

## acamprosate

Axis 1 **Class** glutamate

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-craving in alcohol abstinence after detoxification.

### **Side effects**

Nausea, diarrhoea; caution in pregnancy

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Maintenance of abstinence in alcohol dependence

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# acamprosate

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

NMDA antagonist, GABA and glutamate modulator

## **Neurotransmitter actions**

**Preclinical** Reduces the ethanol-induced dopamine response in N. Accumbens; promotes the release of taurine

**Clinical** Glutamate level in anterior cingulate reduced (<sup>1</sup>H-MRS)

## **Brain circuits**

**Preclinical**

**Clinical** Reduces cue-related brain activity in posterior cingulate cortex (fMRI)

## **Physiological**

**Preclinical** Reduces ethanol consumption and ethanol withdrawal in dependent animals; may act as a “partial co-agonist” at NMDA receptors possibly via a spermidine site

**Clinical** Glutamate level in anterior cingulate reduced (<sup>1</sup>H-MRS)

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## **References**

## agomelatine

Axis 1 **Class** melatonin Bimodal

**Relevant mechanism** receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

Rare cases of transient elevation of hepatic enzymes; little effect on sexual function

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# agomelatine

Axis 2 **Subclass** melatonin, serotonin

Axis 3 **Neurobiological description**

melatonin type 1 and type 2 receptor agonist, serotonin 5-HT<sub>2C</sub> receptor antagonist,

## **Neurotransmitter actions**

**Preclinical** Increases extracellular dopamine (DA) and norepinephrine (NE) in the rat prefrontal cortex and hippocampus; no effect on DA in the nucleus accumbens

**Clinical** Unknown

## **Brain circuits**

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

**Clinical** Prefrontal cortex, hippocampus, amygdala (fMRI)

## **Physiological**

**Preclinical** Increases DA transmission to the dorsal raphe 5-HT neurons; increases 5-HT firing and 5-HT<sub>1A</sub> transmission in the hippocampus; reverses the decrease of neurogenesis produced by prenatal stress; resynchronisation of circadian rhythms; increased neuroplasticity; increase in BDNF, Arc, FGF-2; clock genes

**Clinical** Unknown

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## **References**

## alprazolam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

GAD; panic disorder; short-term treatment of anxiety; alcohol withdrawal (France)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# alprazolam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

**Preclinical** reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy

**Clinical** non- selective PAM

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## **References**

## amisulpride

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia (UK; France)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# amisulpride

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## Neurotransmitter actions

**Preclinical** antagonist at D2 and D3, 5HT7

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

## Brain circuits

**Preclinical**

**Clinical** SPECT - moderate levels of D2/D3 receptor occupancy in striatum and significantly higher levels in thalamus and temporal cortex . PET -no significant binding of amisulpride to 5-HT2A receptors

## Physiological

**Preclinical** Blocks apomorphine-induced climbing and spontaneous grooming in mice; potent blockade of apomorphine-induced effects mediated by dopamine autoreceptors (yawning and hypomotility) compared with those mediated by postsynaptic D2 receptors (e.g. gnawing)

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

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## References



## amitriptyline

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety and reduces chronic pain

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

major depressive disorder; chronic pain

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# amitriptyline

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin and norepinephrine reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Receptor antagonist at histamine H1, ACh M1-4, alpha-1 adrenergic receptors

**Clinical**

## Brain circuits

**Preclinical** Increases extracellular NE in frontal cortex and hypothalamus; increases extracellular dopamine in the nucleus accumbens, hypothalamus, and frontal cortex; increases extracellular 5-HT levels in hypothalamus

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

## Physiological

**Preclinical** Antidepressant-like action in forced swim in rats, mice, and guinea pigs; increase in hippocampus Bcl-2

**Clinical**

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## References

## **amoxapine**

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms in MDD and MDD with psychotic features or agitation

### **Side effects**

Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation; possibility of EPS; Toxic (potentially lethal) in overdose

Axis 5 **Indications (FDA or EMA approved, or as stated)**

major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# amoxapine

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**

norepinephrine and serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Also antagonist of D2, 5HT2, NE alpha-1, histamine H1

**Clinical** PET data - 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.

## Brain circuits

**Preclinical**

**Clinical**

## Physiological

**Preclinical** Catalepsy in mice

**Clinical** PET data - 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.

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## References



# amphetamine (d), amphetamine (d,l)

Axis 2 **Subclass** dopamine, norepinephrine

Axis 3 **Neurobiological description**

dopamine and norepinephrine uptake inhibitor, dopamine releaser

## Neurotransmitter actions

**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

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

## Brain circuits

**Preclinical**

**Clinical** Improves function of DLPFC in executive tasks

## Physiological

**Preclinical**

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

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## References

## aripiprazole

Axis 1 **Class** dopamine Multimodal

**Relevant mechanism** receptor partial agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

Agitation, anxiety, insomnia , akathisia

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia in adults and adolescents; acute mania; agitation in bipolar disorder and schizophrenia; recurrence prevention in bipolar disorder; irritability in autism (US); adjunctive in MDD (US, Japan)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# aripiprazole

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin 5HT1A partial agonist

## **Neurotransmitter actions**

**Preclinical** Partial agonist at D2, D3; 5HT1A partial agonist; weak 5HT2A antagonist

**Clinical** Occupies central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Occupies central dopamine D2 receptors (PET)

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## **References**



## asenapine

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Mania; schizophrenia (US, Canada, Australia)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# asenapine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, 5HT6, 5HT7, NE  
alpha 1 & 2

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical** Striatum, PFC, pituitary

## **Physiological**

**Preclinical**

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**

## **atomoxetine**

Axis 1 **Class** norepinephrine

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Reduces signs and symptoms of ADHD in adults and children.

### **Side effects**

Headache, abdominal pain, decreased appetite, sedation

Axis 5 **Indications (FDA or EMA approved, or as stated)**

ADHD in children >6y and adults

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# atomoxetine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical**      Increases NE and DA in PFC

**Clinical**

## **Brain circuits**

**Preclinical**      increases Fos-positive cells in rat PFC but not in NAc or striatum

**Clinical**            decreases rCBF in midbrain, substantia nigra, thalamus; increase in cerebellum

## **Physiological**

**Preclinical**      Attenuates stress-induced hyperthermia in rat

**Clinical**

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## **References**

## bitopertin

Axis 1 **Class** glycine

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

improves negative symptoms of schizophrenia, especially social and emotional withdrawal, in patients with persistent, predominant negative symptoms, when used adjunctively with antipsychotic therapy

### **Side effects**

Dizziness, nausea, blurred vision

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Not licensed

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# bitopertin

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Selective glycine type1 (Glyt1) reuptake inhibitor

**Neurotransmitter actions**

Preclinical

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical

Clinical

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**References**

## **bupropion**

Axis 1 **Class** dopamine

Multimodal

**Relevant mechanism** reuptake inhibitor and releaser

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Effective in treating depression, smoking cessation, prevention of seasonal MDD

**Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Smoking cessation; major depressive disorder (US and Canada);  
seasonal affective disorder (Canada);

**Committee notes**

**See next page for more detailed neurobiological description,  
references**

# bupropion

Axis 2 **Subclass** dopamine, norepinephrine

Axis 3 **Neurobiological description**

dopamine and norepinephrine reuptake inhibitor, dopamine releaser

## Neurotransmitter actions

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

**Clinical** Does not increase extracellular dopamine levels in striatum (PET); in vitro, moderate to low affinity for human DA transporters in humans (520 nM); negligible affinity for human NE transporters (52,000 nM)

## Brain circuits

**Preclinical**

**Clinical** MRI: increase in blood oxygen level-dependent (BOLD) in hippocampus, amygdala, and prefrontal cortex

## Physiological

**Preclinical** Desensitizes cell body  $\alpha$ 2-adrenergic and 5-HT1A autoreceptors and  $\alpha$ 2-adrenergic on NE and 5-HT terminals; increases  $\alpha$ 1-,  $\alpha$ 2-adrenergic, and 5-HT1A transmission in the rat hippocampus; antidepressant-like action in forced swim test

**Clinical** Does not increase extracellular dopamine levels in striatum (PET); in vitro, moderate to low affinity for human DA transporters in humans (520 nM); negligible affinity for human NE transporters (52,000 nM)

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## References



## **buspirone**

Axis 1 **Class** serotonin

**Relevant mechanism** receptor partial agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

reduces anxiety and tension

### **Side effects**

dizziness, headache, somnolence

Axis 5 **Indications (FDA or EMA approved, or as stated)**

GAD; short term relief of anxiety

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# buspirone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT1A receptor partial agonist

## Neurotransmitter actions

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

**Clinical** Binds to 5HT1A receptors in post-mortem human brain, has downstream effects on dopamine

## Brain circuits

**Preclinical** After microinjection into DRN, hippocampus and amygdala inhibited shock induced vocalization in rats

**Clinical**

## Physiological

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

**Clinical** Binds to 5HT1A receptors in post-mortem human brain, has downstream effects on dopamine

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## References

## carbamazepine, oxcarbazepine

Axis 1 **Class** glutamate ?Multifunctional

**Relevant mechanism** ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-manic, anti-epilepsy, reduces neuropathic pain;

### **Side effects**

Dizziness, somnolence

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Bipolar disorder (not USA); epilepsy

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# carbamazepine, oxcarbazepine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated sodium and calcium channel blocker

## **Neurotransmitter actions**

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

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

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

**Clinical**

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## **References**

## chlordiazepoxide

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Anxiety; alcohol withdrawal (UK); anxiety in GI disorders (Canada; France)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# chlordiazepoxide

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

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## **References**

## chlorpromazine

Axis 1 **Class** dopamine Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms, mania

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia; mania; acute agitation (also porphyria; tetanus; nausea and vomiting; hiccups; behavioural problems in children)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# chlorpromazine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, other receptors antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, NE alpha1, histamine H1, ACh M1-4

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**



## **citalopram**

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder; generalized anxiety disorder; social phobia; obsessive compulsive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# citalopram

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increase in extracellular 5-HT levels in several brain areas; reduces 5-HT<sub>1A</sub> mRNA in the raphe of stressed rats, decreases tryptophan hydroxylase 2 in the raphe; increase in hippocampus Bcl-2

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

## Brain circuits

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

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

## Physiological

**Preclinical** Antidepressant effects in rodent models of depression and anxiety

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

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## References



# clomipramine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin and norepinephrine reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in nucleus accumbens; receptor antagonist at histamine H1, ACh M1-M4, alpha-1 adrenergic receptors

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

## 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

**Clinical** 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

## Physiological

**Preclinical** Antidepressant-like activity in forced swim, chronic unpredictable stress rodent tests; prevents stress-induced decreased expression of membrane glycoprotein 6a, CDC-like kinase 1, G protein alpha q in the hippocampus

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

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## References

## clonazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Epilepsy; panic disorder (US)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# clonazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

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## **References**

## clonidine

Axis 1 **Class** norepinephrine

**Relevant mechanism** receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Reduces signs and symptoms of ADHD in adults and children; antihypertensive; prophylaxis in migraine; adjunct to opiates in cancer pain.

### **Side effects**

Hypotension, somnolence, fatigue

Axis 5 **Indications (FDA or EMA approved, or as stated)**

ADHD in children >6y (US only); hypertension; cancer pain; migraine

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# clonidine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

alpha-2 norepinephrine receptor agonist

## **Neurotransmitter actions**

**Preclinical**      Decreases brain norepinephrine by agonism of alpha-2 norepinephrine autoreceptors

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**      Improves attention and working memory performance and premature responding in rats and monkeys

**Clinical**

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## **References**



## clorazepate

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Short term symptomatic relief of anxiety (Canada, France, Japan);  
alcohol withdrawal (Canada, France)

### **Committee notes**

**See next page for more detailed neurobiological description,  
references**

# clorazepate

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

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## **References**

## clozapine

Axis 1 **Class** dopamine

Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Treatment resistant schizophrenia (US, Europe); reduction of suicide risk in psychosis (US); treatment of psychosis in Parkinson's disease (Europe)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# clozapine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, other receptors antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, NE alpha1 and alpha2, histamine H1, ACh M1-4

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**

## desipramine

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# desipramine

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**

norepinephrine and serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Enhances extracellular levels of NE; weak antagonist at histamine H1, ACh M1-4 alpha-1 adrenergic receptors

**Clinical** Inhibits the tyramine pressor response (NE reuptake inhibition)

## Brain circuits

**Preclinical**

**Clinical**

## Physiological

**Preclinical** Increases mRNA BDNF, calcium calmodulin-dependent protein kinases; decreases TNF; active in forced swim test, especially on climbing behavior

**Clinical** Inhibits the tyramine pressor response (NE reuptake inhibition)

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## References

## desvenlafaxine

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety; decreases vasomotor symptoms in peri-menopause; attenuation of physical painful symptoms

### **Side effects**

GI symptoms, headache, dizziness, insomnia, fatigue, sexual dysfunction. May increase blood pressure at higher doses

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder (US and Australia)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# desvenlafaxine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical** Increase in extracellular 5-HT levels in hypothalamus

**Clinical**

## **Brain circuits**

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

**Clinical**

## **Physiological**

**Preclinical** Increases firing of noradrenaline and 5-HT neurons; antidepressant-like activity in behavioral rodent tests

**Clinical**

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## **References**



## **diazepam**

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Anxiety – particularly GAD; muscle spasms; alcohol withdrawal; status epilepticus

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# diazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**

## donepezil

Axis 1 **Class** acetylcholine

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves or slows worsening of dementia symptoms

### **Side effects**

bradycardia, nausea, diarrhoea, anorexia, abdominal pain, vivid dreams

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Mild, moderate, and severe Alzheimer's disease

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# donepezil

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

cholinesterase inhibitor

**Neurotransmitter actions**

Preclinical      Increases extracellular ACh in all brain regions

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

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

Clinical

---

**References**

## **dosulepin**

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# dosulepin

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin and norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical** Inhibits uptake of SERT and NET. Receptor antagonist at histamine H1, ACh M1-4 , alpha-1 adrenergic receptors

Clinical

## **Brain circuits**

Preclinical

Clinical

## **Physiological**

Preclinical

Clinical

---

## **References**

## **doxepin**

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; v low dose (6mg) for insomnia in USA

### **Committee notes**

**See next page for more detailed neurobiological description, references**

## doxepin

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**

serotonin and norepinephrine reuptake inhibitor

### **Neurotransmitter actions**

**Preclinical** Receptor antagonist at histamine H1, ACh M1-4 (very potent), alpha-1 adrenergic receptors

**Clinical** Very potent histamine H1 inhibitor

### **Brain circuits**

**Preclinical**

**Clinical**

### **Physiological**

**Preclinical**

**Clinical** Very potent histamine H1 inhibitor

---

## **References**



## **duloxetine**

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

Nausea, somnolence, insomnia, and dizziness, sexual dysfunction

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; GAD; diabetic peripheral neuropathic pain; chronic musculoskeletal pain; fibromyalgia (Canada)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# **duloxetine**

Axis 2 **Subclass**      serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

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

**Clinical**          Decreases 5-HT platelet content

## **Brain circuits**

**Preclinical**

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

## **Physiological**

**Preclinical**      Normalization of 5-HT neuron firing activity; antidepressant-like activity in behavioral rodent tests

**Clinical**          Decreases 5-HT platelet content

---

## **References**

## escitalopram

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder; generalized anxiety disorder; social phobia; obsessive compulsive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# escitalopram

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increase in extracellular 5-HT levels in several brain areas

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

## Brain circuits

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

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

## Physiological

**Preclinical** Desensitizes cell body 5-HT<sub>1A</sub> autoreceptors; antidepressant-like activity in behavioral rodent tests

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

---

## References

## estazolam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# estazolam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep

**Clinical** non- selective PAM

---

## **References**

## eszopiclone

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# eszopiclone

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

Preclinical Binds to GABA-A receptors

Clinical

## **Brain circuits**

Preclinical

Clinical

## **Physiological**

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

Clinical

---

## **References**



# flunitrazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

## **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

insomnia (France; Japan; Australia)

## **Committee notes**

**See next page for more detailed neurobiological description, references**

# flunitrazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**

## fluoxetine

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety and reduces compulsive behaviour and 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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; obsessive compulsive disorder; post-traumatic stress disorder; bulimia nervosa; panic disorder; body dysmorphic disorder; premenstrual dysphoric disorder; trichotillomania

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# fluoxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

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

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

## Brain circuits

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

**Clinical** Decreased activity in anterior cingulate cortex in responders in MDD

## Physiological

**Preclinical** Antidepressant-like activity in behavioral rodent tests; desensitizes cell body 5-HT<sub>1A</sub> autoreceptors and terminal 5-HT<sub>1B</sub> autoreceptors; increases mRNA BDNF, calcium calmodulin-dependent protein kinases

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

---

## References

## flupenthixol

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# flupenthixol

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## fluphenazine

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# fluphenazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

**Neurotransmitter actions**

Preclinical antagonist at D1, D2 and D3

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical Catalepsy

Clinical

---

**References**



## flurazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# flurazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**

## fluvoxamine

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder (except in USA); obsessive compulsive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# fluvoxamine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

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

**Clinical** Decreased 5-HT platelet content

## Brain circuits

**Preclinical**

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

## Physiological

**Preclinical** Desensitizes cell body 5-HT<sub>1A</sub> autoreceptors and terminal 5-HT<sub>1B</sub> autoreceptors; antidepressant-like activity in behavioral rodent tests

**Clinical** Decreased 5-HT platelet content

---

## References

## **gabapentin**

Axis 1 **Class** glutamate

**Relevant mechanism** ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-epilepsy, reduces neuropathic pain, reduces anxiety, reduces drug withdrawal craving

**Side effects**

Dizziness, somnolence.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Epilepsy; neuropathic pain.

**Committee notes**

**See next page for more detailed neurobiological description, references**

# **gabapentin**

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated calcium channel blocker, acts at alpha2-delta subunit

## **Neurotransmitter actions**

**Preclinical**      Targets  $\alpha 2\delta$  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 with  $\alpha 2\delta$  type 1 protein. System L transporter substrate

**Clinical**

## **Brain circuits**

**Preclinical**

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

## **Physiological**

**Preclinical**

**Clinical**

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## **References**

## galantamine

Axis 1 **Class** acetylcholine

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves or slows worsening of dementia symptoms

### **Side effects**

Bradycardia, nausea, diarrhoea, anorexia, abdominal pain, vivid dreams

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Mild to moderate Alzheimer's disease

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# galantamine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

cholinesterase inhibitor

**Neurotransmitter actions**

Preclinical      Increases extracellular ACh in all brain regions

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical

Clinical

---

**References**



## **guanfacine**

Axis 1 **Class** norepinephrine

**Relevant mechanism** receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Reduces signs and symptoms of ADHD in adults and children; neuropathic pain; opioid detoxification; sleep hyperhidrosis; withdrawal symptoms in alcohol and opioid withdrawal; anxiety and panic disorder; migraine; premedication for surgery

**Side effects**

Hypotension, somnolence, fatigue

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Hypertension; ADHD in children (Canada)

**Committee notes**

**See next page for more detailed neurobiological description, references**

# guanfacine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

alpha-2 norepinephrine receptor agonist

## **Neurotransmitter actions**

**Preclinical**      Decreases brain norepinephrine by agonism of alpha-2 norepinephrine autoreceptors

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**      Improves attention and working memory performance and premature responding in rats and monkeys

**Clinical**

---

## **References**

# haloperidol

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

## **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

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

## **Committee notes**

**See next page for more detailed neurobiological description, references**

# haloperidol

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, alpha1 adrenergic receptors

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## hydroxyzine

Axis 1 **Class** histamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Decreases anxiety

**Side effects**

Sedation

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Anxiety; allergy

**Committee notes**

**See next page for more detailed neurobiological description, references**

# hydroxyzine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

histamine H1 receptor antagonist

## **Neurotransmitter actions**

**Preclinical**      Binds to Histamine H1, ACh receptors

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

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

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

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

---

## **References**

## iloperidone

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia.

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# iloperidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

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

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical**

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## **References**



## imipramine

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# imipramine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin and norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

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

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Active in antidepressant-like behavioral models; increase in hippocampus BDNF, Bcl-2

**Clinical**

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## **References**

## **isocarboxazid**

Axis 1 **Class** norepinephrine Multifunctional

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **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. irreversible MAOI so duration of action after stopping is 2-3 weeks.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# isocarboxazid

Axis 2 **Subclass** norepinephrine, serotonin, dopamine

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type A and type B

## **Neurotransmitter actions**

**Preclinical** Irreversible MAOI. Increases monoamine levels.  
Increases 5HTP head twitches

**Clinical** Potentiates blood pressure increase to ingestion of tyramine

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Potentiates blood pressure increase to ingestion of tyramine

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## **References**

## lamotrigine

Axis 1 **Class** glutamate

**Relevant mechanism** ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

anti-epilepsy; prevention of depressive episodes in bipolar disorder

### **Side effects**

Skin rash, dizziness

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Prevention of mood episodes in patients with bipolar disorder  
predominantly by preventing depressive episodes; epilepsy

### **Committee notes**

**See next page for more detailed neurobiological description,  
references**

# lamotrigine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated sodium channel blocker

**Neurotransmitter actions**

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

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical

Clinical

---

**References**



# **lisdexamfetamine**

Axis 2 **Subclass** dopamine, norepinephrine

Axis 3 **Neurobiological description**

dopamine and norepinephrine uptake inhibitor, dopamine releaser

## **Neurotransmitter actions**

Preclinical see amphetamine

Clinical see amphetamine

## **Brain circuits**

Preclinical see amphetamine

Clinical see amphetamine

## **Physiological**

Preclinical see amphetamine

Clinical see amphetamine

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## **References**



## **lithium**

Axis 1 **Class** lithium

Multimodal

**Relevant mechanism** cation, enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-manic, mood-stabilizing; used to augment antidepressants

### **Side effects**

Weight gain, tremor, thyroid dysfunction, renal dysfunction

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Bipolar disorder; mania; (US and Europe); recurrent depression; aggressive or self mutilating behaviour (Europe).

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# lithium

Axis 2 **Subclass**      lithium

Axis 3 **Neurobiological description**

Mechanism still to be determined

## **Neurotransmitter actions**

**Preclinical**      Inhibition of Inositol monophosphatase, GMP, GSK-3; increases activity of serotonin and acetyl choline in animal models; modulator of intracellular signalling cascades (multiple); inhibits inositol phosphatase, adenylyl-cyclase

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**              Broad action across all brain regions

## **Physiological**

**Preclinical**      Inositol depletion, decrease brain cAMP

**Clinical**

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## **References**

## lofepramine

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression;

### **Side effects**

Dry mouth, blurry vision, urinary hesitancy, constipation, orthostatic hypotension, sedation, weight gain; Toxic (potentially lethal) in overdose

Axis 5 **Indications (FDA or EMA approved, or as stated)**

major depressive disorder (UK ;Germany; Japan)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# lofepramine

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**  
norepinephrine and serotonin reuptake inhibitor

## **Neurotransmitter actions**

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

**Clinical**

**Brain circuits**

**Preclinical**

**Clinical**

**Physiological**

**Preclinical**

**Clinical**

---

**References**

# lorazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Anxiety ; status epilepticus

**Committee notes**

**See next page for more detailed neurobiological description, references**

# lorazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**

# lormetazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

**Committee notes**

**See next page for more detailed neurobiological description, references**

# lormetazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep; anti-epilepsy

**Clinical** non- selective PAM

---

## **References**



## loxapine

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia (powder aerosol for control of agitation in schizophrenia and bipolar disorder)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# loxapine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, alpha-1 adrenergic receptors

**Clinical** Blocks central D2 and 5HT2A receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Blocks central D2 and 5HT2A receptors (PET)

---

## **References**

## **lurasidone**

Axis 1 **Class** dopamine

Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

EPS, galactorrhea, sedation, dizziness, weight gain. Risk of diabetes, monitoring recommended. Risk of tardive dyskinesia, NMS

Axis 5 **Indications (FDA or EMA approved, or as stated)**

US only: schizophrenia; major depressive episodes associated with bipolar I disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# **lurasidone**

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** antagonist at D2 and D3, 5HT2, 5HT7, partial agonist  
5HT1A

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy; improves cognition in marmoset on difficult  
task

**Clinical**

---

## **References**

## **maprotiline**

Axis 1 **Class** norepinephrine

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

dizziness, somnolence, hyperhidrosis, enuresis

Axis 5 **Indications (FDA or EMA approved, or as stated)**

major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# maprotiline

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

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

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Increase in AMPA subunit expression in hippocampus and striatum

**Clinical**

---

## **References**

## melatonin

Axis 1 **Class** melatonin

**Relevant mechanism** receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Advances circadian phase, decreases sleep latency

**Side effects**

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Sleep onset insomnia in adults age over 55 (not US)

**Committee notes**

**See next page for more detailed neurobiological description, references**

# melatonin

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

melatonin M1 and M2 receptor agonist

**Neurotransmitter actions**

Preclinical

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical

Clinical

---

**References**



## memantine

Axis 1 **Class** glutamate

Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement in dementia symptoms

**Side effects**

Sleepiness, dizziness and balance problems, GI symptoms, raised BP

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Moderate to severe Alzheimer's disease

**Committee notes**

**See next page for more detailed neurobiological description, references**

# memantine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

NMDA antagonist

## **Neurotransmitter actions**

**Preclinical** NMDA antagonist, 5HT3 antagonist

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

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

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

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

---

## **References**



## **methylphenidate (d) and (d,l)**

Axis 2 **Subclass** dopamine, norepinephrine

Axis 3 **Neurobiological description**

dopamine and norepinephrine uptake inhibitor, dopamine releaser

### **Neurotransmitter actions**

**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, NAcc

**Clinical** Occupies DA transporter and increases DA availability in striatum (PET)

### **Brain circuits**

**Preclinical** Induces Fos expression in striatum (cat), persistent c-fos in NAcc, PFC (immature rat), increased c-fos mainly in sensorimotor striatum, but not NAcc (adult rat)

**Clinical**

### **Physiological**

**Preclinical**

**Clinical** Occupies DA transporter and increases DA availability in striatum (PET)

---

## **References**

## **mianserin**

Axis 1 **Class** norepinephrine

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety, promotes sleep

### **Side effects**

Sedation, dizziness, dry mouth, rarely granulocytopenia or agranulocytosis

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# mianserin

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical**      Increases extracellular DA in rat cortex. Antagonist of 5HT2, NE alpha-1 and alpha-2, histamine H1

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical**

---

## **References**

## midazolam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Premedication in anaesthesia; short acting anaesthesia (IV); status epilepticus (IV; intranasal; buccal; rectal)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# midazolam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep; anti-epilepsy

**Clinical** non- selective PAM

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## **References**



## milnacipran

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; fibromyalgia (USA)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# milnacipran

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

## Neurotransmitter actions

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

**Clinical** Small dose-dependent decrease in platelet 5-HT  
reuptake

## Brain circuits

**Preclinical**

**Clinical**

## Physiological

**Preclinical** Increases firing of noradrenaline and 5-HT neurons

**Clinical** Small dose-dependent decrease in platelet 5-HT  
reuptake

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## References

## **mirtazapine**

Axis 1 **Class** serotonin ?Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety; promotes sleep; low level of sexual dysfunction; highly sedative at the beginning of treatment; may stimulate appetite and increase body weight; can reduce post-operative vomiting

**Side effects**

Weight gain; sedation, especially at beginning of treatment

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

**Committee notes**

**See next page for more detailed neurobiological description, references**

# mirtazapine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

## **Neurotransmitter actions**

**Preclinical** Increase in extracellular NE and dopamine in cortex; antagonist at histamine H1, 5HT2, 5HT3, NE alpha-2 receptors.

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

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

**Clinical**

---

## **References**

## **moclobemide**

Axis 1 **Class** norepinephrine Multifunctional

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression, social anxiety disorder

### **Side effects**

May produce orthostatic hypotension; foods containing tyramine must be avoided; must not be used with medications inhibiting 5-HT reuptake

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

## **moclobemide**

Axis 2 **Subclass** norepinephrine, serotonin, dopamine

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type A and type B

### **Neurotransmitter actions**

**Preclinical** Reversible inhibitor. Increase in extracellular dopamine and 5-HT levels in the striatum

**Clinical** Low potentiation of blood pressure increase to ingestion of tyramine

### **Brain circuits**

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

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

### **Physiological**

**Preclinical** Decreased despair in mice behavioral test; increased serotonin and norepinephrine-related behavior after long-term administration; potentiates 5-HTP induced stereotypies; increases phosphorylation of extracellular-regulated kinase (ERK); increase of Bcl-2 and Bcl-xL expression in vitro

**Clinical** Low potentiation of blood pressure increase to ingestion of tyramine

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## **References**

## **modafinil**

Axis 1 **Class** dopamine

?Multimodal

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Promotes wakefulness

### **Side effects**

Headache

Axis 5 **Indications (FDA or EMA approved, or as stated)**

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

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# modafinil

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical** Effects mediated through dopamine; ablating NAcc core blocks modafinil-induced wakefulness in rat

**Clinical** Blocks DA transporters and increases dopamine in brain including NAcc

## **Brain circuits**

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

**Clinical**

## **Physiological**

**Preclinical** Promotes wakefulness

**Clinical** Blocks DA transporters and increases dopamine in brain including NAcc

---

## **References**



## **nalmefene**

Axis 1 **Class** opioid

? Multimodal

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

**Side effects**

Nausea, dizziness, insomnia, decreased appetite

Axis 5 **Indications (FDA or EMA approved, or as stated)**

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

**Committee notes**

**See next page for more detailed neurobiological description, references**

# nalmefene

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

opioid receptor  $\mu$ ,  $\delta$  and  $\kappa$  antagonist

## **Neurotransmitter actions**

**Preclinical** Selective antagonist for  $\mu$  opioid receptors,  $\delta$  opioid receptors and partial agonist at  $\kappa$  receptors

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Improves alcohol and opioid dependence related behaviors

**Clinical**

---

## **References**

## naltrexone

Axis 1 **Class** opioid

? Multimodal

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Maintenance of abstinence in alcohol dependence; adjunct to maintenance of abstinence in opioid dependence

**Committee notes**

**See next page for more detailed neurobiological description, references**

# naltrexone

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

opioid receptor  $\mu$ ,  $\delta$  and  $\kappa$  antagonist

## Neurotransmitter actions

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

**Clinical** Blocks most of mu-opioid and some of delta-opioid receptors after 4 days treatment in abstinent alcoholics (PET)

## Brain circuits

**Preclinical** Prefrontal cortex, nucleus accumbens, arcuate nucleus, ventral tegmental area; tyrosine hydroxylase VTA, substantia nigra; proenkephalin piriform cortex, olfactory tubercle, caudate putamen, NAcc, hypothalamus; CRF hypothalamus, cannabinoid receptor 1

**Clinical** Activation of orbital and cingulate gyri, inferior frontal and middle frontal gyri, and ventral striatum, to alcohol cues reduced in abstinent alcohol-dependent subjects after drug

## Physiological

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

**Clinical** Blocks most of mu-opioid and some of delta-opioid receptors after 4 days treatment in abstinent alcoholics (PET)

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## References

## nefazodone

Axis 1 **Class** serotonin ?Multimodal

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression including insomnia.

### **Side effects**

Rare cases of hepatotoxicity

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder (US)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# nefazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at 5HT2, NE alpha-1 and alpha-2; weak NET and SERT inhibitor

**Clinical** No effect on platelet 5HT2

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** No effect on platelet 5HT2

---

## **References**

## **nortriptyline**

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and chronic pain

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# nortriptyline

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**

norepinephrine and serotonin reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical** Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in nucleus accumbens;. receptor antagonist at histamine H1, ACh M1-4, alpha-1 adrenergic receptors

**Clinical**

**Brain circuits**

**Preclinical**

**Clinical**

**Physiological**

**Preclinical**

**Clinical**

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## **References**



## **olanzapine**

Axis 1 **Class** dopamine

Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms, mania.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

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)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# olanzapine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, other receptors antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3 , 5HT2, NE alpha1, histamine H1, ACh M1-4

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## **oxazepam**

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Anxiety

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# oxazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**

## paliperidone

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Acute and maintenance treatment of schizophrenia in adults

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# paliperidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D2 and D3, NE alpha1 and alpha2, 5HT2A, histamine H1

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** cCatalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## paroxetine

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder; generalized anxiety disorder; social phobia; obsessive compulsive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# paroxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increase in extracellular 5-HT levels in several brain areas

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

## Brain circuits

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

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

## Physiological

**Preclinical** Desensitizes cell body 5-HT<sub>1A</sub> autoreceptors and terminal 5-HT<sub>1B</sub> autoreceptors; antidepressant-like activity in behavioral rodent tests

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

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## References



## perospirone

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia (Japan)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# perospirone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, 5HT3, NE alpha1;  
partial agonist at 5HT1A

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## perphenazine

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia; nausea and vomiting.

**Committee notes**

**See next page for more detailed neurobiological description, references**

# perphenazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3 , 5HT2, NE alpha1, histamine H1, ACh M1-4

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**

## phenelzine

Axis 1 **Class** norepinephrine Multifunctional

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression, GAD panic disorder

### **Side effects**

High probability of producing orthostatic hypotension; Foods containing tyramine must be avoided; Must not be used with medications inhibiting 5-HT reuptake. Irreversible MAOI so duration of action after stopping is 2-3 weeks.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# phenelzine

Axis 2 **Subclass** norepinephrine, serotonin, dopamine

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type A and type B

## Neurotransmitter actions

**Preclinical** Irreversible MAOI. Increased tissue content of 5-HT and NE

**Clinical** Potentiates blood pressure increase to ingestion of tyramine.

## Brain circuits

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

**Clinical**

## Physiological

**Preclinical** Increased transmission at 5-HT1A receptors in the hippocampus, decreased phospholipase C in cortex and hippocampus; active in the forced swim test model of depression

**Clinical** Potentiates blood pressure increase to ingestion of tyramine.

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## References

## **pimozide**

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

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

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# pimozide

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D2 and D3 receptors

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**



## **pipothiazine**

Axis 1 **Class**    dopamine

**Relevant mechanism**    receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia UK, some of Europe, South America

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# pipothiazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

**Neurotransmitter actions**

**Preclinical** Antagonist at D2 and D3, 5HT2, NE alpha1, histamine  
H1, ACh M1-4

**Clinical**

**Brain circuits**

**Preclinical**

**Clinical**

**Physiological**

**Preclinical** Catalepsy

**Clinical**

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**References**

## pregabalin

Axis 1 **Class** glutamate

**Relevant mechanism** ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-epilepsy, reduces neuropathic pain, reduces anxiety, reduces drug withdrawal craving

**Side effects**

Dizziness, somnolence.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

GAD; neuropathic pain; epilepsy

**Committee notes**

**See next page for more detailed neurobiological description, references**

# pregabalin

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated calcium channel blocker, acts at alpha2-delta subunit

## **Neurotransmitter actions**

**Preclinical** Targets  $\alpha 2\delta$  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 with  $\alpha 2\delta$  type 1 protein. System L transporter substrate

**Clinical**

## **Brain circuits**

**Preclinical**

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

## **Physiological**

**Preclinical**

**Clinical**

---

## **References**

## protriptyline

Axis 1 **Class** norepinephrine Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# protriptyline

Axis 2 **Subclass** norepinephrine, serotonin

Axis 3 **Neurobiological description**

norepinephrine and serotonin reuptake inhibitor

## **Neurotransmitter actions**

**Preclinical** Receptor antagonist at histamine H1, ACh M1-4 alpha-1 adrenergic receptors

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical**

---

## **References**

## quazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# quazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**



## quetiapine

Axis 1 **Class** dopamine

Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

Galactorrhea, sedation, dizziness, weight gain; low EPS; QTc issues.  
Risk of tardive dyskinesia, NMS. Clearance reduced in elderly

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia; acute treatment of manic or depressive episodes in bipolar 1 disorder; major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# quetiapine

Axis 2 **Subclass** dopamine, serotonin, norepinephrine

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, norepinephrine reuptake inhibitor (active metabolite)

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3, 5HT2, NE alpha1, alpha2, histamine H1. Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in nucleus accumbens

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## **ramelteon**

Axis 1 **Class** melatonin

**Relevant mechanism** receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Advances circadian phase, decreases sleep latency

**Side effects**

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Sleep-onset insomnia (USA; Japan)

**Committee notes**

**See next page for more detailed neurobiological description, references**

# ramelteon

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

melatonin M1 and M2 receptor agonist

**Neurotransmitter actions**

Preclinical Binds to melatonin M1 and M2 receptors

Clinical

**Brain circuits**

Preclinical

Clinical

**Physiological**

Preclinical

Clinical

---

**References**

## reboxetine

Axis 1 **Class** norepinephrine

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

Urinary hesitancy; may produce tachycardia

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# reboxetine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

## **Neurotransmitter actions**

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

**Clinical** Blocks tyramine pressor response (NE reuptake)

## **Brain circuits**

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

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

## **Physiological**

**Preclinical** Increase in NE transmission through terminal, but not cell body, alpha2-adrenergic autoreceptors; antidepressant-like effect in behavioral models

**Clinical** Blocks tyramine pressor response (NE reuptake)

---

## **References**



# risperidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** antagonist at D2 and D3, NE alpha 1 & 2, 5HT2A,  
histamine H1

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy higher doses

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**



## **rivastigmine**

Axis 1 **Class** acetylcholine

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves or slows worsening of dementia symptoms

### **Side effects**

Bradycardia, nausea, diarrhoea, anorexia, abdominal pain, and vivid dreams

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Mild to moderately severe Alzheimer's disease

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# rivastigmine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

cholinesterase and butyrylcholinesterase inhibitor

## **Neurotransmitter actions**

**Preclinical** Increases extracellular ACh in all brain regions

**Clinical** Enhances memory through ACh

## **Brain circuits**

**Preclinical**

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

## **Physiological**

**Preclinical**

**Clinical** Enhances memory through ACh

---

## **References**

## selegiline

Axis 1 **Class** norepinephrine Multifunctional

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Efficacious in treating MDD 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.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

## selegiline

Axis 2 **Subclass** norepinephrine, serotonin, dopamine

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type B and type A

### Neurotransmitter actions

**Preclinical** Irreversible MAOI. Increase in extracellular striatal dopamine. Metabolite amphetamine

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

### Brain circuits

**Preclinical** Preferential MAO-A in the brain to provide an antidepressant action

**Clinical**

### Physiological

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

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

---

## References

## sertindole

Axis 1 **Class** dopamine Bifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Europe and Australia: schizophrenia patients intolerant to at least one other antipsychotic agent, due to cardiovascular safety concerns

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# sertindole

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1,D2 and D3, NE alpha 1, 5HT2A

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**

## sertraline

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder; generalized anxiety disorder; social phobia; obsessive compulsive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# sertraline

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increase in extracellular 5-HT levels in several brain areas . Weak DAT inhibitor. Reduces 5-HT<sub>1A</sub> mRNA in the raphe of stressed rats

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

## Brain circuits

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

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

## Physiological

**Preclinical** Antidepressant-like activity in behavioral rodent tests

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

---

## References





## sodium oxybate (GHB)

Axis 2 **Subclass** GABA-B

Axis 3 **Neurobiological description**

GABA-B and gammahydroxydutyrate (GHB) receptor agonist

### **Neurotransmitter actions**

**Preclinical** Reduced dopamine 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

**Clinical**

### **Brain circuits**

**Preclinical** Reduces DA turnover in striatum

**Clinical**

### **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

**Clinical**

---

## **References**

## **sulpiride**

Axis 1 **Class**    dopamine

**Relevant mechanism**    receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms. Low EPS. May increase motor agitation and insomnia. Some efficacy in anxiety, depression

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia (UK, France, Germany, Japan); depression (Germany, Japan); anxiety in adults, behavioural problems in children (France)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# sulpiride

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

Preclinical antagonist at D2 and D3

Clinical Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

Preclinical

Clinical

## **Physiological**

Preclinical Catalepsy

Clinical Blocks central dopamine D2 receptors (PET)

---

## **References**

## temazepam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

**Committee notes**

**See next page for more detailed neurobiological description, references**

# temazepam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

**Preclinical**

**Clinical** non- selective PAM

---

## **References**

## thioridazine

Axis 1 **Class** dopamine

Multifunctional

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

Galactorrhea, sedation, dizziness, weight gain, low EPS, QTc issues.

Risk of tardive dyskinesia, NMS

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Treatment-resistant schizophrenia (US)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# thioridazine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, other receptors antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1, D2 and D3 , 5HT2, NE alpha1, histamine H1, Ach M1-4

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

---

## **References**



## **tianeptine**

Axis 1 **Class** glutamate

**Relevant mechanism** Yet to be determined

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

### **Side effects**

Headache, dizziness, insomnia, nightmares, drowsiness, dry mouth, constipation. Low incidence of sexual dysfunction

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder (some European countries)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# tianeptine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

Yet to be determined

## **Neurotransmitter actions**

**Preclinical** Increase in 5-HT reuptake in vivo; attenuates extracellular glutamate in the amygdala in response to stress

**Clinical**

## **Brain circuits**

**Preclinical**

**Clinical**

## **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 6a, G protein alpha q, CREB produced by stress

**Clinical**

---

## **References**

## tranylcypromine

Axis 1 **Class** norepinephrine Multifunctional

**Relevant mechanism** enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **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. Irreversible MAOI so duration of action after stopping is 2-3 weeks.

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# tranylcypromine

Axis 2 **Subclass** norepinephrine, serotonin, dopamine

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type A and type B, dopamine releaser

## **Neurotransmitter actions**

**Preclinical** Irreversible MAOI. Increase of extracellular 5-HT and NE in cortex

**Clinical** Potentiates blood pressure increase to ingestion of tyramine.

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Increase in Bcl-2, Bcl-xL, Arc expression; decreased immobility in the guinea pig; reverses clonidine-induced immobility in the forced swim test

**Clinical** Potentiates blood pressure increase to ingestion of tyramine.

---

## **References**

## **trazodone**

Axis 1 **Class** serotonin

Multimodal

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression including insomnia.

### **Side effects**

Sedation, dry mouth, dizziness. Rarely priapism

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# trazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

## **Neurotransmitter actions**

**Preclinical** Increases extracellular levels of 5-HT in frontal cortex; antagonist at 5HT2, NE alpha-1, weak SERT inhibitor, 5HT1A partial agonist

**Clinical**

## **Brain circuits**

**Preclinical** Full 5-HT1A agonist on cell body 5-HT1A autoreceptors and postsynaptic 5-HT1A receptors in the hippocampus

**Clinical**

## **Physiological**

**Preclinical** Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors; increases 5-HT1A and 2-adrenergic transmission in the rat hippocampus; antidepressant-like action in forced swim test in mice

**Clinical**

---

## **References**

## triazolam

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

### **Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia (not UK, France, Germany)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# triazolam

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical** Broad action across all brain regions

## **Physiological**

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

**Clinical** non- selective PAM

---

## **References**



## trifluoperazine

Axis 1 **Class** dopamine

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms, short term anxiety.

### **Side effects**

EPS (low), galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS

Axis 5 **Indications (FDA or EMA approved, or as stated)**

schizophrenia; short term anxiety

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# trifluoperazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

## **Neurotransmitter actions**

Preclinical Antagonist at D2 and D3

Clinical Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

Preclinical

Clinical

## **Physiological**

Preclinical Catalepsy

Clinical Blocks central dopamine D2 receptors (PET)

---

## **References**

## trimipramine

Axis 1 **Class** serotonin Bimodal

**Relevant mechanism** receptor antagonist

Axis 2 and 3 see next page

Axis 4 **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 overdose

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# trimipramine

Axis 2 **Subclass** serotonin, dopamine

Axis 3 **Neurobiological description**

serotonin 5-HT<sub>2</sub>, dopamine d<sub>2</sub> antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist of dopamine D<sub>2</sub>, NE alpha-1, histamine H<sub>1</sub> (very potent), 5HT<sub>2</sub>

**Clinical** Does not decrease platelet 5-HT (marker for 5-HT reuptake)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Increase in 5-HT transporter density in the cortex

**Clinical** Does not decrease platelet 5-HT (marker for 5-HT reuptake)

---

## **References**

## **valproate**

Axis 1 **Class** glutamate

**Relevant mechanism** ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-manic, anti-epilepsy

### **Side effects**

Weight gain

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Mania (US; UK; India; Japan; Australia); epilepsy; migraine (Japan; India)

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# valproate

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Yet to be determined

## **Neurotransmitter actions**

Preclinical Modulates intracellular signalling.

Clinical

## **Brain circuits**

Preclinical

Clinical

## **Physiological**

Preclinical Anti-epilepsy, inositol depletion, decreases brain cAMP

Clinical

---

## **References**

## **varenicline**

Axis 1 **Class** acetylcholine

**Relevant mechanism** receptor partial agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Replacement and anti-craving substance for nicotine dependence.

### **Side effects**

Nausea (approx. 30%), abnormal dreaming, gastrointestinal symptoms, rarely low mood, sometimes suicidal ideation

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Smoking cessation

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# varenicline

Axis 2 **Subclass**      nicotinic

Axis 3 **Neurobiological description**

alpha4 beta2 nicotinic acetylcholine receptor partial agonist

## Neurotransmitter actions

**Preclinical**      Partial agonist at  $\alpha4\beta2^*$  nAChR so partly mimics effects of nicotine eg on dopamine release; partial agonist at mouse 5-HT3 receptors [4]

**Clinical**           Occupies  $\alpha4\beta2^*$  nAChR in human brain (PET) so partly mimics effects of nicotine

## Brain circuits

**Preclinical**      Chronic administration upregulates nAChRs in the cortex, hippocampus, striatum, and thalamus [13]; increases striatal DRD2/3 availability (SPECT) [14]

**Clinical**           Thalamus, brain stem, cerebellum, middle frontal gyri, corpus callosum

## 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 [15]

**Clinical**           Occupies  $\alpha4\beta2^*$  nAChR in human brain (PET) so partly mimics effects of nicotine

---

## References



## venlafaxine

Axis 1 **Class** serotonin Bifunctional

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

GI symptoms, headache, dizziness, insomnia, fatigue, sexual dysfunction

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder; panic disorder; GAD

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# venlafaxine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

## Neurotransmitter actions

**Preclinical** Increase in extracellular 5-HT and NE levels in several brain areas. SERT binding approx equal for SERT and NET (primate PET)

**Clinical** Decreased 5-HT platelet content

## Brain circuits

**Preclinical**

**Clinical** Decreased glucose metabolism in the orbitofrontal cortex and subgenual anterior cingulate cortex

## Physiological

**Preclinical** Normalization of 5-HT neuron firing activity, sustained decrease firing of NE neurons with increased transmission; antidepressant-like activity in behavioral rodent tests. Normalization of decreased GRK2; May induce permeability-glycoproteins

**Clinical** Decreased 5-HT platelet content

---

## References

## **vilazodone**

Axis 1 **Class** serotonin

Bimodal

### **Relevant mechanism**

reuptake inhibitor and receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

### **Side effects**

GI symptoms, sleep paralysis, dry mouth, dizziness, insomnia. Should be gradually decreased upon discontinuation

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# vilazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor and 5-HT<sub>1A</sub> partial agonist

## **Neurotransmitter actions**

**Preclinical** Increases extracellular levels of 5-HT in frontal cortex and hippocampus; no effect on norepinephrine levels

**Clinical**

## **Brain circuits**

**Preclinical** Preferential activation of cell body 5-HT<sub>1A</sub> autoreceptors rather than postsynaptic 5-HT<sub>1A</sub> receptors

**Clinical** Binds to 5-HT reuptake sites

## **Physiological**

**Preclinical** Antidepressant-like action in rat behavior; reduces anxiety in some behavioral challenges; does not produce a 5-HT syndrome but attenuates it when triggered by a potent 5-HT<sub>1A</sub> agonist

**Clinical**

---

## **References**

## **vortioxetine**

Axis 1 **Class** serotonin

Multimodal

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety , and cognitive dysfunction in depression;

**Side effects**

GI symptoms, headache, dizziness. Low incidence of sexual dysfunction

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Major depressive disorder

**Committee notes**

**See next page for more detailed neurobiological description, references**

# vortioxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor, 5-HT<sub>3</sub>, 5-HT<sub>7</sub>, and 5-HT<sub>1D</sub> receptor antagonist, 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor partial agonist

## **Neurotransmitter actions**

**Preclinical** Increases 5-HT NE, DA, and ACh in ventral hippocampus and prefrontal cortex, histamine in medial prefrontal cortex, 5-HT in nucleus accumbens.

**Clinical** Occupies SERT in raphe nucleus (PET)

## **Brain circuits**

**Preclinical** Increases cortical neurotransmitter activity via disinhibition of the raphe nucleus and peripheral 5-HT receptors .

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Occupies SERT in raphe nucleus (PET)

---

## **References**

## **zaleplon**

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

**Committee notes**

**See next page for more detailed neurobiological description, references**

# **zaleplon**

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** alpha-1 subtype selective PAM

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep; anti-epilepsy

**Clinical** alpha-1 subtype selective PAM

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## **References**





# ziprasidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1,D2 and D3, NE alpha 1 , 5HT2A& 2C, 5HT 1B and 5HT7, partial agonist at 5HT1A and 1D, weak NE and serotonin reuptake inhibitor

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**

## zolpidem

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Insomnia

**Committee notes**

**See next page for more detailed neurobiological description, references**

# zolpidem

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** Alpha-1 subtype selective PAM

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep; anti-epilepsy;

**Clinical** Alpha-1 subtype selective PAM

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## **References**

## **zopiclone**

Axis 1 **Class** GABA

**Relevant mechanism** positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Sleep-promoting

**Side effects**

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

Axis 5 **Indications (FDA or EMA approved, or as stated)**

insomnia (Not US)

**Committee notes**

**See next page for more detailed neurobiological description, references**

# zopiclone

Axis 2 **Subclass** GABA-A positive allosteric modulator

Axis 3 **Neurobiological description**

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

## **Neurotransmitter actions**

**Preclinical** Binds to GABA-A receptors

**Clinical** non- selective PAM

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict

**Clinical** non- selective PAM

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## **References**



# **zotepine**

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**  
dopamine and serotonin antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1 and D2, NE alpha 1 , 5HT2A& 2C, 5HT6, 5HT7, weak NE reuptake inhibitor

**Clinical** Blocks central dopamine D2 receptors (SPECT)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical**

**Clinical** Blocks central dopamine D2 receptors (SPECT)

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## **References**



## **zuclopenthixol**

Axis 1 **Class**    dopamine

**Relevant mechanism**    receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

### **Side effects**

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

Axis 5 **Indications (FDA or EMA approved, or as stated)**

Schizophrenia; acute mania

### **Committee notes**

**See next page for more detailed neurobiological description, references**

# zuclopenthixol

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D1, D2 antagonist

## **Neurotransmitter actions**

**Preclinical** Antagonist at D1 and D2, NE alpha1, 5HT2, histamine H1

**Clinical** Blocks central dopamine D2 receptors (PET)

## **Brain circuits**

**Preclinical**

**Clinical**

## **Physiological**

**Preclinical** Catalepsy

**Clinical** Blocks central dopamine D2 receptors (PET)

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## **References**

