activity of brain structures innervated by 5-HT and NE neurons

Human

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DIAZEPAM

Brand Names: Valium, Diastat

Pharmacology
GABA

Mode of Action
PAM

Approved Indications
Anxiety-particularly generalized anxiety disorder; Muscle spasms; Alcohol withdrawal; Status epilepticus

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 20-70 hours, active metabolite desmethyldiazepam 36-96 hours. It is metabolized into desmethyldiazepam and oxazepam. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: in anxiety 2-10 mg/day 2-4 times a day; in alcohol withdrawal 10 mg 2-4 times a day for the first day and then decrease dose as required.

Pregnancy
Diazepam increases the incidence of cleft palate in mice. Most human studies do not show an increase in cleft palate or other defects in babies exposed during pregnancy. A neonatal withdrawal syndrome has been described. It might be preferable to use benzodiazepines that are less likely to accumulate in the fetus and infant such as lorazepam or clonazepam.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; myorelaxant; anxiolytic; slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

DIPHENHYDRAMINE

Brand Names: Benadryl, Dimedrol, Daedalon, Nytol, Banophen

Pharmacology
histamine

Mode of Action
antagonist

Approved Indications
Allergy

Efficacy
OTC use in insomnia

Side Effects
Sedation, dry mouth, tachycardia, toxic in overdose

Practical Notes
It is a potent anticholinergic agent, which explains its action as an antiparkisonian agent. Its elimination half-life increases with age: in children it is about 5 hours, 9 in adults, and 14 in the elderly. Diphenhydramine is a moderate inhibitor of cytochrome 2D6 and can double the plasma levels of co-administered substrates, like metoprolol and propafenone. This interaction is greater in women even after correcting for weight. Alcohol can increase its drowsiness effect. It has significant abuse potential and its abrupt discontinuation after prolonged use can produce withdrawal symptoms.
Recommended doses: 25-50 mg at bedtime for insomnia; for allergies can be dosed up to 100 mg (severe).

Pregnancy
Based on experimental animal studies and at least 1 human study, diphenhydramine is not expected to increase the risk of congenital anomalies. A hypothesis-generating human study has suggested associations between diphenhydramine use and a number of abnormalities. A case of apparent neonatal withdrawal has been reported after later pregnancy exposure to this drug.

Neurobiology

Pharmacology and mode of action

receptor antagonist (H1)

Neurotransmitter Effects

Preclinical

Antagonist at histamine H1 receptors and potent anti muscarinic (ACh M1-4 antagonist)

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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DISULFIRAM

Brand Names: Antabuse

Pharmacology
alcohol

Mode of Action
enzyme inhibitor

Approved Indications
Alcohol dependence

Efficacy
—

Side Effects
Headaches, fatigue, sleepiness, anxiety. Peripheral neuropathy (rare)

Practical Notes
Being tested for cocaine dependence. Can markedly increase the levels of phenytoin. It increases prothrombin time in patients taking oral anticoagulants.
Recommended doses: 250-500 mg/day.

Pregnancy
In experimental animals, administration of disulfiram with ethanol #1290 potentiated the embryotoxic effects of ethanol. It is not clear whether the same potentiation occurs in humans. There are case reports of normal and abnormal pregnancy outcome in humans exposed to disulfiram with and without exposure to ethanol.

Neurobiology

Pharmacology and mode of action

enzyme inhibitor

Neurotransmitter Effects

Preclinical

Inhibits dopamine-beta-hydroxylase and so increases brain dopamine levels in rat

Human

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Physiological

Preclinical

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Human

Inhibits acetaldehyde dehydrogenase, acetaldehyde build-up after drinking alcohol causes unpleasant effects.

Brain Circuits

Preclinical

—

Human

—

DONEPEZIL

Brand Names: Aricept

Pharmacology
acetylcholine

Mode of Action
enzyme inhibitor

Approved Indications
Mild, moderate and severe Alzheimer's disease

Efficacy
Improves or slows worsening of dementia symptoms

Side Effects
Bradycardia, nausea, diarrhoea, anorexia, abdominal pain, muscle cramps, sleep disturbance

Practical Notes
Minimal drug-drug pharmacokinetic interactions, apart from possible increased elimination by carbamazepine, phenytoin, and rifampin. Strong CYP2D6 inhibitors (fluoxetine, paroxetine)can increase plasma levels of dovepezil, therefore requiring proportional dose adjustment.
Recommended doses: 5 mg/day at any time and may be increased to 10 mg after 4-6 weeks according to side effects and response

Pregnancy
Based on experimental animal studies, donepezil use during pregnancy is not expected to increase the risk of congenital malformations. We did not locate human data.

Neurobiology

Pharmacology and mode of action

enzyme inhibitor (acetylcholinesterase)

Neurotransmitter Effects

Preclinical

Increases extracellular ACh in all brain regions

Human

—

Physiological

Preclinical

Increases attention in a mouse model of Alzheimers disease. Increases REM sleep

Human

Increases REM sleep and post-sleep memory consolidation

Brain Circuits

Preclinical

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Human

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DOSULEPIN

Brand Names: Prothiaden, Dothep, Thaden, Dopress

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
Not available USA. Available in some individual countries in Europe, the Far East and Africa. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 25-50 mg at bedtime and increase by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects and response up to a dose of 225 mg/day.

Pregnancy
Based on experimental animal data reviewed in a secondary source, dothiepin therapy during pregnancy is not expected to increase the risk of congenital malformations. There is a human case report of abnormal pregnancy outcome as well as other reports of normal outcome following dothiepin therapy.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (SERT and NET)

Neurotransmitter Effects

Preclinical

Inhibits uptake of SERT and NET. Antagonist at H1, ACh M1-4, NE alpha-1 receptors

Human

—

Physiological

Preclinical

—

Human

Suppresses REM sleep

Brain Circuits

Preclinical

—

Human

—

DOXEPIN

Brand Names: Deptran, Sinequan, Silenor

Pharmacology
norepinephrine, serotonin

Mode of Action
multimodal

Approved Indications
Major depressive disorder; insomnia in USA

Efficacy
Improves symptoms of depression

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: For insomnia, very low doses (3 and 6 mg). For depression, 25-50 mg at bedtime and increase by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects and response, up to a dose of 300 mg/day.

Pregnancy
Based on experimental animal data and a few human reports, doxepin is not expected to increase the risk of congenital malformations.

Pharmacology and mode of action

reuptake inhibitor (NET, SERT), receptor antagonist (5-HT2)

Neurotransmitter Effects

Preclinical

Inhibits uptake of SERT and NET. Antagonist at H1 (very potent), ACh M1-4, 5-HT2, NE alpha-1 receptors

Human

Very potent H1 inhibitor

Physiological

Preclinical

—

Human

Increases sleep quality and efficiency at low dose; suppresses REM sleep at antidepressant doses

Brain Circuits

Preclinical

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Human

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DULOXETINE

Brand Names: Cymbalta, Irenka

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor (SERT and NET)

Approved Indications
Major depressive disorder; Generalized anxiety disorder; Diabetic peripheral neuropathic pain; Chronic musculoskeletal pain; Fibromyalgia (Canada)

Efficacy
Improves symptoms of depression and anxiety

Side Effects
Nausea, somnolence, insomnia, dizziness, sexual dysfunction. Must be gradually decreased for discontinuation

Practical Notes
Doses of 120 mg/day are needed to inhibit NET. Moderate inhibitor of CYP2D6. Metabolized by CYP1A2 and levels are increased by some fluoroquinolones, like ciprofloxacine but not levofloxacin, whereas smoking, by inducing CYP1A2, decreases duloxetine levels by 30%.
Recommended doses: 30-60 mg with food and may be increased as tolerated according to side effects and response by 30 mg increments at two-week intervals up to a dose of 120 mg/day in one dose.

Pregnancy
Based on experimental animal studies and limited human reports, duloxetine exposure is not anticipated to increase the risk of congenital anomalies. Warnings about possible adverse neonatal effects are based on case reports and experience with other serotonin and serotonin-norepinephrine reuptake inhibitors.

Pharmacology and mode of action

reuptake inhibitor (SERT and NET)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas.

Human

Decreases 5-HT platelet content

Physiological

Preclinical

Normalization of 5-HT neuron firing activity. Increase in mRNA of neurotrophins (BDNF, Bcl-2, Bcl-xL, FGF-2, NT-3), Arc, and decrease of pro-apoptotic proteins (Bax, p53, Bad)

Human

Decrease in tyramine pressor response at 120 mg/day (NET inhibition). Suppresses REM sleep.

Brain Circuits

Preclinical

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Human

Decreases emotional memory formation; increases amygdala activity for memory retrieval of mood-incongruent ítems; enhances ventral striatal activity in response to incentive processing

ESCITALOPRAM

Brand Names: Cipralex, Lexapro

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT)

Approved Indications
Major depressive disorder; Panic disorder; Generalized anxiety disorder; Social anxiety disorder; Obsessive compulsive disorder

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts

Side Effects
GI symptoms, anxiety and/or changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation

Practical Notes
Possibility of dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be should be done when using high doses. Active enantiomer of citalopram. Metabolized by CYP2C19. Should not be used at doses higher than 10mg/day with tamoxifen because of small inhibitory effect on CYP2D6, which transforms tamoxifen into its active metabolite. Dose of 20mg/day will approximately double CYP2D6 substrate levels (desipramine, metoprolol). **Recommended doses:** 10 mg with food is the starting dose with doubling of the dose after one or more weeks. Doses above 30 mg should be monitored with a EKG. Doses of 40 mg/day have been used in depression and OCD.

Pregnancy
Based on experimental animal studies and human reports, therapeutic use of citalopram or escitalopram is not expected to increase the risk of congenital anomalies. Use of serotonin reuptake inhibitors late in pregnancy can be associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, and gastrointestinal signs.

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas

Human

Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors

Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)

Human

Somewhat greater effects on decreased activity in anterior cingulate cortex, most frontal and parietal areas than citalopram

ESTAZOLAM

Brand Names: Eurodin, ProSom

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way,
and are distinguished only by pharmacokinetics unless otherwise indicated.
Half-life 20-30 hr. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: 1 mg at bedtime and may be increased to 2 mg as required.

Pregnancy
We have not located studies on pregnancy effects of estazolam.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep

Human

Anxiolytic, sleep promoting.

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

ESZOPICLONE

Brand Names: Lunesta

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 5.5-7 hours. May be selective for alpha-2 and alpha-3 subtypes of GABA-A receptor, relevant to anxiolysis. It is mainly metabolized by the 3A4 cytochrome and its inhibitors, like erythromycine, clarithromycine, fluoxetine and grapefruit juice, will increase the action of clonazepam. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: 1-3 mg at bedtime.

Pregnancy
Based on experimental animal studies and limited human experience, zopiclone or eszopiclone exposure during early pregnancy is not expected to increase the risk of congenital abnormalities. Use of more widely-studied sedative hypnotics during pregnancy might be preferable.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

—

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy

Human

Anxiolytic, sleep promoting.

Brain Circuits

Preclinical

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Human

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FLIBANSERIN

Brand Names: Addyi

Pharmacology
serotonin

Mode of Action
receptor agonist (5-HT1A), receptor antagonist (5-HT2A)

Approved Indications
Acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women.

Efficacy

Side Effects
Dizziness, nausea, fatigue, sleepiness, trouble sleeping. Risk of hypotension when taken with alcohol.

Practical Notes
The medication should be taken at bedtime, as used in the controlled trials, to minimize side effects. Flibanserin is mainly metabolized by the CYP 450 3A4 cytochrome, but also the 2C19. Inhibitors of 3A4 should be avoided.

Recommended doses: 100 mg at bedtime.

Pregnancy
Based on experimental animal studies, flibanserin therapy during pregnancy is not expected to increase congenital malformations.

Neurobiology

Pharmacology and mode of action

receptor agonist (5-HT1A), receptor antagonist (5-HT2A)

Neurotransmitter Effects

Preclinical

—

Human

Flibanserin is a full 5-HT1A agonist on presynaptic autoreceptors in the raphe and frontal cortex and a partial agonist in the hippocampus. Acute flibanserin administration increases extracellular norepinephrine and dopamine in the frontal cortex

Physiological

Preclinical

Acute and subacute flibanserin administration suppresses the firing rate of 5-HT neurons in anesthetized rats, but firing normalizes with prolonged administration as a result of desensitization of the 5-HT1A autoreceptor. Flibanserin does not induce self-administration in rats, suggesting no abuse potential.

Human

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Brain Circuits

Preclinical

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Human

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FLUMAZENIL

Brand Names: Anexate, Romazicon

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Reversal of sedative effects of agonist drugs at the benzodiazepine receptor

Efficacy

Side Effects
Occasionally anxiety after acute administration. Care must be taken in those patients who have been taking agonist drugs at the benzodiazepine receptor, when anxiety or seizures may reappear

Practical Notes
IV formulation. Half-life 40-80 minutes. It is rapidly eliminated through liver metabolism and moderate cirrhosis will increase its half-life by about 50% and severe cirrhosis will triple it. Age and sex do not affect its half-life.

Recommended doses: 0.4 to 1 mg iv to reverse the sedative effect of benzodiazepine receptor agonists and up to 3 mg in case of overdose.

Pregnancy
No information

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor antagonist

Neurotransmitter Effects

Preclinical

—

Human

Binds to alpha-1, alpha-2, alpha-3, alpha-5 subtypes of the GABA-A receptor and with lower affinity to the α4 or alpha-6 subtypes

Physiological

Preclinical

Antagonises positive allosteric actions on GABA function of of drugs acting at the GABA-A benzodiazepine receptor

Human

—

Brain Circuits

Preclinical

Reversal of sedative effects of agonist drugs at the benzodiazepine receptor

Human

Binds to GABA-A receptors throughout the brain (11C flumazenil PET)

F

FLUNITRAZEPAM

Brand Names: Rohypnol, Hypnodorm, Silece, Nervocuril, Flutrace, Bibittoace, Fluninoc

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia (France; Japan; Australia)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Highly abusable as is lipophilic so can be 'snorted'. Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only a few. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 10-40 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 0.5 to 1 mg at bedtime with a maximum of 2 mg.

Pregnancy
Flunitrazepam has not been adequately evaluated for pregnancy effects.

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

FLUOXETINE

Brand Names: Prozac, Sarafem, Selfemra

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT)

Approved Indications
Major depressive disorder; Obsessive compulsive disorder; Post-traumatic stress disorder; Bulimia nervosa; Panic disorder; Body dysmorphic disorder; Premenstrual dysphoric disorder; Trichotillomania

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts

Side Effects
GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. No need for down titration upon discontinuation as has very long half-life

Practical Notes
Complete inhibition of CYP2D6 and will increase levels of substrates about 4 fold (desipramine, metoprolol, haloperidol). Significant inhibition of CYP2C9 (caution with warfarin). Its main metabolite has a very long half-life (about one week) so duration of action can last up to 5 weeks.
Recommended doses: initial dose 10-20 mg in the morning and titrated up after a few weeks. The usual maximal dose in depression is 60 mg/day, which is the target dose in bulimia, and a dose of up to 80 mg/day in OCD.

Pregnancy
Based on experimental animal studies and human experience, fluoxetine is not expected to increase the risk of major congenital anomalies. Human studies have inconsistently reported associations of fluoxetine use during pregnancy and heart defects in the offspring. Use of fluoxetine late in pregnancy can be associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, or gastrointestinal signs. Use of fluoxetine after 20 weeks gestation has been associated with an increased risk of neonatal pulmonary hypertension in some studies but not in others. Long-term neurodevelopmental studies suggest that antenatal fluoxetine exposure, unlike maternal depression, does not adversely affect outcome.

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas.

Human

Occupies 80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors; increases mRNA BDNF, calcium calmodulin-dependent protein kinases

Human

Decreased REM sleep, increased REM latency, sleep normalizes 10 days after stopping

Brain Circuits

Preclinical

Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)

Human

Decreased activity in anterior cingulate cortex in responders in major depressive disorder

F

FLUPENTHIXOL

Brand Names: Depixol, Fluanxol, flupendura, Deanxit

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Co-administration with drugs that prolong the QT interval should be avoided; these include amiadorone, erythromycin, and moxifloxacin. Depot available.

Recommended doses: 1 mg orally 3 times a day and titrated by 1 mg increments every 2-3 days up to a maximum of 24 mg/day. Equivalence of the depot should follow these ratios: 3 mg/day equals about 12 mg every 2 weeks or 24 mg every 4 weeks.

Pregnancy
Flupenthixol use has only been reported in a small number of pregnancies. Available data do not permit an estimate of flupenthixol effects on human development.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

—

Human

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FLUPHENAZINE

Brand Names: Modecate, Prolixin, Decanoate, Permitil

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia

Efficacy
Improvement of psychotic symptoms.

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Oral, injectable and depot available. Sometimes used in mania. It is metabolized by cytochrome 2D6 and its level will be at least doubled by 2D6 inhibitors such as fluoxetine and paroxetine. Slow 2D6 metabolizers may have increased side effects and ultra rapid metabolizers may not respond as well, thus doses may be adjusted accordingly.
Recommended doses: 2.5-10 mg/day divided in 3-4 doses both orally and intra-muscularly with maximal doses of 40 and 10 mg/day, respectively. The depot can be started at 12.5 mg every 2 weeks and titrated up in 12.5 increments up to a dose of 100 mg.

Pregnancy
Fluphenazine treatment during pregnancy interfered with embryo development in mice. There are no controlled studies of fluphenazine in human pregnancies. Transient neonatal complications including extrapyramidal symptoms might be seen following 3rd trimester exposure.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3 receptors

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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FLURAZEPAM

Brand Names: Dalmane

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life is short, but metabolized to desalkylflurazepam, half-life 36-120 hours. This active metabolite contributes to its prolonged action. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.
Recommended doses: 15-30 mg at bedtime.

Pregnancy
Based on experimental animal studies, flurazepam therapy during pregnancy is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

FLUVOXAMINE

Brand Names: Faverin, Luzox

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT)

Approved Indications
Major depressive disorder (except in USA); Obsessive compulsive disorder

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts

Side Effects
GI symptoms, anxiety and/or changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation

Practical Notes
Potent inhibition of CYP1A2 and increases the half life of caffeine from 5 to 31 hours, increases levels of substrates (acetaminophen/paracetamol, clozapine, olanzapine, clomipramine, duloxetine, theophylline). Inhibits CYP2C9 (caution with warfarin). Prolongs effect of melatonin.
Recommended doses: 50 mg at bedtime and increase to 100 mg after 4-7 days. After 2 weeks the dose can be increased by 50 mg/day increments weekly up to a dose of 300 mg/day. Doses higher than 150 mg should be divided in two.

Pregnancy
Based on experimental animal studies and limited human experience, fluvoxamine is not expected to increase the risk of congenital malformations. Use of other serotonin reuptake inhibitors late in pregnancy has been associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, and gastrointestinal signs and with persistent pulmonary hypertension of the newborn although there are no specific reports with fluvoxamine.

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas; sigma1 agonist; reduces tyrosine hydroxylase in locus coeruleus

Human

Decreased 5-HT platelet content

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors

Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

—

Human

After treatment in OCD, levels of rCBF decreased in caudate and putamen in both responders and non-responders; in responders, rCBF in thalamus was decreased. In healthy volunteers, decreases amygdala activation to unpleasant pictures

GABAPENTIN

Brand Names: Neurontin, Gralise, Gabarone, Fanatrex

Pharmacology
glutamate

Mode of Action
alpha-2 delta calcium channel blocker

Approved Indications
Epilepsy; Neuropathic pain.

Efficacy
Anti-epilepsy; Reduces neuropathic pain; Reduces anxiety

Side Effects
Dizziness, somnolence

Practical Notes
Similar to pregabalin, less well-absorbed; excreted by kidney; sometimes used to treat restless legs syndrome; emerging evidence of reduction in drug withdrawal craving e.g. cannabis. Half-life is 5-7 hours.
Recommended doses: initial dose can be 300 mg 2-3 times a day and gradually increased according to response up to a dose of 1,800 mg/day.

Pregnancy
Gabapentin treatment of experimental animals was associated with fetal growth impairment and developmental delay. There are case reports of normal and abnormal pregnancy outcome after gabapentin therapy; small controlled studies have not suggested an increase in malformation risk.

Pharmacology and mode of action

alpha-2 delta calcium channel blocker

Neurotransmitter Effects

Preclinical

Targets alpha2-delta subunit of calcium channel. Decreases presynaptic calcium currents and calcium-dependent vesicle docking at the presynaptic membrane leading to decreased release of glutamate, substance P, NE. Anxiolytic activity of pregabalin lost in transgenic mice without α2δ type 1 protein.

Human

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Physiological

Preclinical

—

Human

Increases slow wave sleep

Brain Circuits

Preclinical

—

Human

Reduces the activation of the amygdala and insula during anticipatory or emotional processing (fMRI)

GALANTAMINE

Brand Names: Nivalin, Razadyne, Razadyne ER, Reminyl, Lycoremine

Pharmacology
acetylcholine

Mode of Action
enzyme inhibitor (acetylcholinesterase), alpha -7 nicotinic receptor positive allosteric modulator

Approved Indications
Mild to moderate Alzheimer's disease

Efficacy
Improves or slows worsening of dementia symptoms

Side Effects
Bradycardia, nausea, diarrhoea, anorexia, abdominal pain, sleep disturbances, agitation, dizziness

Practical Notes
It is metabolized by several pathways, such as the cytochromes 2D6 and 3A4, and glucuronidation; exposure to galantamine will increase only up to 50% by potent inhibitors or in slow 2D6 metabolizers, and to a much lesser extent by 3A4 inhibitors. Is also a positive allosteric modulator of the ACh nicotinic receptor, and thus modulates ACh release.
Recommended doses: 4 mg twice a day and increased to 8 mg twice a day after 4 weeks, and then 12 mg twice a day after another 4 weeks according to side effects and response.

Pregnancy
Galantamine did not produce congenital anomalies when tested in rats and rabbits. We did not locate human data.

Neurobiology

Pharmacology and mode of action

enzyme inhibitor (acetylcholinesterase), alpha -7 nicotinic receptor positive allosteric modulator

Neurotransmitter Effects

Preclinical

Increases extracellular ACh in all brain regions

Human

—

Physiological

Preclinical

—

Human

Increases REM sleep

Brain Circuits

Preclinical

—

Human

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GUANFACINE

Brand Names: Intuniv,Tenex

Pharmacology
norepinephrine

Mode of Action
receptor agonist (alpha-2)

Approved Indications
Attention deficit hyperactivity disorder in children (USA, Europe, Canada); also hypertension

Efficacy
Reduction of signs and symptoms of attention deficit hyperactivity disorder in adults and children; Neuropathic pain; Sleep hyperhidrosis; Withdrawal symptoms in alcohol and opioid withdrawal; Anxiety; Migraine

Side Effects
Hypotension, somnolence, fatigue

Practical Notes
Eliminated by the kidneys, but also metabolized by the cytochrome 3A4: potent inhibition increases exposure three-fold and inhibition reduces it by 70%. Sustained release oral preparation available. Often combined with stimulant for resistant attention deficit hyperactivity disorder. Hypotensive action counteracts action of stimulants to increase BP. Sometimes used as premedication for surgery.
Recommended doses: 1 mg in the morning and increased at weekly intervals by 1 mg up to 4 mg/day (6 mg with the slow release preparation).

Pregnancy
Based on experimental animal studies, use of guanfacine is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

receptor agonist (alpha-2 NE)

Neurotransmitter Effects

Preclinical

Decreases brain norepinephrine release by agonism of alpha-2 norepinephrine autoreceptors

Human

—

Physiological

Preclinical

Improves attention, working memory performance and premature responding in rats and monkeys (post-synaptic effects)

Human

Mildly sedative, decreases BP, hypothermia, inconsistent effects on attention

Brain Circuits

Preclinical

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Human

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HALOPERIDOL

Brand Names: Haldol, Serenase

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia; Mania and hypomania; Mental or behavioural problems such as aggression, hyperactivity and self mutilation in the mentally retarded and in patients with organic brain damage; Adjunct to short-term management of moderate to severe psychomotor agitation; excitement; Violent or dangerously impulsive behaviour; Intractable hiccup; Restlessness and agitation in the elderly; Tourette syndrome and severe tics; Childhood behavioural disorders, especially when associated with hyperactivity and aggression

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
It is metabolized by cytochrome 2D6 and its level are at least doubled by 2D6 inhibitors such as fluoxetine and paroxetine. Slow 2D6 metabolizers may have increased side effects and ultra rapid metabolizers may not respond as well, thus doses may be adjusted accordingly. Depot available.

Recommended doses: 1-15 mg/day orally in divided doses according to response desired (i.e. agitation versus overall antipsychotic action) and side effects. Immediate-release injection is 2-5 mg and can be repeated every hour until desired effect is obtained. Long-acting dose every 4 weeks is between 10-20 mg depending on the prior oral maintenance dose.

Pregnancy
Haloperidol can cause abnormal embryo development in experimental animals. Human experience has not suggested an increased risk of congenital anomalies. Exposure during later pregnancy can cause extrapyramidal side effects in the neonate as in the adult.

Neurobiology

Pharmacology and mode of action
receptor antagonist (D2)

Neurotransmitter Effects

Preclinical
Antagonist at D1, D2 and D3, NE alpha-1 receptors

Human
Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical
—

Human
—

Brain Circuits

Preclinical
—

Human
—

HYDROXYZINE

Brand Names: Atarax, Vistaril

Pharmacology
histamine

Mode of Action
receptor antagonist (H1)

Approved Indications
Anxiety; allergy

Efficacy
Decreases anxiety

Side Effects
Sedation

Practical Notes
It has no anti-cholinergic activity. It can prolong the QTc interval and should not be given with other drugs that prolong QTc. Similarly, it should not be given with inhibitors of cytochrome 3A4, like erythromycin, clarithromycin, fluoxetine and grapefruit juice, and activators will decrease hydroxyzine exposure. Its half-life is 20 hours in adults and 7 hours in children.

Recommended doses: 50 mg/day in three divided doses with the largest dose at bedtime, up to a daily dose of 100 mg/day.

Pregnancy
Hydroxyzine produced adverse pregnancy effects in rodents. There is limited published experience during human pregnancy.

Pharmacology and mode of action

receptor antagonist (H1)

Neurotransmitter Effects

Preclinical

Binds to H1, ACh M1-4 receptors

DA and norepinephrine NE in the rat prefrontal cortex and hippocampus; no effect on DA in the N.Acc.

Human

30mg occupies 70% of brain H1 receptors (PET); anticholinergic adverse effects in overdose

Physiological

Preclinical

Slows rat reaction times; causes anticholinergic effects similarly to chlorpheniramine and promethazine

Human

Reduces anxiety; promotes sleep; anti-allergy; causes sedation and impairment of driving skills

Brain Circuits

Preclinical

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Human

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ILOPERIDONE

Brand Names: Fanapt

Pharmacology
serotonin, dopamine

Mode of Action
receptor antagonist (5-HT2, D2)

Approved Indications
Schizophrenia

Efficacy
Improvement of psychotic symptoms

Side Effects
Dizziness, sedation, weight gain, galactorrhea (low), EPS (low). Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients.

Practical Notes
Taking iloperidone with food will decrease its initial hypotensive effect. The half-life is between 13 and 30 hours. It is metabolized by both cytochrome 2D6 and 3A4, thus dose reduction by half should be used by inhibitors of the cytochrome, like fluoxetine, paroxetine and erythromycin, respectively, and higher doses could be used in the presence of 3A4 enhancers like carbamazepine.

Recommended doses: 1 mg twice a day and each dose can be increased by 1 mg each day over the first week, while monitoring for side effects and blood pressure. The usual regimen is 12-24 mg/day in two doses up to a dose of 32 mg/day.

Pregnancy
Based on experimental animal studies, iloperidone therapy is not expected to increase the risk of congenital malformations. There are no human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2,)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, 5-HT2A, NE alpha-1 receptors. Chronic treatment significantly decreases 5-HT2 receptor numbers in rat

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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IMIPRAMINE

Brand Names: Tofranil

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor (SERT and NET)

Approved Indications
Major depressive disorder; Panic disorder

Efficacy
Improves symptoms of depression and anxiety

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; toxic (potentially lethal) in overdosage

Practical Notes
Partly metabolized to desipramine. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine) , and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 25-50 mg at bedtime and increase by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects, response, or plasma level determination when available, up to a dose of 300 mg/day.

Pregnancy
Based on experimental animal studies and human reports, imipramine therapy during pregnancy is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (SERT and NET)

Neurotransmitter Effects

Preclinical

Inhibits SERT and NET; increases extracellular 5-HT and NE levels: antagonist at H1, ACh M1-4, NE alpha-1 receptors

Human

—

Physiological

Preclinical

Increase in hippocampal BDNF, Bcl-2

Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

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Human

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ISOCARBOXAZID

Brand Names: Enerzer, Marplan, Marplon

Pharmacology
serotonin, norepinephrine, dopamine

Mode of Action
enzyme inhibitor (MAO-A and -B)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
High probability of producing orthostatic hypotension; foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake.

Practical Notes
Irreversible MAOI so duration of action after stopping is 2-3 weeks. Serotonin reuptake inhibitors must be avoided during that time.

Recommended doses: 10 mg twice a day increased by 10 mg/day every week to 40-60 mg/day according to side effects and response.

Pregnancy
Isocarboxazid has not been adequately evaluated for pregnancy effects in experimental animals. Human data are inadequate.

Pharmacology and mode of action

enzyme inhibitor (MAO-A and -B)

Neurotransmitter Effects

Preclinical

Monoamine oxidase A and B irreversible inhibitor. Increases monoamine levels. Increases 5-HTP-induced head twitches

Human

Potentiates BP increase by ingestion of tyramine

Physiological

Preclinical

—

Human

Markedly suppresses REM sleep

Brain Circuits

Preclinical

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Human

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LAMOTRIGINE

Brand Names: Lamictal

Pharmacology
glutamate

Mode of Action
voltage-gated sodium channel blocker

Approved Indications
Prevention of mood episodes in patients with bipolar disorder predominantly by preventing depressive episodes; Epilepsy

Efficacy
Anti-epilepsy; Prevention of depressive episodes in bipolar disorder

Side Effects
Dizziness, rash

Practical Notes
Stevens-Johnson Syndrome is a dangerous cutaneous reaction occasionally associated with lamotrigine; risk is much reduced by slow dose titration. Despite concern about its use in women of child bearing potential, less risky than valproate (foetal malformations). Half-life is 30 hours and doses need not be fractionated.

Recommended doses: 25 mg/day and dose can be doubled every two weeks up to about 300 mg/day. Further increases could be implemented after ensuring that the plasma level is not in the toxic range. In epilepsy, it can be used up to 500 mg/day. Dose should be halved when given with valproate

Pregnancy
An increase in oral clefts was suspected after lamotrigine exposure during pregnancy based on results from one pregnancy registry but not confirmed in other registries or in a large record-linkage study.

Neurobiology

Pharmacology and mode of action

voltage-gated sodium channel blocker

Neurotransmitter Effects

Preclinical

Inhibits release of glutamate in brain in vitro; may also block voltage-activated calcium channels

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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LEVOMILNACIPRAN

Brand Names: Fetzima

Pharmacology
norepinephrine, serotonin

Mode of Action
reuptake inhibitor (NET,SERT)

Approved Indications
Major depressive disorder (USA)

Efficacy
Improves symptoms of depression and anxiety

Side Effects
GI symptoms,headache, dizziness, insomnia, hot flush, hyperhidrosis, palpitations, heart rate increase, dry mouth, hypertension, sexual dysfunction

Practical Notes
May increase heart rate and blood pressure. Not recommended following myocardial infarction. Does not inhibit any CYP enzymes and is not metabolized by the liver.

Recommended doses: 20 mg/day for the first 2 days (may be extended to in case of intolerance) and increased to a therapeutic dose of 40 mg/day. Dose can be increased to 80 and 120 mg/day at 2-week intervals while monitoring heart rate and blood pressure.

Pregnancy
Levomilnacipram did not increase malformations in rats or rabbits, although embryotoxicity occurred in both species, and pup death occurred in rats.

Pharmacology and mode of action

reuptake inhibitor (NET,SERT)

Neurotransmitter Effects

Preclinical

Potently inhibits NE (IC50 = 10.5 nM) and 5-HT (19.0 nM) reuptake (human transporter) in vitro. 2-fold greater potency for norepinephrine

relative to serotonin reuptake inhibition (i.e. NE/5-HT potency ratio: 0.6).

Human

—

Physiological

Preclinical

Efficacious in models of anti-depressive/anti-stress activity

Human

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Brain Circuits

Preclinical

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Human

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LISDEXAMFETAMINE

Brand Names: Elvanse, Vyvanse

Pharmacology
dopamine, norepinephrine

Mode of Action
reuptake inhibitor (DAT, NET), releaser (DA, NE)

Approved Indications
attention deficit hyperactivity disorder

Efficacy
Improves symptoms of attention deficit hyperactivity disorder

Side Effects
Weight loss, insomnia

Practical Notes
This is a prodrug to dextroamphetamine, with the same pharmacological effects but slower onset of action, thus has less abuse liability.

Recommended doses: 20-30 mg in the morning and increased weekly up to a dose of 70 mg, while monitoring heart rate and blood pressure.

Pregnancy
Studies in rats showed decreases in pup weight and litter size following prenatal amphetamine and methamphetamine exposure. Limited human data showed adverse effects on intrauterine growth, neonatal behavior, and central nervous system development, with possible effects on long-term neurodevelopment. These effects were associated with amphetamine abuse and might not apply to therapeutic use of these agents.

Pharmacology and mode of action

reuptake inhibitor (DAT, NET), releaser (DA, NE)

Neurotransmitter Effects

Preclinical

See amphetamine

Human

Little data

Physiological

Preclinical

See amphetamine

Human

Probably as amphetamine

Brain Circuits

Preclinical

See amphetamine

Human

Probably as amphetamine

LITHIUM

Brand Names: Lithobid, Eskalith

Pharmacology
lithium

Mode of Action
enzyme interactions

Approved Indications
Bipolar disorder; Mania; (USA and Europe); recurrent depression; Aggressive or self mutilating behaviour (Europe).

Efficacy
Anti-manic; Mood-stabilizing; Used to augment antidepressants

Side Effects
Weight gain, tremor, parathyroid, thyroid and renal dysfunction

Practical Notes
Narrow therapeutic ratio so customary to monitor lithium levels. Hypothesis about mechanism of action relates to calcium regulated or substrates of calcium regulated pathways involved in gene transcription. By altering the calcium signalling architecture lithium acts to corrects putative genetic deficits in bipolar disorder.

Recommended doses: 600 mg at bedtime and can titrated rapidly to 1,200 in bipolar disorder. Dose must be adjusted according to plasma level 12 hours after the last dose. As an adjunct in unipolar depression, levels of 0.5-0.8 mEq/L should be aimed for and 0.5-1.2 for bipolar disorder.

Pregnancy
Lithium exposure during pregnancy has been associated with an increased risk of cardiac malformations in some studies but not in others. Fetal echocardiography might be useful in the evaluation of exposed pregnancies. Lithium therapy in pregnancy has been associated with maternal, fetal, and neonatal complications.

Neurobiology

Pharmacology and mode of action

enzyme modulator

Neurotransmitter Effects

Preclinical

Inhibition of Inositol monophosphatase, adenylyl-cyclase, GMP, glycogen synthase kinase 3; increases activity of serotonin and acetyl choline in animal models; modulator of intracellular signalling cascades (multiple)

Human

—

Physiological

Preclinical

Inositol depletion, decreases brain cAMP

Human

—

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

LOFEPRAMINE

Brand Names: Gamanil, Lomont, Amplit

Pharmacology
norepinephrine, serotonin

Mode of Action
reuptake inhibitor (NET and SERT)

Approved Indications
Major depressive disorder (UK, Germany, Japan)

Efficacy
Improves symptoms of depression

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation, weight gain

Practical Notes
Extensively metabolized to desipramine. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 70 mg at bedtime and increased by 70 mg every week up to a dose of 280 mg/day. The minimal therapeutic dose is generally 140 mg/day. Desipramine plasma level 12 hours after the last dose can help guide the regimen.

Pregnancy
Based on experimental animal studies, use of lofepramine during pregnancy is not anticipated to increase the risk of congenital anomalies. We have not located human data.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET, SERT)

Neurotransmitter Effects

Preclinical

Inhibits norepinephrine uptake in vitro (rat brain), and weak serotonin reuptake inhibitor; weak antagonist at H1, ACh M1-4, alpha-1 adrenergic receptors (as desipramine)

Human

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Physiological

Preclinical

—

Human

Lowers platelet 5-HT content and suppresses REM sleep

Brain Circuits

Preclinical

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Human

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LOFEXIDINE

Brand Names: Britlofex

Pharmacology
norepinephrine

Mode of Action
receptor agonist (alpha-2)

Approved Indications
Hypertension

Efficacy
Ameliorates symptoms in opiate withdrawal

Side Effects
Hypotension, somnolence, fatigue

Practical Notes
May cause less hypotension than clonidine when used in opiate withdrawal. Half-life is 11 hours.

Recommended doses: initial dose is 0.8 mg in two divided doses and can be increased by 0.4 to 0.8 mg/day up to a dose of 2.4 mg/day according to response and cardiovascular parameters. No single dose should be greater than 0.8 mg.

Pregnancy
No information

Neurobiology

Pharmacology and mode of action

receptor agonist (alpha-2 NE)

Neurotransmitter Effects

Preclinical

Decreases brain norepinephrine release by agonism of alpha-2 norepinephrine autoreceptors

Human

—

Physiological

Preclinical

Pretreatment with lofexidine attenuates stress-induced reinstatement of alcohol seeking and decreases alcohol self-administration in rat

Human

In withdrawing alcoholics, decreases BP, heart rate and plasma catecholamines

Brain Circuits

Preclinical

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Human

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LORAZEPAM

Brand Names: Ativan

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Anxiety; Status epilepticus

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting; Used IV/IM for rapid tranquillisation

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life is short (10-20 hours). No dose adjustment necessary in liver impairment. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 1-3 mg/day in 2-3 divided doses and doses can be titrated according to response, up to a dose of 10 mg/day in divided doses.

Pregnancy
Experimental animal studies do not suggest that clinical use of lorazepam increases the risk of congenital malformations. Administration near delivery might cause sedation or decreased tone in the infant.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Increases fast activity on EEG; myorelaxant; anxiolytic; slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

LORMETAZEPAM

Brand Names: Loramet, Noctamid

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 8-15 hours. No dose adjustment necessary in liver impairment. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 0.5-1 mg at bedtime. Such a dose is the equivalent of lorazepam 0.5 mg and oxazepam 10 mg.

Pregnancy
No information

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

LOXAPINE

Brand Names: Loxapac Loxitane Adasuve

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia (tablet) (USA, Canada, France); Powder aerosol for control of agitation in schizophrenia and bipolar disorder (Europe)

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Also available in liquid form for oral use and an intra-muscular injectable form is available in several countries. The inhaled form leads to peak plasma level within minutes. Half-life for the oral preparation is 4 hours, and 8 hours for the inhaled product in adults, and 13-17 hours in children and adolescents.

Recommended doses: initial dose is 10 mg twice daily, up to 25 mg twice daily in severe patients, and titrated to 60-100 mg in divided doses in over 7-10 days. The maximum daily dose is 250 mg.

Pregnancy
Loxapine experimental animal studies have given mixed results with respect to congenital anomalies. There are no human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha-1 receptors

Human

Blocks central D2 and 5-HT2A receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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LURASIDONE

Brand Names: Latuda

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia (USA, Canada, UK and Europe); Major depressive episodes associated with bipolar I disorder (USA and Canada)

Efficacy
Improvement of psychotic symptoms; Improvement in depressive symptoms

Side Effects
Sedation, dizziness, EPS, galactorrhea, weight gain (low). Risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients. Risk of tardive dyskinesia, NMS

Practical Notes
NE alpha-2 action, 5-HT1A and 5-HT7 actions may be relevant. It is extensively metabolized by the cytochrome 3A4 and its level can be robustly increased by inhibitors, like erythromycin and grapefruit, fluoxetine (as much as 9-fold by ketoconazole), whereas inducers will decrease its plasma levels, like rifampicin (by 80%) and St-John's wort. No precautions necessary when used with lithium, valproate, or oral contraceptives. Because it is a permeability glycoprotein substrate, the inhibitor diltiazem, but not digoxin, doubles its plasma level. It has to be taken with food of about 350 calories for adequate absorption.

Recommended doses: initial dose in schizophrenia is 40-80 mg in one dose and 20 mg for bipolar depression. Dose can be increased gradually up to 120 mg/day in bipolar depression and to 160 mg in schizophrenia.

Pregnancy
Based on experimental animal studies, lurasidone therapy during pregnancy is not expected to increase the risk of congenital malformations. There are no human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

antagonist at D2 and D3, 5-HT2A, 5-HT7 receptors, partial agonist at 5-HT1A receptor

Human

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Physiological

Preclinical

Improves cognition in marmoset on difficult task

Human

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Brain Circuits

Preclinical

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Human

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MAPROTILINE

Brand Names: Deprilept, Ludiomil, Psymion

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor (NET)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
Dizziness, somnolence, hyperhidrosis, enuresis

Practical Notes
Lowers seizure threshold, Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 25 mg at bedtime and increased by 25 mg increments every 3-7 days to 75 mg. Further increments can be implemented gradually up to a dose of 225 mg/day

Pregnancy
Based on experimental animal studies and limited human experience, maprotiline is not expected to increase the incidence of congenital abnormalities.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Increase in extracellular levels of NE and dopamine in the frontal cortex; antagonist at NE alpha-1, H1, 5-HT2 receptors

Human

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Physiological

Preclinical

Change in AMPA subunit expression in hippocampus and striatum

Human

Suppresses REM sleep (moderately)

Brain Circuits

Preclinical

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Human

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MELATONIN

Brand Names: Circadin

Pharmacology
melatonin

Mode of Action
receptor agonist (Mel1 and Mel2)

Approved Indications
Sleep onset insomnia in adults age over 55 (not USA)

Efficacy
Advances circadian phase; Decreases sleep latency

Side Effects

Practical Notes
Circadin is a prolonged release preparation of endogenous melatonin hormone.

Recommended doses: Low doses (0.1-3 mg) of melatonin should be given in afternoon for phase advance and higher doses (3-10 mg) in the evening to preferentially decrease sleep latency.

Pregnancy
Melatonin is present normally during pregnancy. Adverse effects of exogenous melatonin have not been shown.

Neurobiology

Pharmacology and mode of action

receptor agonist (Mel1 and Mel2)

Neurotransmitter Effects

Preclinical

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Human

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Physiological

Preclinical

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Human

Shortens sleep onset latency and advances circadian phase

Brain Circuits

Preclinical

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Human

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MEMANTINE

Brand Names: Ebixa, Abixa, Axura, Akatinol, Namenda, Memox

Pharmacology
glutamate

Mode of Action
receptor antagonist (NMDA)

Approved Indications
Moderate to severe Alzheimer's disease

Efficacy
Improvement in dementia symptoms

Side Effects
Sleepiness, dizziness and balance problems, restlessness, nausea, other GI symptoms

Practical Notes
Blocks magnesium site on NMDA receptor, has a reversible action, unlike ketamine/PCP. Half-life is very long (60-100 hours therefore liable to accumulation). May act additionally as ACh nicotinic receptor antagonist, D2 receptor agonist. No dose adjustment for liver impairment and limit maximal dose by half only in severe renal impairment.

Recommended doses: 5 mg in the morning and after 1 week increase to 5 mg twice a day. Daily dose can be increased to 15 and then 20 mg in two divided doses at one week intervals.

Pregnancy
Based on experimental animal studies, therapy with memantine is not expected to increase the risk of congenital malformations. We did not locate human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (NMDA)

Neurotransmitter Effects

Preclinical

NMDA and 5-HT3 receptor antagonist

Human

Enhances glutamate through presynaptic mechanisms, neuroprotective through blocking glutamate, blocks NMDA receptors in vivo

Physiological

Preclinical

Increases intra-sleep wakefulness, effects blocked by D1 antagonist. Normalizes inflammation-induced disruption of neural encoding in hippocampus (rat in vivo)

Human

Reports of dissociation, confusion and stimulation, disturbance of balance; produces an early anxiogenic response in emotion-potentiated startle

Brain Circuits

Preclinical

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Human

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METHADONE

Brand Names: Methadose,Dolophine

Pharmacology
opioid

Mode of Action
receptor agonist (μ)

Approved Indications
Opioid dependence (substitution therapy); Pain (USA)

Efficacy
Useful in the treatment of moderate to severe pain

Side Effects
Sedation, nausea, constipation, confusion, respiratory depression (can be fatal). Increased QT dispersion, QT interval prolongation

Practical Notes
Liquid, tablet and intravenous formulations are available. It is metabolized by several P450 enzymes and drug-drug interactions are quite variable.

Recommended doses: it is usually prescribed only by physicians who have received an exemption from their national regulatory agency. 20-30 mg should be sufficient to control opiate withdrawal symptoms, under medical supervision. Additional doses of 5-10 mg can be added at 2-3 hour intervals if insufficient. The maximal dose on the first day should not exceed 40 mg.

Pregnancy
Experimental animal studies show congenital anomalies to be increased in the offspring of some species after pregnancy exposure to high dose levels of methadone. The main concern in humans has been neonatal withdrawal after antepartum exposure to methadone.

Neurobiology

Pharmacology and mode of action

receptor agonist (μ)

Neurotransmitter Effects

Preclinical

Combines agonist activity at the μ opioid receptor with antagonism at the NMDA receptor

Human

PET studies show very low receptor occupation necessary for therapeutic effects

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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METHYLPHENIDATE (D) AND (D.L)

Brand Names: Ritalin, Concerta, Biphentin, Foquest

Pharmacology
dopamine, norepinephrine

Mode of Action
reuptake inhibitor (DAT, NET), releaser (DA, NE)

Approved Indications
Attention deficit hyperactivity disorder in children >6y and adults

Efficacy
Reduces signs and symptoms of attention deficit hyperactivity disorder in adults and children; Used to treat narcolepsy

Side Effects
Headache, insomnia, nervousness, decreased appetite

Practical Notes
(d) enantiomer used less often than the racemic mixture. A number of slow release formulations are available with longer durations of action (usually once daily) and lower abuse liability.

Recommended doses: Racemate, immediate release, 10 mg in the morning and early afternoon and can be increased to 20 mg twice a day. The doses of the D stereoisomer should be half as those of the racemate. The slow release preparations producing sustained levels for 12 hours are given once a day in the morning; the starting dose can vary approximately between 10 and 20 mg depending on the brand and titrated gradually according to response and cardiovascular parameters. The maximum dose can vary between 72-80 mg/day. The 16-hour preparation is started at 25 mg in the morning and titrated gradually up to a dose of 100 mg.

Pregnancy
Based on experimental animal studies and a limited number of human pregnancies, methylphenidate is not expected to increase the risk of congenital anomalies.

Pharmacology and mode of action

Based on experimental animal studies and a limited number of human pregnancies, methylphenidate is not expected to increase the risk of congenital anomalies.

Neurotransmitter Effects

Preclinical

Blocks DA transporter and to a lesser extent NE transporter. May cause nonvesicular release of DA through the dopamine transporter (DAT) by promoting the exchange for cytosolic DA. Increases extracellular NE and DA in PFC, N.Acc. Effects are use dependent ie maximal when neurones are active

Human

Occupies DAT and increases DA availability in striatum (PET)

Physiological

Preclinical

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Human

Promotes wakefulness, increased blood pressure and heart rate, insomnia. Increased ratings of "active /alert/ energetic", "stimulated," "shaky," and "jittery"

Brain Circuits

Preclinical

Induces Fos expression in striatum (cat), persistent c-fos in N.Acc., PFC (immature rat), increases c-fos mainly in sensorimotor striatum, but not N.Acc. (adult rat)

Human

Normalises abnormal cognitive function and associated fMRI signals in patients with attention deficit hyperactivity disorder

MIANSERIN

Brand Names: Lumin, Tolvon, Lerivon

Pharmacology
norepinephrine

Mode of Action
receptor antagonist (alpha-2), reuptake inhibitor (NET)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety; Promotes sleep

Side Effects
Sedation, dizziness, dry mouth, rarely granulcytopenia or agranulocytosis

Practical Notes
Low probability of sexual dysfunction. Metabolized by CYP1A2, 2D6, and 3A4 and few interactions anticipated.

Recommended doses: 30 mg at bedtime and titrated at two-week intervals to 60 and 90 mg, as required.

Pregnancy
Mianserin has not been systematically studied for pregnancy effects.

Neurobiology

Pharmacology and mode of action

receptor antagonist (alpha-2), reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Increases extracellular DA in rat cortex. Antagonist at 5-HT2, NE alpha-1 and alpha-2, H1 receptors

Human

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Physiological

Preclinical

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Human

Sedation and impairment of driving skills in healthy volunteers after acute dosing but not next day.

Brain Circuits

Preclinical

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Human

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MIDAZOLAM

Brand Names: Dormicum, Hypnovel, Versed

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Premedication in anaesthesia; Short acting anaesthesia (IV); Status epilepticus (IV; intranasal; buccal; rectal)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life is 1-4 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 1-2.5 mg intravenously over 2 minutes, may repeat in 3-5 minutes.

Pregnancy
Based on experimental animal studies, midazolam use during pregnancy is not expected to increase the risk of congenital anomalies. Use near delivery can result in neonatal respiratory depression

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

MILNACIPRAN

Brand Names: Ixel, Savella, Dalcipran, Toledomin

Pharmacology
norepinephrine, serotonin

Mode of Action
reuptake inhibitor (NET,SERT)

Approved Indications
Major depressive disorder (France, other European countries, Japan); fibromyalgia (USA)

Efficacy
Improves symptoms of depression and anxiety

Side Effects
GI symptoms,headache, dizziness, insomnia, hot flush, hyperhidrosis, palpitations, heart rate increase, dry mouth, hypertension, sexual dysfunction

Practical Notes
May increase heart rate and blood pressure. Does not inhibit any CYP enzymes and is not metabolized by the liver.

Recommended doses: 25 mg twice daily and increased to 50 mg twice daily after a few days; can be increased by 50 mg/day steps every 2 weeks; the usual dose for fibromyalgia is 100 mg twice a day, up to a dose of 300 mg/day in two divided doses.

Pregnancy
Based on experimental animal studies, therapy with milnacipran is not expected to increase the incidence of congenital malformations. We did not locate human data.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET,SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular levels of 5-HT and NE in cortex. Transporter binding in vivo approximately equal for SERT and NET (primate PET)

Human

Small dose-dependent decrease in platelet 5-HT reuptake

Physiological

Preclinical

Increases firing of noradrenaline and 5-HT neurons

Human

Increase REM latency but not total REM sleep; increase in total sleep time

Brain Circuits

Preclinical

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Human

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MIRTAZAPINE

Brand Names: Zipsin, Remeron, Avanza

Pharmacology
norepinephrine, serotonin

Mode of Action
receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety; Promotes sleep (in doses 7.5-15) Can reduce post-operative vomiting

Side Effects
Weight gain; sedation, especially at beginning of treatment

Practical Notes
Low level of sexual dysfunction. Metabolized by CYP1A2, 2D6, and 3A4 and few interactions anticipated. Smoking reduces levels by about 30%.

Recommended doses: initial dose should be 30 mg at bedtime, which is the minimal therapeutic dose; daytime sedation may be more rapidly reversed if not started at 15 mg. Dose may be increased at two-week intervals up to a dose of 60 mg.

Pregnancy
Based on experimental animal studies and human experience, mirtazapine exposure during pregnancy is not expected to increase the risk of congenital anomalies. There are only nine reported cases of use during breastfeeding.

Pharmacology and mode of action

receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)

Neurotransmitter Effects

Preclinical

Increase in extracellular NE and DA in cortex; antagonist at H1, 5-HT2, 5-HT3, NE alpha-2 receptors.

Human

Binds to cortical H1 receptors (PET)

Physiological

Preclinical

Increase in mRNA of neurotrophins (BDNF, NGF, NT-3) and decrease of pro-apoptotic proteins (Bax, Bcl-xL, p53, Bad)

Human

Does not suppress REM sleep. Sedation and impairment of driving skills in healthy volunteers after acute dosing but not next day.

Brain Circuits

Preclinical

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Human

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MOCLOBEMIDE

Brand Names: Aurorix, Manerix

Pharmacology
serotonin, norepinephrine, dopamine

Mode of Action
reversible enzyme inhibitor (MAO-A)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and social anxiety disorder

Side Effects
Insomnia (if taken too late in the day)

Practical Notes
No tyramine diet necessary, no sexual dysfunction. Potent inhibitor of CYP2C19 substrates (warfarin, omeprazole, phenytoin).

Recommended doses: 150 mg after breakfast and lunch. It can be titrated up by 150 mg/day increments at weekly intervals to 600 and 750 mg/day in a single morning dose, without having to implement a low tyramine diet.

Pregnancy
We did not locate human studies on pregnancy effects of moclobemide, although there are case reports of normal outcome after pregnancy exposure.

Pharmacology and mode of action

reversible enzyme inhibitor (MAO-A)

Neurotransmitter Effects

Preclinical

Reversible inhibitor. Increase in extracellular DA and 5-HT levels in the striatum

Human

Low potentiation of BP increase to ingestion of tyramine

Physiological

Preclinical

Increased 5-HT and NE-related behavior after long-term administration; potentiates 5-HTP induced stereotypies; increases phophorylation of extracellular-regulated kinase (ERK); increase of Bcl-2 and Bcl-xL expression in vitro

Human

No apparent effect on sleep

Brain Circuits

Preclinical

Increase in mineralocorticoid receptor levels in cortex, amygdala, and anterior pituitary

Human

High occupation of MAO-A (74%) with maximal recommended dose of 600 mg/day in cortical regions, basal ganglia, and midbrain

MODAFINIL

Brand Names: Provigil

Pharmacology
dopamine

Mode of Action
reuptake inhibitor (DAT)

Approved Indications
Excessive sleepiness associated with narcolepsy; Excessive sleepiness associated with obstructive sleep apnea and shift work disorder (not Europe)

Efficacy
Promotes wakefulness

Side Effects
Headache, insomnia

Practical Notes
Armodafinil, the R-enantiomer of modafinil, is a moderate inducer of cytochrome 3A4 and may thus reduce the efficacy of oral contraceptive pills and cyclosporine. The half-life of armodafinil is 15 hours and that of S-modafinil is 4 hours.

Recommended doses: 50-100 mg twice a day in the morning and at noon. Doses may be increased rapidly up to 400 mg/day in two divided doses.

Pregnancy
Based on experimental animal studies, modafinil and armodafinil are not expected to increase congenital malformations.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (DAT)

Neurotransmitter Effects

Preclinical

Effects mediated through DA; ablating N.Acc. core blocks modafinil-induced wakefulness in rat

Human

Blocks DAT and increases dopamine in brain including N.Acc.

Physiological

Preclinical

Promotes wakefulness

Human

Promotes wakefulness, improves attention-related psychomotor task performance especially in sleep-deprived subjects

Brain Circuits

Preclinical

Increases cfos in hypothalamus (TMN and perifornical area) and at higher doses in striatum and cingulate in rats

Human

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NALMEFENE

Brand Names: Selincro, Revex

Pharmacology
opioid

Mode of Action
receptor antagonist (μ, δ), receptor partial agonist (κ)

Approved Indications
Reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification (Europe); Management of opiate overdose

Efficacy
Reduces heavy drinking days (binges) in alcohol dependence; Some evidence it may help pathological gambling

Side Effects
Nausea, dizziness, insomnia, decreased appetite

Practical Notes
Current advice is to use along with a behavioural enhancement program. No dose adjustment required for mild to moderate liver or renal impairment. Half-life is 12 hours.

Recommended doses: 18 mg as necessary before anticipated drinking alcohol only if there have not been any opioids in the last 10 days.

Pregnancy
Based on experimental animal studies, modafinil and armodafinil are not expected to increase congenital malformations.

Pharmacology and mode of action

receptor antagonist (μ, δ), receptor partial agonist (κ)

Neurotransmitter Effects

Preclinical

Selective antagonist for μ and δ receptors; partial agonist at κ receptors. D1 receptors increased transiently in rat

Human

Blocks brain μ receptors for 24 hours (PET)

Physiological

Preclinical

Improves alcohol and opioid dependence related behaviors

Human

HPA activation

Brain Circuits

Preclinical

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Human

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NALOXONE

Brand Names: Narcan, Evzio

Pharmacology
opioid

Mode of Action
receptor antagonist (μ)

Approved Indications
Opioid acute overdose, combination with buprenorphine for opiate dependence

Efficacy

Side Effects

Practical Notes
Not absorbed orally. Onset of action: IV, 2 minutes and IM, 5 minutes; half-life about 1.5 hours and duration of action is only 30-60 minutes.

Recommended doses: 0.4 mg and may repeat the dose every 2-3 minutes.

Pregnancy
Based on experimental animal studies, use of naloxone during pregnancy is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

receptor antagonist (μ)

Neurotransmitter Effects

Preclinical

Antagonises mu opioid receptors, and with lower affinity κ- and δ-opioid receptors .

Human

Approximately 13 microg/kg of naloxone required to produce an estimated 50% receptor occupation in human brain, consistent with the clinical dose of naloxone used to reverse opiate overdose (0.4 mg-1.2 mg).

Physiological

Preclinical

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Human

May induce a normalization of the opioid system and HPA axis function, as reflected by normal levels and normal circadian rhythm of levels of beta-endorphin, ACTH, and cortisol. Atypical hypo-responsivity to stressors during cycles of heroin addiction and

Brain Circuits

Preclinical

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Human

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NALTREXONE

Brand Names: Revia, Depade, Vivitrol

Pharmacology
opioid

Mode of Action
receptor antagonist (μ,κ)

Approved Indications
Maintenance of abstinence in alcohol dependence; Adjunct to maintenance of abstinence in opioid dependence

Efficacy
Reverses respiratory depression in opiate overdose; Reduces frequency and severity of relapse to drinking in alcohol dependence; Blocks effects of opiates in opiate dependence

Side Effects
Non-specific GI symptoms, can cause liver damage in high doses

Practical Notes
Depot IM injection available for opiate and alcohol addiction. Implant under investigation. Use in alcohol abstinence requires co-treatment with psychotherapy. rs1799971 SNP in the μ receptor gene associated with efficacy of naltrexone treatment for alcohol dependence. Liver function should be monitored.

Recommended doses: 50 mg daily, only if no opioids have been taken in the last 10 days.

Pregnancy
Based on experimental animal studies and limited human reports, naltrexone therapy during pregnancy is not expected to increase the risk of congenital malformations. Behavioral effects of prenatal naltrexone exposure have been proposed in experimental animal studies but not established.

Neurobiology

Pharmacology and mode of action

receptor antagonist (μ,κ)

Neurotransmitter Effects

Preclinical

Blocks opioid receptors. Blocks alcohol-induced activation of dopaminergic pathways in the brain

Human

Blocks most of μ and some of δ receptors after 4 days' treatment in abstinent alcoholics (PET)

Physiological

Preclinical

Improves alcohol and opioid dependence related behaviors; attenuates food intake; reduces stress-induced increase in serum corticosterone

Human

Increases plasma epinephrine and NE response to cold pressor test

Brain Circuits

Preclinical

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Human

Reduces activation of orbital and cingulate gyri, inferior frontal and middle frontal gyri, and ventral striatum, to alcohol cues in abstinent alcohol-dependent subjects

NEFAZODONE

Brand Names: Dutonin, Serzone

Pharmacology
serotonin

Mode of Action
receptor antagonist (5-HT2), receptor agonist (5-HT1A)

Approved Indications
Major depressive disorder (USA)

Efficacy
Improves symptoms of depression including insomnia

Side Effects
Rare cases of hepatotoxicity

Practical Notes
Low level of sexual dysfunction. Withdrawn in Europe, Canada and Japan because of hepatic risk. Potent inhibitor of CYP3A4 (will markedly raise levels of all substrates: felodipine, cyclosporine, sildenafil, mevacor, rapid clearance benzodiazepines eg alprazolam).

Recommended doses: 200 mg in two divided doses. Can be increased by 100-200 mg steps on a weekly basis up to a total daily dose of 600 mg. Can be used in a single nighttime dose.

Pregnancy
Based on experimental animal studies and a small number of cases of exposed human pregnancies, nefazodone is not expected to increase the incidence of congenital abnormalities.

Neurobiology

Pharmacology and mode of action

receptor antagonist (5-HT2), receptor agonist (5-HT1A)

Neurotransmitter Effects

Preclinical

Antagonist at 5-HT2, NE alpha-1 and alpha-2 receptors; agonist at 5-HT1A receptors; weak NET and SERT inhibitor

Human

No effect on platelet 5-HT2 levels

Physiological

Preclinical

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Human

Does not suppress REM sleep

Brain Circuits

Preclinical

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Human

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NITRAZEPAM

Brand Names: Alodorm, Arem, Insoma, Insomin, Mogadon, Nitrados, Nitrazadon, Nitrosun, Ormodon, Paxadorm, Remnos, Somnite, Hirusukamin

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only a few. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 29-40 hours. Nitrazepam is metabolized by several liver enzymes, which may explain inter-individual variability in sensitivity to its side effects. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 5-10 mg at bedtime.

Pregnancy
Nitrazepam produced adverse effects on rat but not mouse development, probably related to metabolic activation in the rat. There are a few human case reports and small series.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Anxiolytic; slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

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Human

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NORTRIPTYLINE

Brand Names: Aventyl, Pamelor

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor (NET)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and chronic pain

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; Toxic (potentially lethal) in overdosage

Practical Notes
An active metabolite of amitriptyline. At low doses (<50 mg) is primarily an antagonist at 5-HT2 receptors. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: 25-50 mg at bedtime. Increase dose by 25 mg every 3-5 days as required to a usual daily dose of 75-150 mg, up to a dose of 200 mg, or as indicated by a plasma level determination.

Pregnancy
Nortriptyline did not appear to increase the risk of birth defects in humans. Tricyclic antidepressants including nortriptyline have been associated with neonatal complications of varying severity but limited long-term follow-up data has not shown neurodevelopmental delays in these babies. Infants exposed through breastfeeding have low or undetectable concentrations of nortriptyline and its metabolites.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Increases 5-HT and NE in frontal cortex, in medial prefrontal cortex, 5-HT in N.Acc; receptor antagonist at 5-HT2, H1, ACh M1-4 and NE alpha-1 receptors

Human

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Physiological

Preclinical

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Human

Suppresses REM sleep

Brain Circuits

Preclinical

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Human

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OLANZAPINE

Brand Names: Zyprexa

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia; Acute treatment of manic or mixed episodes associated with bipolar I disorder; Maintenance treatment of bipolar I disorder; Olanzapine and fluoxetine in combination in depressive episodes associated with bipolar I disorders (USA only)

Efficacy
Improvement of psychotic symptoms; Mania; Depression

Side Effects
Weight gain, sedation, EPS, galactorrhea (low), dizziness, risk of tardive dyskinesia, NMS. Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Depot available USA, Europe. Metabolized by CYP 1A2: levels are increased by some fluoroquinolones, like ciprofloxacine but not levofloxacin, whereas heavy smoking by inducing CYP1A2 decreases olanzapine levels by 65%, therefore requiring corresponding adjustments of daily regimens. Half-life is 33 hours.

Recommended doses: 5-10 mg in one dose with a target (oral or intramuscular) of 10 mg within several days. The dose may be increased at intervals of no less than one week. Maximum approved dose is 20 mg/day (oral or intramuscular), although oral daily dose of up to 40 mg has been shown to be safe. For the depot preparation, the dose is 210-300 mg every 2 weeks or 405 every 4 weeks depending on the oral stabilization dose.

Pregnancy
Based on experimental animal studies and human experience, olanzapine therapy during pregnancy is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3 , 5-HT2, NE alpha-1, H1, ACh M1-4 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

Sedative and anticholinergic effects. Increases slow wave sleep

Brain Circuits

Preclinical

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Human

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OXAZEPAM

Brand Names: Serax

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Anxiety

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 5-15 hours. Minimal liver metabolism. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 15-30mg in 3 divided doses. In anxiety associated with alcohol withdrawal, 45-120 mg/day in 3-4 divided doses.

Pregnancy
Based on experimental animal studies, use of oxazepam during pregnancy is not anticipated to increase the risk of congenital anomalies. Human reports on pregnancy outcome do not suggest an increased risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

Human

Anxiolytic; slows eye saccades; promotes sleep. Slower uptake than most benzodiazepines so lower abuse liability

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

PALIPERIDONE

Brand Names: Invega

Pharmacology
dopamine, serotonin, norepinephrine

Mode of Action
receptor antagonist (D2, 5-HT2, NE alpha-2)

Approved Indications
Acute and maintenance treatment of schizophrenia and schizoaffective disorder in adults

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS. Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Active metabolite of risperidone, depot available and can be given in the deltoid muscle with a smaller needle than for other depots. Not metabolized by cytochrome P450 and no dose adjustment for mild to moderate liver impairment, but doses should be decreased by half in moderate and severe renal impairment.

Recommended doses: commonly 6 mg in one daily dose, but 3 mg and 1.5 mg capsules are also available in some countries. Dose can be increased by 3 mg/day every 5 days to a maximum of 12 mg/day. Sustena dosing should be 150 mg on day 1 and 100 mg on day 8, followed by doses 25-150 mg every 4 weeks depending on response. Trinza should only follow stabilization for at least four months on Sustena; it can be given about 7 days before or after the next normally scheduled dose of Sustena using a dose multiplier of 3.5 for this 3-month preparation.

Pregnancy
Based on experimental animal studies, paliperidone therapy during pregnancy is not expected to increase the risk of congenital anomalies. We did not locate human studies on pregnancy outcome.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2, NE alpha-2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, NE alpha-1 and alpha-2, 5-HT2A, H1 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PAROXETINE

Brand Names: Seroxat, Paxil, Brisdelle, Pexeva

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT)

Approved Indications
Major depressive disorder; Panic disorder; generalized anxiety disorder; social anxiety disorder; obsessive compulsive disorder; post traumatic stress disorder

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts

Side Effects
GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction.

Practical Notes
Must be gradually decreased for discontinuation. Complete inhibition of CYP2D6 and will increase levels of substrates about 4 fold (desipramine, metoprolol, haloperidol); weight gain in long-term administration; kidney excreted. Should not be used with tamoxifen because of small inhibitory effect on CYP2D6, which transforms tamoxifen into its active metabolite (endoxifen).

Recommended doses: 10 or 20 mg/day (12.5 or 25 mg of the constant release; CR) with food, starting with the lower doses in panic disorder. Dose can be increased by 10 mg/day (12.5 mg CR) at intervals no shorter than one week up to a dose of 50-60 mg/day (75 mg CR).

Pregnancy
Paroxetine has been associated with cardiovascular abnormalities in some epidemiology studies, but findings have not been consistent. Experimental animal studies do not suggest an increased risk of congenital anomalies. Use of paroxetine late in pregnancy can be associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, and gastrointestinal signs. Long-term neurodevelopmental studies suggested that antenatal exposure to fluoxetine, sertraline, or paroxetine does not adversely affect outcome, unlike maternal depression

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas

Human

Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors

Human

Decreases REM sleep, increases REM latency; decreases self-rated erotic stimulation with corresponding activity changes in related brain structures

Brain Circuits

Preclinical

Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)

Human

Reduction to normal of enhanced activity in pregenual anterior cingulate and enhancement to normal of attenuated prefrontal regions

PEROSPIRONE

Brand Names: Lullan

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia (Japan)

Efficacy
Improvement of psychotic symptoms.

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Metabolized by three P450 cytochromes and levels not influenced by other drugs. Plasma half-life 3 hours, but it generates an active metabolite.

Recommended doses: 4 mg three times a day and can be increased gradually to 16 mg three times a day, up to a dose of 48 mg/day in divided doses. Frequency of dosing can be reduced.

Pregnancy
No information

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, 5-HT3, NE alpha-1 receptors; partial agonist at 5-HT1A receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PERPHENAZINE

Brand Names: Trilafon

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia; Nausea and vomiting

Efficacy
Improvement of psychotic symptoms; Anxiety and agitation; Mania; Nausea and vomiting.

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Mainly metabolized by cytochrome 2D6; in poor metabolizers or in the presence of the potent inhibitor paroxetine, the plasma levels of perphenazine are increased more than three fold.

Recommended doses: 4-8 mg three times a day and can be increased to 16 mg as required. Maximum is 24 mg/day for nausea and vomiting, 64 mg/day in psychosis all in divided doses. Intramuscular dose is 5 mg every 6 hours as necessary up to a dose of 30 mg/day.

Pregnancy
Perphenazine can increase the incidence of congenital anomalies in experimental animal studies, although very high dose levels appear to be required for this toxicity. Limited human studies have not shown an increase in congenital anomalies

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha-1, H1, ACh M1-4 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PHENELZINE

Brand Names: Nardil

Pharmacology
serotonin, norepinephrine, dopamine

Mode of Action
enzyme inhibitor (MAO-A and -B)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression (including atypical depression), generalised anxiety disorder, panic disorder, social anxiety disorder and PTSD

Side Effects
High probability of producing orthostatic hypotension; foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake.

Practical Notes
Irreversible MAOI so duration of action after stopping is 2-3 weeks. Serotonin reuptake inhibitors must not be used during that period. May significantly inhibit CYP 1A2, 2C9/19, 2D6, precautions are indicated.

Recommended doses: 15 mg twice a day and increased weekly by 15 mg/day up to a dose of 90 mg/day.

Pregnancy
Monoamine oxidase inhibitors are usually avoided during pregnancy due to their potential vasoconstrictive effects and due to the availability of better-studied antidepressant treatments.

Pharmacology and mode of action

enzyme inhibitor (MAO-A and -B)

Neurotransmitter Effects

Preclinical

Irreversible MAOI. Increases tissue content of 5-HT and NE

Human

Potentiates BP increase to ingestion of tyramine.

Physiological

Preclinical

Increases transmission at 5-HT1A receptors in the hippocampus, decreased phospholipase C in cortex and hippocampus

Human

Markedly suppresses REM sleep

Brain Circuits

Preclinical

Desensitization of cell body 5-HT1A autoreceptors on 5-HT neurons; decreased firing activity of NE and DA neurons

Human

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PIMAVANSERIN

Brand Names: Nuplazid

Pharmacology
serotonin

Mode of Action
receptor antagonist (5-HT2A)

Approved Indications
hallucinations and delusions in psychosis associated with Parkinson's disease

Efficacy

Side Effects
Peripheral oedema (low incidence), hallucinations (low incidence)

Practical Notes
Metabolized by several P450 cytochromes, including 3A4. In the presence of potent inhibitors of 3A4 (like erythromycin, indinavir, ketoconazole, fluoxetine or daily grapefruit consumption) the dose of pimavanserin should be reduced by half, whereas in the presence of inducers (like carbamazepine, phenytoin, and St. John's Wort) dose may be increased. No dose adjustment needed in mild to moderate renal impairment. Half-life is 55 hours.

Recommended doses: 34- 40 mg once daily.

Pregnancy
No information

Pharmacology and mode of action

receptor antagonist (5-HT2A)

Neurotransmitter Effects

Preclinical

Antagonist at 5-HT2A receptors, some antagonist action at 5-HT2C receptors (~2% of 2A affinity)

Human

Single oral dose of 10 mg fully saturates 5-HT2A receptors in human brain as determined by [11C]N-methylspiperone PET.

Physiological

Preclinical

Attenuates 5-HT2A receptor agonist-induced head-twitch behavior in rats; reduces MK-401-induced hyperactivity in mice

Human

Increases slow wave sleep

Brain Circuits

Preclinical

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Human

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PIMOZIDE

Brand Names: Orap

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia; Tourette syndrome and resistant tics (Europe only).

Efficacy
Improvement of psychotic symptoms; Improvement of chorea, tic disorder and Gilles de la Tourette in children and adults

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
For tics it is second/third line treatment as there are safer alternatives. Dose dependent QT prolongation. It is metabolized by cytochromes 1A2, 2D6, and 3A4, it is contraindicated with drugs with potential to inhibit any of these isoenzymes because of the QTc prolongation. Half-life is 55 hours.

Recommended doses: 1-2 mg/day in two divided doses for Tourette's syndrome and 2-4 mg once daily for schizophrenia. Add 2-4 mg/day at weekly intervals up to a dose of 20 mg/day in normal metabolizers (4 mg/day in slow 2D6 metabolizers).

Pregnancy
Based on experimental animal studies, pimozide is not anticipated to increase the risk of congenital anomalies. Extrapyramidal effects can be seen in the newborn after third trimester maternal exposure.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3 receptors

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PIPOTIAZINE

Brand Names: Piportil

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia (UK, some of Europe, South America)

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Properties similar to chlorpromazine; depot available.

Recommended doses: 50-100 mg IM and may increase by 25 mg every 2-3 weeks up to a dose of 250 mg every 3-4 weeks.

Pregnancy
No informaion

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, 5-HT2, NE alpha-1, H1, ACh M1-4 receptors

Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PITOLISANT

Brand Names: Wakix

Pharmacology
histamine

Mode of Action
receptor antagonist (H3)

Approved Indications
Narcolepsy

Efficacy
Promotes wakefulness in narcolepsy and may also do so in obstructive sleep apnoea and Parkinson's disease

Side Effects
GI symptoms, increased appetite and weight gain, headache, insomnia

Practical Notes
It does not appear to have any active metabolite and is not a substrate or an inhibitor of permeability glycoproteins. Half-life is 12 hours.

Recommended doses: 9 mg/day in the morning with food and can be increased to 18 mg (or decreased to 4.5 mg) after one week. Dose may be increased up to a dose of 36 mg at week 3.

Pregnancy
No informaion

Pharmacology and mode of action

receptor antagonist (H3)

Neurotransmitter Effects

Preclinical

Binds selectively to H3 receptors, antagonist and inverse agonist

Human

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Physiological

Preclinical

Enhances wakefulness during the lights-off (active) period of both orexin (–/–) and wild-type mice. Improves consolidation processes in the fear conditioning task in mice

Human

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Brain Circuits

Preclinical

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Human

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PRAMIPEXOLE

Brand Names: Mirapex, Mirapexin, Sifrol

Pharmacology
dopamine

Mode of Action
receptor agonist (D2)

Approved Indications
Parkinson's disease; restless legs syndrome

Efficacy
depression

Side Effects
sedation, dizziness, dyskinesia, sleep disturbance, confusion, hallucinations, impulse control disorder, visual impairment, fatigue, weight loss

Practical Notes
Can be used as monotherapy or in combination for depression. Risk of triggering compulsive behaviours, eg pathological gambling and hypersexuality especially at higher doses. Half-life is 8-10 hours. It is not metabolized by the liver, nor does it inhibit any liver enzymes. It is excreted by kidneys 90% unchanged.

Recommended doses: 0.25 mg twice a day and can be doubled on a weekly basis according to response, up to a dose of 6 mg/day.

Pregnancy
Pramipexole antagonizes implantation and increases resorption in rats, probably by decreasing prolactin. Early human pregnancy is not dependent on prolactin as is rat pregnancy. Based on studies in rats and rabbits, an increase in malformations is not anticipated in women treated with pramipexole during pregnancy, but lactation might be impaired.

Pharmacology and mode of action

receptor agonist (D2)

Neurotransmitter Effects

Preclinical

Agonist at these receptors in order of affinity: D3, D4, NE α2B, 5-HT1A, D2S

Human

Binds to D2/D3 receptors in the prefrontal cortex, amygdala, and medial and lateral thalamus (PET)

Physiological

Preclinical

In rodents, ameliorates behavioral deficits related to apathy, depression and anxiety induced by dopaminergic lesions.

Human

Reduces alertness, causes pupil dilatation, increased heart rate, reduced prolactin and thyroid stimulating hormone, and increased growth hormone level in healthy volunteers. Diminishes dopamine-mediated responses to both rewarding and aversive taste stim

Brain Circuits

Preclinical

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Human

(MRI) Increased cerebral blood flow compared with placebo in the caudate nucleus, putamen, middle frontal, supplementary motor area, and brainstem (substantia nigra), but reduced cerebral blood flow in the posterior thalamus, cerebellum, and visual areas

PRAZOSIN

Brand Names: Minipress, Vasoflex, Pressin, Hypovase

Pharmacology
norepinephrine

Mode of Action
receptor antagonist (alpha-1)

Approved Indications
Hypertension

Efficacy
Used for nightmares in PTSD

Side Effects
Hypotension, sedation, fatigue

Practical Notes
Dose recommended for nightmares 10 mg, so titration necessary to avoid hypotension. Prazosin is a substrate for permeability glycoproteins (p-GP). Therefore inducers like rifampicin (but also others like St. John's Wort), reduce the level of prazosin that has led to loss of its anti-hypertensive effect. In contrast, inhibition of p-GP by verapamil increases peak plasma concentration of prazosin and potentiates its hypotensive effects.

Recommended doses: 1 mg at bedtime and dose can be progressively increased up to 6 mg in women and 10 mg in men, while monitoring blood pressure.

Pregnancy
Based on experimental animal studies, therapy during pregnancy with prazosin is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

receptor antagonist (alpha-1)

Neurotransmitter Effects

Preclinical

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Human

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Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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PREGABALIN

Brand Names: Lyrica

Pharmacology
glutamate

Mode of Action
alpha-2 delta calcium channel blocker

Approved Indications
Generalized anxiety disorder; Neuropathic pain; Epilepsy

Efficacy
Anti-epilepsy; Reduces neuropathic pain; Reduces anxiety; Reduces drug withdrawal craving

Side Effects
Dizziness, sedation

Practical Notes
Similar to gabapentin, better absorbed; excreted unchanged by kidney. Half-life is about 6 hours. It should never be stopped abruptly and should be tapered over a minimum of 1 week.

Recommended doses: as side effects may vary between patients, 25-50 mg may be given twice a day and gradually increased as tolerated in no less than a week up to a dose of 600 mg/day.

Pregnancy
Pregabalin had adverse effects on embryo development and viability in rats at plasma concentrations about twice those achieved in humans on therapy. We did not locate human data.

Pharmacology and mode of action

alpha-2 delta calcium channel blocker

Neurotransmitter Effects

Preclinical

Targets alpha2-delta subunit of calcium channel. Decreases presynaptic calcium currents and calcium-dependent vesicle docking at the presynaptic membrane leading to decreased release of glutamate, substance P, NE. Anxiolytic activity of pregabalin is lost in transgenic mice without α2δ type 1 protein

Human

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Physiological

Preclinical

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Human

Increases slow wave sleep

Brain Circuits

Preclinical

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Human

Report of reduction in concentration of glutamate in insula (MRS); decreases insula connectivity (fMRI) and clinical pain ratings in chronic pain patients.

PROMETHAZINE

Brand Names: Phenergan, Promethegan, Phenadoz

Pharmacology
histamine, dopamine

Mode of Action
receptor antagonist (H1, D2)

Approved Indications
Allergy; nausea; insomnia in UK

Efficacy
Used for psychosis in some countries

Side Effects
Drowsiness, dizziness, fatigue, dry mouth, constipation, akathisia, extrapyramidal symptoms, risk of TD, NMS. Toxic in overdose

Practical Notes
Often used for agitation in the elderly and sedation in children. Half-life is 18 hours.

Recommended doses: 12.5-25 mg and may be repeated as necessary every 4-6 hours up to a dose of 100 mg/24 hours.

Pregnancy
Based on human experience with promethazine, adverse outcome is not anticipated with early pregnancy exposure. Use close to delivery could, in theory, increase the risk of respiratory depression of the newborn. There are no data on lactation use, but theoretical considerations suggest that non-phenothiazine antihistamines might be preferable.

Pharmacology and mode of action

receptor antagonist (H1, D2)

Neurotransmitter Effects

Preclinical

Antagonist at H1 receptors, also ACh M1-4, 5-HT2, D2 receptors, alpha-7-nicotinic acetylcholine receptor. Inhibits NMDA-mediated membrane currents

Human

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Physiological

Preclinical

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Human

Cognitive impairment when given in daytime. Half-life is 18 hours

Brain Circuits

Preclinical

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Human

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PROTRIPTYLINE

Brand Names: Vivactil

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor (NET)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; Toxic (potentially lethal) in overdosage

Practical Notes
Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine), and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers.

Recommended doses: initial dose is 25 mg/day at bedtime increased every 3-5 days by 25mg to about 75mg/day over 2-4 weeks. Further increases should be implemented as required according to side effects, response and plasma level determination when available up to a dose of 150mg/day.

Pregnancy
Experimental animal studies did not suggest that protriptyline increased the risk of congenital anomalies. A withdrawal syndrome in infants exposed to other tricyclic antidepressants has been described.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Receptor antagonist at H1, ACh M1-4 and NE alpha-1 receptors

Human

—

Physiological

Preclinical

—

Human

Suppresses REM sleep

Brain Circuits

Preclinical

—

Human

—

QUAZEPAM

Brand Names: Doral, Dormalin

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 27-41 hours. Absorption is markedly decreased (two-fold) in the fasting state.

Recommended doses: 15-30 mg at bedtime.

Pregnancy
Based on experimental animal studies, quazepam therapy during pregnancy is not expected to increase the risk of congenital anomalies. Neonatal withdrawal has been seen after maternal exposure to other

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy; anti-conflict

Human

Sleep promoting

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

QUETIAPINE

Brand Names: Seroquel

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2) and reuptake inhibitor (NET)
(metabolite)

Approved Indications
Schizophrenia; Acute treatment of manic or depressive episodes in bipolar 1 disorder; Major depressive disorder

Efficacy
Improvement of psychotic symptoms, augments effects of antidepressants effect on depressive symptoms

Side Effects
Sedation, dizziness, weight gain; galactorrhea (low), EPS (low); Risk of tardive dyskinesia, NMS. Clearance reduced in elderly; Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients.

Practical Notes
Dose regimens for benefits are consistent with receptor affinity: low doses for sedation, high doses for schizophrenia, and intermediate doses for depression. Metabolized by CYP 3A4: ketoconazole increases its levels 3 fold and carbamazepine decreases its level by 80%, therefore precautions are required with CYP 3A4 inhibitors and inducers. Lamotrigine may decrease levels of quetiapine by 60%.

Recommended doses: 12.5-100 mg immediate release at bedtime for insomnia, 150-300 mg/day of the extended release for unipolar depression in mid-evening (may be started at 50mg/day and titrated by 50 mg increments as tolerated over a week), 300-600 mg of the extended release for bipolar depression also in mid-evening, and 400-800 mg/day in schizophrenia that can be titrated gradually over one week.

Pregnancy
Based on experimental animal studies and limited human reports, quetiapine is not expected to increase the risk of congenital anomalies.

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2) and reuptake inhibitor (NET)(metabolite)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha-1 and alpha-2, H1 receptors. Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in N.Acc.

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

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Human

Sedative and anticholinergic effects

Brain Circuits

Preclinical

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Human

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RAMELTEON

Brand Names: Rozerem

Pharmacology
melatonin

Mode of Action
receptor agonist (Mel1 and Mel2)

Approved Indications
Sleep-onset insomnia (USA, Japan)

Efficacy
Advances circadian phase; Decreases sleep latency

Side Effects

Practical Notes
Synthetic version of melatonin. Should not be used with cytochrome 1A2 inhibitors, like fluvoxamine and ciprofloxacine, because levels of ramelteon are increased multiple fold. Half-life is 1-3 hours.

Recommended doses: 8 mg at bedtime

Pregnancy
Based on experimental animal studies, ramelteon therapy during pregnancy is not anticipated to increase the risk of congenital anomalies. No reports were located on use in human pregnancy or lactation.

Neurobiology

Pharmacology and mode of action

receptor agonist (Mel1 and Mel2)

Neurotransmitter Effects

Preclinical

Binds to melatonin Mel1 and Mel2 receptors

Human

—

Physiological

Preclinical

—

Human

Shortens sleep onset latency and advances circadian phase

Brain Circuits

Preclinical

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Human

—

REBOXETINE

Brand Names: Edronax

Pharmacology
norepinephrine

Mode of Action
reuptake inhibitor (NET)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
Urinary hesitancy; May produce tachycardia

Practical Notes
Low probability of sexual dysfunction. Metabolized by CYP3A4 and levels will be increased by inhibitors, such as erythromycins, fluconazole, fluoxetine and grapefruit juice, and decreased by inducers like carbamazepine, rifampin, and
St John's Wort.

Recommended doses: 2 mg twice a day for 2 weeks and may titrate to 4 mg twice a day thereafter, up to a dose of 6 mg twice a day.

Pregnancy
No information

Pharmacology and mode of action

reuptake inhibitor (NET)

Neurotransmitter Effects

Preclinical

Increase in extracellular NE in cortex, increase in DA in hippocampus

Human

Blocks tyramine pressor response (NE reuptake)

Physiological

Preclinical

Increase in NE transmission through terminal, but not cell body, NE alpha-2 autoreceptors

Human

Increases cortisol and heart rate; improves recall of positive memories in healthy volunteers and depressed patients; decreases subjective ratings of hostility and elevated energy

Brain Circuits

Preclinical

Increase in blood oxygen level-dependent (BOLD) signal in hippocampus and cortex. Increase in BDNF, Bcl-xL, Bcl-2 expression

Human

Increases brain activity in thalamus, dorsolateral prefrontal and occipital cortex to negative emotional stimuli; increases amygdala responses to positive emotional stimuli

RISPERIDONE

Brand Names: Risperdal, Belivon

Pharmacology
dopamine, serotonin, norepinephrine

Mode of Action
receptor antagonist (D2, 5-HT2, NE alpha-2)

Approved Indications
Schizophrenia; Manic episodes in bipolar disorder; Short-term treatment of persistent aggression in patients with Alzheimer's; Conduct disorder in children > 5 y and adolescents with learning disability

Efficacy
Improvement of psychotic symptoms; adjunctive in depression and OCD

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS. Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
NE alpha-2 norepinephrine actions may be relevant. Depot available. Metabolized by cytochrome 2D6 into its active metabolite paliperidone, which has a similar receptor affinity profile but is not liver metabolized. Consequently, inhibition or induction of 2D6 does not change the overall level of the active moieties and has no significant clinical consequences. Half-life of risperidone plus its active metabolite is about 20 hours.

Recommended doses: 1 mg/day and increased daily by 1 mg/day until desired effect is obtained in schizophrenia/mania. Usual dose is 4-8 mg/day given at bedtime up to a daily dose of 16 mg/day. As adjunctive in depression, starting dose is 0.25-0.5 mg at bedtime and increased every two weeks to a total dose of 2 mg/day. As adjunctive in OCD, starting dose is 0.5 mg at bedtime and increased gradually up to a dose of 3 mg/day. Long acting dose is 25 mg every two weeks and the dose may be increased to 37.5 mg and then 50 mg every two weeks.

Pregnancy
Based on experimental animal studies and limited human experience, therapy with risperidone during pregnancy is not anticipated to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2, NE alpha-2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, NE alpha 1 and 2, 5-HT2A, H1 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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RIVASTIGMINE

Brand Names: Exelon

Pharmacology
acetylcholine

Mode of Action
enzyme inhibitor (acetylcholinesterase, butyrylacetycholinesterase)

Approved Indications
Mild to moderately severe Alzheimer's disease

Efficacy
Improves or slows worsening of dementia symptoms

Side Effects
Bradycardia, nausea, diarrhoea, anorexia, abdominal pain, headache and sleep disturbances

Practical Notes
Transdermal patch available. Cytochrome P450 enzymes are not involved in its metabolism and it is excreted by kidneys. It is not expected to interfere in vivo with the metabolism of drugs metabolized by P450 enzymes based on in vitro experiments.

Recommended doses: 1.5 mg twice daily increased by 3 mg/day at two week intervals to a maximum of 6 mg twice daily. Starting dose for patches: one daily delivering 4.6 mg/24 hours and increased after 4 weeks to the daily patch delivering 9.5 mg/24 hours, up to a dose of the patch delivering 13.3 mg/24 hours after another 4 weeks.

Pregnancy
No information

Pharmacology and mode of action

enzyme inhibitor (acetylcholinesterase, butyrylacetycholinesterase)

Neurotransmitter Effects

Preclinical

Increases extracellular ACh in all brain regions

Human

Enhances memory through ACh

Physiological

Preclinical

—

Human

Increases REM sleep

Brain Circuits

Preclinical

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Human

After 3 months' treatment, PET revealed 11-C nicotine binding sites were significantly increased in several cortical brain regions

SELEGILINE

Brand Names: Eldepryl, Emsam, Zelapar

Pharmacology
dopamine, norepinephrine, serotonin

Mode of Action
enzyme inhibitor (MAO-B and -A)

Approved Indications
Parkinson's disease; major depressive disorder

Efficacy
Efficacious in treating major depressive disorder using the transdermal formulation producing a preferential MAO type A inhibition

Side Effects
Foods with high tyramine content should be avoided; Must not be used with medications inhibiting 5-HT reuptake. irreversible MAOI so duration of action after stopping is 2-3 weeks.

Practical Notes
Transdermal application by-passes enough GI MAO-A to allow metabolism of tyramine in the gut, thus minimising tyramine-induced hypertensive crisis. Partly metabolised to l-methamphetamine by CYP2B6 mainly, but 3A4 as well.

Recommended doses: in Parkinson's disease, 2.5 mg twice daily and increased to 5 mg twice daily as required. In depression, one patch of 6 mg every day without tyramine restriction, increased as required at two weeks intervals to 9 and 12 mg with tyramine restriction.

Pregnancy
Human and experimental animal data on selegiline are limited. Monoamine oxidase inhibitors are often avoided during pregnancy due to their potential vasoconstrictive effects and potential for drug-drug interactions.

Neurobiology

Pharmacology and mode of action

enzyme inhibitor (MAO-B and -A)

Neurotransmitter Effects

Preclinical

Monoamine oxidase A and B irreversible inhibitor. Increase in extracellular striatal dopamine. Metabolite amphetamine

Human

(Orally) potentiates BP increase to ingestion of tyramine. Probable that antidepressant effect is achieved by MAO-A inhibition in the brain

Physiological

Preclinical

Transient decrease in tyrosine hydroxylase mRNA in the striatum; decreased immobility in behavioral test only with MAO-A inhibitory regimens

Human

Increases REM latency

Brain Circuits

Preclinical

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Human

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SERTINDOLE

Brand Names: Serdolect, Serlect

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia patients intolerant to at least one other antipsychotic agent, due to cardiovascular safety concerns (Europe and Australia)

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Prolongs QTc, extensive ECG monitoring needed. It is metabolized by cytochromes 2D6 and 3A4 and, despite this dual metabolism, it should not be used with inhibitors of either of these enzymes because of its QTc prolongation effect. Half-life is 3 days.

Recommended doses: 4 mg/day increased by 4 mg/day every 4-5 days according to desired response up to a dose of 24 mg/day.

Pregnancy
No information

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, NE alpha-1, 5-HT2A receptors

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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SERTRALINE

Brand Names: Lustral, Zoloft

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT)

Approved Indications
Major depressive disorder; Panic disorder; Generalized anxiety disorder; Social anxiety disorder; Obsessive compulsive disorder; Post traumatic stress disorder

Efficacy
Improves symptoms of depression and anxiety and reduces compulsive behaviour and obsessional thoughts

Side Effects
GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. Must be gradually decreased on discontinuation

Practical Notes
Partial inhibition of CYP2D6 at high doses (150 mg/day), but metabolized by multiple CYP enzymes and not subject to altered plasma levels by other drugs.

Recommended doses: 25 mg/day in the morning with food for panic disorder and increased to 50 mg/day after one week, but 50 mg/day initially for all other disorders. Doses can then be increased by 50 mg/day every two weeks as necessary. Maximal dose is 200 mg/day, but used successfully in OCD up to 450 mg/day.

Pregnancy
Based on experimental animal studies and human experience, sertraline is not expected to increase the risk of congenital anomalies. Human studies have inconsistently reported associations of sertraline use during pregnancy and various defects in the offspring. Use of serotonin re-uptake inhibitors late in pregnancy has been associated with a mild transient neonatal syndrome of central nervous system, motor, respiratory, and gastrointestinal signs. Use of fluoxetine, sertraline, or paroxetine was associated with an increased risk of neonatal pulmonary hypertension in some but not all studies. Long-term neurodevelopmental studies suggest that antenatal exposure to fluoxetine, sertraline, or paroxetine does not adversely affect outcome.

Neurobiology

Pharmacology and mode of action

reuptake inhibitor (SERT)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT levels in several brain areas . Weak DAT inhibitor. Reduces 5-HT1A mRNA in the raphe nucleus of stressed rats

Human

Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Physiological

Preclinical

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Human

Decreased REM sleep, increased REM latency

Brain Circuits

Preclinical

Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)

Human

Increased connectivity between anterior cingulate cortex and limbic regions and increased limbic activation to negative content pictures

SODIUM OXYBATE (GHB)

Brand Names: Xyrem

Pharmacology
GABA

Mode of Action
(receptor agonist (GABA-B and gammahydroxybutyrate (GHB)

Approved Indications
Cataplexy in narcolepsy (USA, Europe, Canada); Alcohol dependence (Austria; Italy)

Efficacy
Very sedating; Improves cataplexy in narcolepsy when given at night

Side Effects
Sedation, sleep promoting, marked enhancement of SWS, abused as party drug. Commonly causes dizziness, headache, nausea. Highly dangerous when taken with alcohol

Practical Notes
Half-life is 30-60 minutes.

Recommended doses: 2.25 g while in bed and the second dose to be taken 2.5-4 hours later. This dose can be increased or decreased at two-week intervals as necessary by 0.75 g per dose. It is usually effective at 6-9 g /night.

Pregnancy
Sodium oxybate did not produce congenital anomalies in rats or rabbits, although fetal and postnatal viability were decreased in rats.

Neurobiology

Pharmacology and mode of action

receptor agonist (GABA-B and gammahydroxybutyrate (GHB)

Neurotransmitter Effects

Preclinical

Reduces DA release, increased serotonin turnover, increased level of acetylcholine, altered presynaptic release of GABA and glutamate, decreased binding to NMDA receptors, increased plasma concentration of neurosteroids

Human

—

Physiological

Preclinical

Hypothermia, hypertension,tachycardia, increased activity of renal sympathetic nerves, EEG and behavioral changes, including absence-like seizures and slow wave sleep, impaired spatial learning

Human

Very sedating, increases slow wave sleep

Brain Circuits

Preclinical

Reduces DA turnover in striatum

Human

—

SULPIRIDE

Brand Names: Eglonyl, Dolmatil, Sulpor, Dogmatil

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia (UK, France, Germany, Japan); Depression (Germany, Japan); Anxiety in adults, behavioural problems in children (France)

Efficacy
Improvement of psychotic symptoms; Low EPS; Some efficacy in anxiety and depression

Side Effects
EPS (low incidence), galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS. May increase motor agitation and insomnia

Practical Notes
Mood-elevating, ameliorates social anxiety. It is only excreted by the kidneys and a dose reduction of about 50% should be used in the presence of renal impairment. Half-life is 7 hours.

Recommended doses: 50-300 mg in one or two doses for anxiety; 50-150 mg in one or two doses for depression and can be titrated to 300 mg/day in divided doses; 400 mg twice daily for schizophrenia and can be titrated up to 1,600-2,400 total daily dose (depending on the country).

Pregnancy
We did not locate complete developmental studies on sulpiride.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3 receptors

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

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Human

—

Brain Circuits

Preclinical

—

Human

—

SUVOREXANT

Brand Names: Belsomra

Pharmacology
orexin

Mode of Action
receptor antagonist (OR1, OR2)

Approved Indications
Insomnia

Efficacy
Sleep-promoting

Side Effects
Morning somnolence, half-life is around 9 hrs at 10mg dose. At doses >20 mg motor impairment, driving impairment, and more rarely unconscious night time activity and effects resembling mild cataplexy

Practical Notes
It is metabolized by cytochrome 3A4 and strong inhibitors, like ketoconazole, increase exposure three fold, whereas moderate inhibitors, like erythromycin, fluconazole, and grapefruit, increase exposure two fold. Strong 3A4 inducers, like carbamazepine, phenytoin, and rifampin, can prevent the clinical effects of suvorexant. It does not alter the levels of other medications. Half-life is approximately 9 hours at 10 mg dose.

Recommended doses: 10 mg at bedtime and subsequently can be increased to 15 mg and 20 mg as needed. It has been studied up to 40 mg at bedtime, but produced increased next day somnolence.

Pregnancy
Based on experimental animal studies, suvorexant therapy during pregnancy is not expected to increase the risk of congenital malformations. We have not located human data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (OR1, OR2)

Neurotransmitter Effects

Preclinical

Binds to orexin1 and orexin2 receptors, (pKi (nM) OX1R: 1.2; OX2R: 0.6)

Human

—

Physiological

Preclinical

Reduces locomotor activity and promotes sleep in rats, dogs and rhesus monkeys

Human

Reduces intra-sleep waking at 10mg dose, and sleep onset latency and total sleep time at higher doses.

Brain Circuits

Preclinical

Binds to OR receptors in lateral hypothalamus

Human

—

TANDOSPIRONE

Brand Names: Sediel, Lukang

Pharmacology
serotonin

Mode of Action
receptor partial agonist (5-HT1A)

Approved Indications
Psychosomatic disorder; Neurotic disorder (Japan and China)

Efficacy
Depressive mood; Anxiety; Agitation; Insomnia due to psychosomatic disorder; Depressive mood and fear due to neurotic disorder

Side Effects
Dizziness, drowsiness, insomnia, headache, GI disorders, dry mouth. Risk of serotonin syndrome, malignant syndrome

Practical Notes
Tandospirone is mainly metabolized by cytochrome 3A4; usual dose adjustment are indicated when used with inhibitors and inducers of this enzyme. Half-life is 2-3 hours.

Recommended doses: 10 mg three times a day and the dose may be increased by 10 mg/day increments as tolerated and required up to a dose of 60 mg/day in divided doses.

Pregnancy
No information

Pharmacology and mode of action

receptor partial agonist (5-HT1A)

Neurotransmitter Effects

Preclinical

Potent and selective 5-HT1A receptor partial agonist, metabolite has some antagonist action at NE alpha-2 receptors

Human

60 mg induced a significant decrease in body temperature and increase in growth hormone. PET- no significant reduction of [(11)C]WAY 100635 binding following the administration of 30 mg or 60 mg tandospirone

Physiological

Preclinical

Chronic tandospirone treatment reversed the psychosocial stress-induced increase in latency in the NSF test and decrease in the density of DCX-positive cells in the dentate gyrus of the dorsal and ventral hippocampus.

Human

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Brain Circuits

Preclinical

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Human

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TEMAZEPAM

Brand Names: Restoril, Normison

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Temazepam is not metabolized by the liver and almost entirely excreted by kidneys. Half-life 7-12 hours. Synergistic action with alcohol, as for all benzodiazepine receptor agonists.

Recommended doses: 15 mg at bedtime and can be increased to 30 mg if ineffective.

Pregnancy
Experimental animal studies have not shown an increase in malformations with temazepam treatment. There is a case report of fetal death following the combination of temazepam and diphenhydramine. Use of benzodiazepines in late pregnancy might be associated with newborn side effects.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non- selective PAM

Physiological

Preclinical

—

Human

Sleep-promoting.

Brain Circuits

Preclinical

—

Human

Broad action across all brain regions

THIORIDAZINE

Brand Names: Melleril

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Treatment-resistant schizophrenia (USA)

Efficacy
Improvement of psychotic symptoms

Side Effects
Galactorrhea, sedation, dizziness, weight gain, low EPS, QTc issues. Risk of tardive dyskinesia, NMS. Risk of diabetes; monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Prolongs QTc, monitoring needed. It is metabolized by cytochrome 2D6 and must not be used with any inhibitor of this enzyme, like fluoxetine, paroxetine, duloxetine and bupropion, or in slow 2D6 metabolizers. Half-life is 24 hours. Discontinued in many countries because of cardiac toxicity.

Recommended doses: 50-100 mg three times a day titrated carefully up to a dose of 800 mg/day in divided doses.

Pregnancy
Valproic acid use during pregnancy is associated with a 1-2% incidence of lumbar meningomyelocele. This abnormality can be diagnosed during the second trimester of pregnancy with ultrasound examination and amniocentesis. Other congenital anomalies have al.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha-1, H1, ACh M1-4

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

—

Human

Sedative and anticholinergic effects. Increases slow wave sleep

Brain Circuits

Preclinical

—

Human

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TIANEPTINE

Brand Names: Stablon, Tatinol, Coaxil, Salymbra

Pharmacology
glutamate

Mode of Action
yet to be determined

Approved Indications
Major depressive disorder (some European countries)

Efficacy
Improves symptoms of depression

Side Effects
Headache, dizziness, insomnia, nightmares, drowsiness, dry mouth, constipation. Low incidence of sexual dysfunction

Practical Notes
Mechanism unclear - to be determined. May be abused. Metabolized by CYP3A3. Half-life is about 3 hours.

Recommended doses: 12.5 mg three times a day and dose may be increased to 50 mg/day in divided doses.

Pregnancy
Tianeptine did not impair experimental animal reproduction according to the product labeling, but we have not been able to review details of the study.

Neurobiology

Pharmacology and mode of action

unclear

Neurotransmitter Effects

Preclinical

μ opioid receptor agonist. Increase in 5-HT reuptake in vivo; attenuates extracellular glutamate in the amygdala in response to stress

Human

—

Physiological

Preclinical

No net change in 5-HT transmission in the rat brain; reverses depressant-like effect of prenatal stress; increase in BDNF protein in amygdala; reverses reduction of NGF, membrane glycoprotein 6-alpha, G protein alpha q, CREB produced by stress

Human

Does not change sleep architecture

Brain Circuits

Preclinical

—

Human

—

TOPIRAMATE

Brand Names: Topamax

Pharmacology
GABA, glutamate

Mode of Action
facilitation of GABA transmission, receptor antagonist on AMPA and KA

Approved Indications
Epilepsy, Migraine, Weight loss (in combination with phentermine)

Efficacy
Alcohol dependence, methamphetamine and cocaine addiction; Obesity; Antipsychotic-induced weight gain; Binge-eating disorder

Side Effects
Dizziness, weight loss, paraesthesiae, somnolence, nausea, diarrhoea, fatigue, depression. Rarely acute myopia and secondary angle closure glaucoma. Pregnancy category D (positive evidence of human foetal risk)

Practical Notes
Topiramate is excreted by kidneys unchanged. It induces cytochrome 3A4 and reduces oestrogens and therefore the effectiveness of oral contraceptives. Half-life is about 24 hours.

Recommended doses: 25-50 mg/day in two divided doses. Dose can be increased weekly by 50 mg/day. Maximum recommended dose is 800 mg/day in divided doses, although usual doses are commonly in the 200-400 mg/day range.

Pregnancy
Topiramate produced abnormal pregnancy outcome in experimental animals. Human case reports and registry data have identified both normal and abnormal pregnancy outcome after topiramate exposure. The occurrence of oral clefts in one registry population led to a warning in the product labeling. An association between oral clefts and topiramate use during pregnancy was also reported in a case control study. A 2015 meta-analysis reported an odds ratio for oral clefts of 6.26, 95% CI: 3.13-12.51. Pregnancy registers are enrolling women exposed to topiramate during pregnancy.

Pharmacology and mode of action

facilitation of GABA transmission, receptor antagonist on AMPA and KA

Neurotransmitter Effects

Preclinical

1) facilitation of GABA A-mediated currents ; 2) antagonism of AMPA and kainate glutamate receptors; 3) inhibition of L-type calcium channels and limitation of calcium-dependent second messenger systems; 4) limitation of activity-dependent depolarization and excitability of voltage-dependent sodium channels; 5) activation of potassium conductance and 6) weak inhibition of carbonic anhydrase isoenzymes — CA-II and CA-IV

Human

—

Physiological

Preclinical

Suppresses ethanol drinking and stress-induced increases in alcohol consumption in C57BL/6 mice

Human

—

Brain Circuits

Preclinical

—

Human

—

TRANYLCYPROMINE

Brand Names: Parnate

Pharmacology
serotonin, norepinephrine, dopamine

Mode of Action
enzyme inhibitor (MAO-A and -B), releaser (DA, NE)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression

Side Effects
High probability of producing orthostatic hypotension; Foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake.

Practical Notes
Irreversible MAOI so duration of action after stopping is 2-3 weeks. Serotonin reuptake inhibitors must not be used during that period. Metabolized by CYP 2A6 and does not inhibit any CYP enzymes.

Recommended doses: initiate at 10 mg in the morning and after lunch. Increase dose at 1-3 week intervals by 10 mg/day up to a dose of 60 mg/day. May be given as a single dose in the morning if it does not cause peaks in blood pressure.

Pregnancy
Tranylcypromine and other monoamine oxidase inhibitors have been suspected of decreasing uterine blood flow and increasing the risk of adverse pregnancy outcome. Data to substantiate this suspicion have not been conclusive. Monoamine oxidase inhibitors are avoided during pregnancy due to their potential vasoconstrictive effects and drug-drug and drug-food interactions.

Pharmacology and mode of action

enzyme inhibitor (MAO-A and -B), releaser (DA, NE)

Neurotransmitter Effects

Preclinical

Monoamine oxidase A and B irreversible inhibitor. Increase of extracellular 5-HT and NE in cortex

Human

Potentiates BP increase to ingestion of tyramine.

Physiological

Preclinical

Increase in Bcl-2, Bcl-xL, Arc expression

Human

Increased REM latency

Brain Circuits

Preclinical

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Human

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TRAZODONE

Brand Names: Molipaxin, Deprax, Desyrel, Oleptro, Trittico

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT), receptor agonist (5-HT1A), receptor antagonist (5-HT2)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression including insomnia

Side Effects
Sedation, dry mouth, dizziness. Rarely priapism

Practical Notes
Widely used in North America and Japan in its immediate release preparation in insomnia. Low level of sexual dysfunction. Slow release preparation probably leads to more sustained inhibition of serotonin reuptake. Metabolized by CYP3A4 and levels will be increased by inhibitors, such as erythromycins, fluconazole, fluoxetine and grapefruit juice, and decreased by inducers like carbamazepine, rifampin, and St John's Wort.

Recommended doses: for insomnia, 25-150 mg at bedtime. In depression, 150 mg in two divided doses of the immediate release preparation and increased by 50 mg/day every 3-4 days up to a dose of 600 mg/day according to tolerability. For the slow release preparation, start with 150 mg at bedtime and increase by 75 mg/day every 3-4 days up to a dose of 375 mg in a single dose.

Pregnancy
Based on experimental animal studies and limited experience in human pregnancies, trazodone therapy is not expected to increase the incidence of congenital anomalies

Pharmacology and mode of action

reuptake inhibitor (SERT), receptor agonist (5-HT1A), receptor antagonist (5-HT2)

Neurotransmitter Effects

Preclinical

Increases extracellular levels of 5-HT in frontal cortex; antagonist at 5-HT2, NE alpha-1 receptors, weak SERT inhibitor, 5-HT1A receptor agonist

Human

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Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors; increases 5-HT1A and NE alpha-2 transmission in the rat hippocampus

Human

Increases slow wave sleep

Brain Circuits

Preclinical

Full 5-HT1A agonist on cell body 5-HT1A autoreceptors and postsynaptic 5-HT1A receptors in the hippocampus

Human

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TRIAZOLAM

Brand Names: Halcion

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia (not UK, France, Germany)

Efficacy
Anxiolytic; Muscle relaxant; Anticonvulsant; Sleep-promoting

Side Effects
Sedation, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 1.5-5 hours. It is metabolized by cytochrome 3A4. Inhibitors of the 3A4, like fluoxetine, erythromycin, ketoconazole, but also oral contraceptives, reduce its clearance. St. John's Wort will increase it. Synergistic effects with alcohol can produce severe sedation, behavioral changes, anterograde amnesia, and intoxication.

Recommended doses: 0.125 mg at bedtime and dose can be increased to 0.25 mg, up to a dose of 0.5 mg.

Pregnancy
Based on experimental animal studies, triazolam use during pregnancy is not expected to increase the risk of congenital anomalies. Better-studied benzodiazepines including lorazepam and clonazepam may be preferred during pregnancy or lactation.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy; anti-conflict

Human

Slows eye saccades; promotes sleep, anxiolytic.

Brain Circuits

Preclinical

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Human

Broad action across all brain regions

TRIFLUOPERAZINE

Brand Names: Stelazine, Jatroneural, Modalina, Terfluzine, Trifluoperaz, Triftazin

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia; Short-term anxiety

Efficacy
Improvement of psychotic symptoms; Short-term anxiety

Side Effects
EPS (low), galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
Less weight gain than most other dopamine blockers, take with food. Low dose (2-4 mg) for anxiety, and may be helpful for augmentation in treatment resistant depression. Higher dose from 5 mg for psychosis. Half-life is 10-20 hours.

Recommended doses: for anxiety, 1-2 mg /day with a maximum of 6 mg/day; for psychosis, 2-5 mg 2-3 times a day aiming for a daily dose of 15-20 mg/day. Maximum is 40 mg/day.

Pregnancy
rifluoperazine at high exposure levels interferes with embryo development in experimental animals. Studies in humans did not suggest an increased risk of birth defects or adverse pregnancy outcomes.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3 receptors

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

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Human

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Brain Circuits

Preclinical

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Human

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TRIMIPRAMINE

Brand Names: Surmontil, Rhotrimine, Stangyl

Pharmacology
serotonin, dopamine

Mode of Action
receptor antagonist (5-HT2 and D2)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression. Useful as a bedtime sedative in low doses

Side Effects
Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; Toxic (potentially lethal) in overdosage

Practical Notes
Mechanism unclear, to be determined. At low doses (<50 mg) is primarily an antagonist at H1 and 5HT2 receptors. Mainly metabolized by CYP2D6; one quarter of dose to be used in slow metabolizers and in the presence of strong CYP2D6 inhibitors (fluoxetine, paroxetine) , and one half of dose with moderate inhibitors (bupropion and duloxetine). Higher doses may be necessary in ultra-rapid metabolizers. Does not block norepinephrine or serotonin reuptake.

Recommended doses: 25-50 mg at bedtime and increase by 25 mg every 3-5 days to about 75-100 mg over 2 weeks. Further increases should be implemented as required according to side effects, response, or plasma level determination when available, up to a dose of 300 mg/day.

Pregnancy
Trimipramine interfered with embryo development in experimental animals at dose levels well above those used clinically. There are human case reports of normal outcome after pregnancy exposure.

Pharmacology and mode of action

receptor antagonist (5-HT2, D2)

Neurotransmitter Effects

Preclinical

Antagonist of dopamine D2, NE alpha-1, H1 (very potent), 5-HT2 receptors

Human

Does not decrease platelet 5-HT (marker for 5-HT reuptake)

Physiological

Preclinical

Increase in 5-HT transporter density in the cortex

Human

Does not suppress REM sleep. Sleep promoting

Brain Circuits

Preclinical

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Human

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VALPROATE

Brand Names: Depakene,Depacon,Stavzor

Pharmacology
glutamate

Mode of Action
yet to be determined

Approved Indications
Mania (USA, UK, India, Japan, Australia); Epilepsy; Migraine (Japan; India)

Efficacy
Anti-manic; Anti-epilepsy

Side Effects
Weight gain, sedation, elevated liver enzymes, hair loss,

Practical Notes
There is considerable concern about its use in women of child bearing potential because of the risk of fetal malformations. Valproate is metabolized by multiple liver enzymes and mitochondrial beta-oxidation and not therefore not subjected to clinically relevant drug-drug interactions. Half-life is 9-16 hours. Increases half-life of lamotrigine two-fold.

Recommended doses: 500 mg/day in two doses with a maximal of 1,000 mg/day for migraines; 500-1,000 mg/day in two doses for mania and can be increased by 500 mg/day according to side effects, response, or plasma level determination when available, up to a dose of 3,000 mg/day.

Pregnancy
Valproic acid use during pregnancy is associated with a 1-2% incidence of lumbar meningomyelocele. This abnormality can be diagnosed during the second trimester of pregnancy with ultrasound examination and amniocentesis. Other congenital anomalies have also been associated with valproic acid exposure during pregnancy. The prevalence of birth defects was reported to be higher than with other anticonvulsants, although there was statistical overlap with malformation rates of some of the comparator agents. Valproic acid exposure during pregnancy might lead to neurodevelopmental delay. Registration of pregnant women on anticonvulsants is encouraged.

Neurobiology

Pharmacology and mode of action

unclear

Neurotransmitter Effects

Preclinical

Modulates intracellular signalling.

Human

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Physiological

Preclinical

Anti-epilepsy, inositol depletion, decreases brain cAMP

Human

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Brain Circuits

Preclinical

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Human

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VARENICLINE

Brand Names: Champix, Chantix

Pharmacology
acetylcholine

Mode of Action
receptor partial agonist (nicotinic receptors)

Approved Indications
Smoking cessation

Efficacy
Replacement (substitution treatment) and anti-craving substance for nicotine dependence and withdrawal

Side Effects
Nausea (approx. 30%), abnormal dreaming, gastrointestinal symptoms, rarely low mood, sometimes suicidal ideation

Practical Notes
Efficacy rates appear to be variable in the general population. More than 90% is excreted by kidneys. Half-life is 24 hours.Continuous abstinence from tobacco associated with multiple nAChR subunit genes (including CHRNB2, CHRNA5, and CHRNA4); incidence of nausea is associated with several nAChR subunit genes.

Recommended doses: 0.5 mg daily, after 3 days increase to 0.5 mg twice daily, and may increase after one week to 1 mg twice daily. Smoking can be stopped one to two weeks after starting the medication, 8-35 days, or gradually over 3 months.

Pregnancy
Based on experimental animal studies, use of varenicline during pregnancy is not expected to increase the risk of congenital malformations. There is a report of 23 exposed human pregnancies with no malformations.

Pharmacology and mode of action

receptor partial agonist (nicotinic receptors)

Neurotransmitter Effects

Preclinical

Partial agonist at α4β2* nicotinic acetylcholine receptor so partly mimics effects of nicotine eg on DA release; partial agonist at mouse 5-HT3 receptors

Human

Saturates α4β2* nicotinic acetylcholine receptor in human brain (PET) at low dose so partly mimics effects of nicotine

Physiological

Preclinical

Attenuates the effects of nicotine; decreases DNMT mRNA, reduces the binding of MeCP2 to GAD67 promoters, and increases the levels of GAD67 in the frontal cortex

Human

—

Brain Circuits

Preclinical

Chronic administration upregulates nicotinic acetylcholine receptors in the cortex, hippocampus, striatum and thalamus; increases striatal D2/3 availability (SPECT)

Human

—

V VENLAFAXINE

Brand Names: Effexor

Pharmacology
serotonin, norepinephrine

Mode of Action
reuptake inhibitor (SERT and NET)

Approved Indications
Major depressive disorder; Panic disorder; Generalized anxiety disorder

Efficacy
Improves symptoms of depression and anxiety

Side Effects
GI symptoms, headache, dizziness, insomnia, fatigue, sexual dysfunction, hypotension.

Practical Notes
Doses of 225mg/day needed to inhibit NET. Caution in patients with hypertension. Must be gradually decreased on discontinuation. Metabolized by CYP2D6, but inhibition will only switch the ratio of venlafaxine:desvenlafaxine without increasing the total levels of the two drugs, therefore no dose adjustment necessary with 2D6 inhibitors.

Recommended doses: Consider starting with 37.5 mg/day for one week, especially for panic disorder; otherwise use 75 mg/day and increase dose by 75 mg/day at intervals of about two weeks, but no less than 4 days, as required up to a dose of 375 mg/day.

Pregnancy
Based on experimental animal studies and limited human reports, venlafaxine and its active metabolite desmethylvenlafaxine are not anticipated to increase the risk of congenital anomalies. Transient and usually mild neonatal complications have been reported for venlafaxine and other serotonergic antidepressants.

Pharmacology and mode of action

reuptake inhibitor (SERT and NET)

Neurotransmitter Effects

Preclinical

Increase in extracellular 5-HT and NE levels in several brain areas. SERT binding approximately equal for SERT and NET (primate PET)

Human

Decreased 5-HT platelet content

Physiological

Preclinical

Normalization of 5-HT neuron firing activity, sustained decrease in firing of NE neurons with increased transmission; normalization of decreased GRK2; is a substrate for permeability-glycoproteins

Human

Decrease in tyramine pressor response at 225 mg/day (NET inhibition), suppresses REM sleep

Brain Circuits

Preclinical

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Human

Decreased glucose metabolism in the orbitofrontal cortex and subgenual anterior cingulate cortex

VILAZODONE

Brand Names: Viibryd

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT), receptor partial agonist (5-HT1A)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety

Side Effects
GI symptoms, dry mouth, dizziness, insomnia. Should be gradually decreased upon discontinuation

Practical Notes
Low level of sexual dysfunction. Metabolized by CYP 3A4. Inhibition of CYP3A4 by ketoconazole increases vilazodone by about 50% and induction by carbamazepine decreases by about 50%. Half-life is 24 hours.

Recommended doses: 10 mg/day with food for one week then increase to 20 mg/day, which is an effective dose. Maximum dose is 40 mg/day.

Pregnancy
Based on experimental animal studies, therapy with vilazodone is not expected to increase the risk of congenital malformations. We did not locate human data.

Pharmacology and mode of action

reuptake inhibitor (SERT), receptor partial agonist (5-HT1A)

Neurotransmitter Effects

Preclinical

Increases extracellular levels of 5-HT in frontal cortex and hippocampus; no effect on NE levels

Human

—

Physiological

Preclinical

Does not produce a 5-HT syndrome but attenuates it when triggered by a potent 5-HT1A agonist

Human

Marked REM suppression, slow wave sleep increased

Brain Circuits

Preclinical

Preferential activation of cell body 5-HT1A autoreceptors rather than postsynaptic 5-HT1A receptors

Human

Binds to 5-HT reuptake sites

VORTIOXETINE

Brand Names: Brintellix, Trintellix

Pharmacology
serotonin

Mode of Action
reuptake inhibitor (SERT), receptor partial agonist (5-HT1A), receptor antagonist (5-HT3)

Approved Indications
Major depressive disorder

Efficacy
Improves symptoms of depression and anxiety, and cognitive dysfunction in depression

Side Effects
GI symptoms, headache, dizziness. Low incidence of sexual dysfunction

Practical Notes
No sexual dysfunction at doses < 15 mg/day. Metabolized mainly by CYP 2D6 but also 3A4. Moderate inhibitors of CYP 2D6, like bupropion, increase plasma levels by about 50%. Half-life is about 3 days.

Recommended doses: 5 or 10 mg/day as initial dose and can be increased to 15-20 mg as necessary.

Pregnancy
Based on experimental animal studies, use of vortioxetine during pregnancy is not expected to increase the risk of congenital malformations. There are no human data

Pharmacology and mode of action

reuptake inhibitor (SERT), receptor partial agonist (5-HT1A), receptor antagonist (5-HT3)

Neurotransmitter Effects

Preclinical

Increases 5-HT NE, DA, and ACh in ventral hippocampus and prefrontal cortex, histamine in medial prefrontal cortex, 5-HT in N.Acc. Receptor agonist 5-HT1A, partial agonist 5-HT1B, antagonist 5-HT3, 5-HT7, 5-HT1D

Human

Lower occupancy of SERT than SSRIs in its lower range of antidepressant efficacy

Physiological

Preclinical

—

Human

Suppresses REM sleep

Brain Circuits

Preclinical

Increases cortical neurotransmitter activity via disinhibition of the raphe nucleus and peripheral 5-HT receptors .

Human

—

ZALEPLON

Brand Names: Sonata, Andante, Starnoc

Pharmacology
GABA

Mode of Action
benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Very short half-life, can be used during the night 5 hours or more before driving etc. Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 1-1.5 hours. Only inducers of 3A4 decrease zaleplon levels (four-fold by rifampicin). Synergistic effects with alcohol can produce severe sedation, behavioral changes, anterograde amnesia, and intoxication.

Recommended doses: 10 mg at bedtime and may be increased to 20 mg.

Pregnancy
Based on experimental animal studies, therapy during pregnancy with zaleplon is not expected to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

alpha-1 subunit selective benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Alpha-1 subtype selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy

Human

Sleep-promoting in first few hours after dosing.

Brain Circuits

Preclinical

—

Human

—

ZIPRASIDONE

Brand Names: Geodon, Zeldox

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia; Monotherapy for the acute treatment of bipolar manic or mixed episodes (USA, Canada, Australia); Adjunct to lithium or valproate for the maintenance treatment of bipolar disorder

Efficacy
Improvement of psychotic symptoms and mania

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain (low), QTc issues. Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended as a class warning. Class warning for increased mortality in elderly dementia patients

Practical Notes
Two thirds of ziprasidone is metabolized by aldehyde oxidase and one third by cytochrome 3A4, thus little potential to be affected by drugs metabolized by P450 enzymes. Half-life is 10 hours but twice a day dosing has been show efficacious. Needs to be taken with food (about 500 calories) to be well absorbed. May require EKG monitoring if used with drugs that prolong QTc. Intramuscular preparation is available.

Recommended doses: 40 mg twice a day and can be increased every two days as necessary up to a dose of 100 mg twice a day. The IM dose is 10-20 mg and can be repeated up to a dose of 40 mg/day.

Pregnancy
Ziprasidone interfered with embryo development in experimental animals. There are no controlled human data on pregnancy or lactation.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, NE alpha 1, 5-HT2A, 5-HT2C, 5-HT1B and 5-HT7 receptors, partial agonist at 5-HT1A and 5-HT1D receptors, weak NET and SERT inhibitor

Human

Blocks central D2 receptors (PET)

Physiological

Preclinical

—

Human

Sedative and anticholinergic effects, increases slow wave sleep

Brain Circuits

Preclinical

—

Human

—

ZOLPIDEM

Brand Names: Stilnoct, Ambien

Pharmacology
GABA

Mode of Action
alpha-1 subunit selective benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia

Efficacy
Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Selective for alpha-1 subtype of GABA-A receptor, relevant to sleep/sedation. Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 2-4 hours. A low-dose sublingual preparation has been marketed in the USA for middle-of-the night awakening provided there is at least a four-hour period before getting out of bed. Sleep-related complex behaviours, such as sleep-walking, have been reported, appear dose-dependent, and are increased by alcohol consumption.

Recommended doses: 5-10 mg at bedtime or half of these doses as rescue during the night. Doses should be halved in women because plasma levels are 40% higher than in men.

Pregnancy
Based on experimental animal studies and limited human data, zolpidem is not anticipated to increase the risk of congenital anomalies.

Neurobiology

Pharmacology and mode of action

alpha-1 subunit selective benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Alpha-1 subtype selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

—

Human

—

ZOPICLONE

Brand Names: Zimovane

Pharmacology
GABA

Mode of Action
alpha-1 subunit selective benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Approved Indications
Insomnia (not USA)

Efficacy
Sleep-promoting

Side Effects
Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Practical Notes
Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are largely distinguished by pharmacokinetics unless otherwise indicated. Half-life 5-7 hours. It is metabolized mainly by cytochrome 3A4, thus inhibitors, like erythromycin, clarithromycin, ketoconazole, ritonavir, approximately double the levels of zopiclone , whereas concomitant use of inducers, like carbamazepine, rifampin, phenobarbital, phenytoin, and St-John's wort, may require an increase in dose. Sleep-related complex behaviors, such as sleep-walking, have been reported, appear dose-dependent, and increased by alcohol consumption.

Recommended doses: 3.5, 5, or 7.5 mg at bedtime.

Pregnancy
Based on experimental animal studies and limited human experience, zopiclone or eszopiclone exposure during early pregnancy is not expected to increase the risk of congenital abnormalities. Use of more widely-studied sedative hypnotics during pregnancy might be preferable.

Neurobiology

Pharmacology and mode of action

benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator)

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors

Human

Non-selective PAM

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict

Human

Slows eye saccades; promotes sleep, anxiolytic.

Brain Circuits

Preclinical

—

Human

—

ZOTEPINE

Brand Names: Losizopilon ,Lodopin , Setous, Zoleptil

Pharmacology
dopamine, serotonin

Mode of Action
receptor antagonist (D2, 5-HT2)

Approved Indications
Schizophrenia (Japan)

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
May require EKG monitoring for QTc prolongation. Metabolized by both cytochromes 1A2 and 3A4, thus less susceptible for drug-drug interactions. Half-life is 14 hours.

Recommended doses: 25 mg three times a day and increased as required every 4 days up to a dose of 300 mg/day in three divided doses.

Pregnancy
No information

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2, 5-HT2)

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2, NE alpha 1, 5-HT2A, 5-HT2C, 5-HT6, 5-HT7 receptors, weak NET inhibitor

Human

Blocks dopamine D2 receptors (SPECT)

Physiological

Preclinical

—

Human

Sedative and anticholinergic effects

Brain Circuits

Preclinical

—

Human

—

ZUCLOPENTHIXOL

Brand Names: Clopixol, Cisordinol, Acuphase

Pharmacology
dopamine

Mode of Action
receptor antagonist (D2)

Approved Indications
Schizophrenia; Acute mania

Efficacy
Improvement of psychotic symptoms

Side Effects
EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Practical Notes
It is metabolized by both cytochromes 2D6 and 3A4. Potent inhibitors of 2D6 (fluoxetine and paroxetine) increase levels by about 80%, and the 3A4 inducer carbamazepine decreases them by about 70%. Half-life is 20 hours. When the depot preparation is used, these interactions are no longer significant and need not be taken into account.

Recommended doses: 10-50 mg/day in 2-3 doses and can be increased every 2-3 days in 10-20 mg increments up to a maximum of 100 mg/day. It can be given in a single dose upon stabilization of clinical condition. IM: 50-150 mg and can be repeated very 2-3 days for a maximum cumulative dose of 400 mg and no longer than 2 weeks. Long-acting decanoate dose is 100 mg (peak of action is about 7 days) and 100-200 mg can be injected after 1-4 weeks; usual regimen is 150-300 mg every 2-4 weeks.

Pregnancy
Zuclopenthixol did not increase malformations in rats and rabbits. We did not locate human pregnancy data.

Neurobiology

Pharmacology and mode of action

receptor antagonist (D2)

Neurotransmitter Effects

Preclinical

Antagonist at D1 and D2, NE alpha-1, 5-HT2, H1 receptors

Human

Blocks central dopamine D2 receptors (PET)

Physiological

Preclinical

—

Human

—

Brain Circuits

Preclinical

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Human

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NBN ABBREVIATIONS

Pharmacological Domain

ACh	Acetylcholine
Ca	Calcium
DA	Dopamine
Glu	Glutamate
H	Histamine
Li	Lithium
Mel	Melatonin
NE	Norepinephrine
S	Serotonin
0	Opioid
Or	Orexin

Mode of Action

An	Antagonist
CB	Channel blocker
EI	Enzyme inhibitor
I	Inhibitor
Na	Sodium
NRe	Neurotransmitters Releaser
Re	Releaser
R	Reuptake
RI	Reuptake Inhibitor
RA	Receptor Agonist
RAn	Receptor Antagonist
RPA	Receptor Partial Agonist
Rev	Reversible

ADDITIONAL ABBREVIATIONS

DAT	Dopamine reuptake transporter
EPS	Extrapyramidal syndrome
GABA	Gamma aminobutyric acid
GHB	Gammahydroxybutyrate
GI	Gastrointestinal
HR	Heart rate
IM	Intramuscular
MAOI	Monoamine oxidase inhibitor
NMDA	N-methyl-D-aspartate
NMS	Neuroleptic malignant syndrome
NET	Norepinephrine reuptake transporter
OCD	Obsessive compulsive disorder
PAM	Positive allosteric modulators
PTSD	Post-traumatic stress disorder
REM	Rapid eye movement
SSRI	Selective serotonin reuptake inhibitor
SERT	Serotonin reuptake transporterv
SPC	Summary of Product Characteristics
EMA	European medical Agency
FDA	Food and Drug Administration
RCT	Randomized Controlled Trial

ABOUT ECNP

ECNP is Europe's leading independent scientific association for research into disorders of the brain and their treatments, with a mission to advance the science of the brain, promote better treatment and enhance brain health. Information about ECNP, its aims and activities, can be found at www.ecnp.eu.