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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Reduces the ethanol-induced dopamine response in N. Accumbens; promotes the release of taurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Glutamate level in anterior cingulate reduced (¹H-MRS)</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Reduces cue-related brain activity in posterior cingulate cortex (fMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Glutamate level in anterior cingulate reduced (¹H-MRS)</td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Reduces ethanol consumption and ethanol withdrawal in dependent animals; may act as a “partial co-agonist” at NMDA receptors possibly via a spermidine site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Glutamate level in anterior cingulate reduced (¹H-MRS)</td>
</tr>
</tbody>
</table>

**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-HT2C 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-HT1A 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

**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**

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds to GABA-A</td>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
</tr>
<tr>
<td>receptors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad action</td>
<td>Broad action across all brain</td>
<td>non-selective PAM</td>
</tr>
<tr>
<td>across all brain</td>
<td>regions</td>
<td></td>
</tr>
<tr>
<td>regions</td>
<td></td>
<td></td>
</tr>
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</table>

**Physiological**

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy</td>
<td>reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>antagonist at D2 and D3, 5HT7</td>
<td>Blocks central dopamine D2 receptors. no significant binding of amisulpride to 5-HT2A receptors (PET)</td>
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**Brain circuits**

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<tr>
<td>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</td>
<td></td>
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**Physiological**

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<tbody>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Blocks central dopamine D2 receptors. no significant binding of amisulpride to 5-HT2A receptors (PET)</td>
<td></td>
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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 overdosage

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**

**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 overdosage

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.

**References**
amphetamine (d), amphetamine (d,l)

Axis 1 **Class**  dopamine  Multimodal

**Relevant mechanism**  reuptake inhibitor and releaser

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of ADHD and narcolepsy

**Side effects**

Weight loss, insomnia

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

ADHD; narcolepsy

**Committee notes**

See next page for more detailed neurobiological description, 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) |

**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**

<table>
<thead>
<tr>
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<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td><strong>Partial agonist</strong> at D2, D3; 5HT1A partial agonist; weak 5HT2A antagonist</td>
<td></td>
<td>Occupies central dopamine D2 receptors (PET)</td>
</tr>
</tbody>
</table>

**Brain circuits**

**Preclinical**

**Clinical**

**Physiological**

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<td>Occupies central dopamine D2 receptors (PET)</td>
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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)

**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
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

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  

References
bupropion

Axis 1 **Class** dopamine **Class** 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 α2-adrenergic and 5-HT1A autoreceptors and α2-adrenergic on NE and 5-HT terminals; increases α1-, α2-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)

**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

**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**

---

**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

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
</tr>
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</table>

### Brain circuits

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Broad action across all brain regions</td>
<td>non-selective PAM</td>
</tr>
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</table>

### Physiological

<table>
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<tr>
<th></th>
<th>Preclinical</th>
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<tbody>
<tr>
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<td>Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy</td>
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</tr>
</tbody>
</table>

## 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-HT1A 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

References
**clomipramine**

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 compulsive behaviour and thoughts.

**Side effects**

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

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

Major depressive disorder; obsessive compulsive disorder; panic disorder; cataplexy in narcolepsy

**Committee notes**

See next page for more detailed neurobiological description, 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; reincreased activity in amygdala to negative valence stimuli; reincreased 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)

---

**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**

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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**

**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

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonist at D1, D2 and D3, 5HT2, NE alpha1 and alpha2, histamine H1, ACh M1-4</td>
<td>Blocks central dopamine D2 receptors (PET)</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blocks central dopamine D2 receptors (PET)</td>
</tr>
</tbody>
</table>

**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 overdosage

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)

---

**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**

**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**

**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**

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<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
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**Brain circuits**

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<tr>
<th>Preclinical</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Broad action across all brain regions</td>
<td></td>
</tr>
</tbody>
</table>

**Physiological**

<table>
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<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**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 Alzheimer's disease. Increases REM sleep

*Clinical*
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 overdosage

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 overdosage

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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor antagonist at histamine H1, ACh M1-4 (very potent), alpha-1 adrenergic receptors</td>
<td>Very potent histamine H1 inhibitor</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Increase in extracellular 5-HT levels in several brain areas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Decreases 5-HT platelet content</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Decreases emotional memory formation; increases amygdala activity for memory retrieval of mood-incongruent items; enhances ventral striatal activity in response to incentive processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Normalization of 5-HT neuron firing activity; antidepressant-like activity in behavioral rodent tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Decreases 5-HT platelet content</td>
</tr>
</tbody>
</table>

### References
**escitalopram**

Axis 1 **Class** serotonin

**Relevant mechanism** reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Implements 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-HT1A 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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
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**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Broad action across all brain regions</td>
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</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces motor activity and promotes sleep</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

---

**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**

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**Physiological**

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<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in extracellular 5-HT levels in several brain areas.</td>
<td>Occupies 80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)</td>
<td>Decreased activity in anterior cingulate cortex in responders in MDD</td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant-like activity in behavioral rodent tests; desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors; increases mRNA BDNF, calcium calmodulin-dependent protein kinases</td>
<td>Occupies 80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Antagonist at D1, D2 and D3</td>
<td>Blocks central dopamine D2 receptors (PET)</td>
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**Brain circuits**

<table>
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<tr>
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<tbody>
<tr>
<td>Catalepsy</td>
</tr>
</tbody>
</table>

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

**Physiological**

<table>
<thead>
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</table>

<table>
<thead>
<tr>
<th>Clinical</th>
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</thead>
</table>

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**
<table>
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<tr>
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**Brain circuits**
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<td>Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy</td>
<td>non-selective PAM</td>
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</table>

**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-HT1A autoreceptors and terminal 5-HT1B 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 α2δ 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 α2δ 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*  

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**

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preclinical</strong></td>
<td>Binds to Histamine H1, ACh receptors</td>
<td>30mg occupies 70% of brain H1 receptors (PET); anticholinergic adverse effects in overdose</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>30mg occupies 70% of brain H1 receptors (PET);</td>
<td>anticholinergic adverse effects in overdose</td>
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**Brain circuits**

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<th>Clinical</th>
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<td><strong>Preclinical</strong></td>
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**Physiological**

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<th>Clinical</th>
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<td></td>
<td>anticholinergic adverse effects in overdose</td>
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</tr>
</tbody>
</table>

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

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 overdosage

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

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**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Irreversible MAOI. Increases monoamine levels.</td>
</tr>
<tr>
<td></td>
<td>Increases 5HTP head twitches</td>
</tr>
<tr>
<td>Clinical</td>
<td>Potentiates blood pressure increase to ingestion of tyramine</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
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<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Preclinical</td>
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<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td></td>
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<tr>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Potentiates blood pressure increase to ingestion of tyramine</td>
</tr>
</tbody>
</table>

**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 1 **Class** dopamine Multimodal

**Relevant mechanism** reuptake inhibitor and releaser

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of ADHD

**Side effects**

Weight loss, insomnia

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

ADHD

**Committee notes**

See next page for more detailed neurobiological description, 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

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

---

**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 overdosage

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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
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**Brain circuits**

<table>
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<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td></td>
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**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

### References
Iormetazepam

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 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
**Iurasidone**

**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 1 **Class** dopamine          Multimodal

**Relevant mechanism** reuptake inhibitor and releaser

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Reduces signs and symptoms of ADHD in adults and children. Used to treat narcolepsy

**Side effects**

Headache, insomnia, nervousness, decreased appetite

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
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 granulcytopenia 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

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**

<table>
<thead>
<tr>
<th></th>
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<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Increase in extracellular levels of 5-HT and NE in cortex. Transporter binding approx equal for SERT and NET (primate PET)</td>
<td>Small dose-dependent decrease in platelet 5-HT reuptake</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
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<th></th>
<th>Preclinical</th>
<th>Clinical</th>
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<tbody>
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<td>Increases firing of noradrenaline and 5-HT neurons</td>
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**Physiological**

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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

**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)

---

**References**
nefazodone

Axis 1 **Class** serotonin

**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
n馈adone

Axis 2  **Subclass**  serotonin

Axis 3  **Neurobiological description**
5HT2 receptor antagonist

**Neurotransmitter actions**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonist at 5HT2, NE alpha-1 and alpha-2; weak NET and SERT inhibitor</td>
<td>No effect on platelet 5HT2</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect on platelet 5HT2</td>
<td></td>
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</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect on platelet 5HT2</td>
<td></td>
</tr>
</tbody>
</table>

**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 overdosage

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**

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**

**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**
<table>
<thead>
<tr>
<th><strong>paliperidone</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axis 1</strong></td>
</tr>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td><strong>Relevant mechanism</strong></td>
</tr>
<tr>
<td><strong>Axis 2 and 3</strong></td>
</tr>
<tr>
<td><strong>Axis 4</strong></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>Improvement of psychotic symptoms.</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
</tr>
<tr>
<td>EPS, galactorrhea, sedation, dizziness, weight gain. Risk of tardive dyskinesia, NMS</td>
</tr>
<tr>
<td><strong>Axis 5</strong></td>
</tr>
<tr>
<td><strong>Indications (FDA or EMA approved, or as stated)</strong></td>
</tr>
<tr>
<td>Acute and maintenance treatment of schizophrenia in adults</td>
</tr>
<tr>
<td><strong>Committee notes</strong></td>
</tr>
<tr>
<td>See next page for more detailed neurobiological description, references</td>
</tr>
</tbody>
</table>
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-HT1A autoreceptors and terminal 5-HT1B 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)

---

**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.

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)

---

**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*  

---

**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 α2δ 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 α2δ 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 overdosage

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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Broad action across all brain regions</td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces motor activity and promotes sleep; anti-epilepsy; anti-conflict</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**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
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**

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase in extracellular NE</strong></td>
<td>Increase in cortex, increase in DA in hippocampus</td>
<td>Blocks tyramine pressor response (NE reuptake)</td>
</tr>
<tr>
<td><strong>Brain circuits</strong></td>
<td>Increase in blood oxygen level-dependent (BOLD) in hippocampus and cortex. Increase in BDNF, Bcl-xL, Bcl-2 expression</td>
<td>Increased brain activity in thalamus, dorsolateral prefrontal and occipital cortex to negative emotional stimuli; increases amygdala responses to positive emotional stimuli</td>
</tr>
<tr>
<td><strong>Physiological</strong></td>
<td>Increase in NE transmission through terminal, but not cell body, alpha2-adrenergic autoreceptors; antidepressant-like effect in behavioral models</td>
<td>Blocks tyramine pressor response (NE reuptake)</td>
</tr>
</tbody>
</table>

**References**
risperidone

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; moderate to severe manic episodes in bipolar disorder; short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a

**Committee notes**

See next page for more detailed neurobiological description, 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-HT1A 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 1 **Class**  GABA  Bifunctional

**Relevant mechanism**  receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Very sedating, improves cataplexy in narcolepsy when given at night.

**Side effects**

Sedation, sleep promoting, marked enhancement of SWS, abused as party drug. Commonly causes dizziness, headache, nausea

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

Cataplexy in narcolepsy (US  Europe Canada); alcohol dependence (Austria; Italy)

**Committee notes**

See next page for more detailed neurobiological description, 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**
- Reduces DA turnover in striatum

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

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds to GABA-A receptors</td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Broad action across all brain regions</td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-selective PAM</td>
</tr>
</tbody>
</table>

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**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**

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<th>Preclinical</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td>Antagonist at D1, D2 and D3, 5HT2, NE alpha1, histamine H1, Ach M1-4</td>
<td>Blocks central dopamine D2 receptors (PET)</td>
</tr>
</tbody>
</table>

**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**

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**Brain circuits**

Preclinical

Clinical

**Physiological**

<table>
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<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalepsy</td>
<td>Blocks central dopamine D2 receptors (PET)</td>
</tr>
</tbody>
</table>

**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 overdosage

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-HT2, dopamine d2 antagonist
**Neurotransmitter actions**

**Preclinical**  Antagonist of dopamine D2, NE alpha-1, histamine H1 (very potent), 5HT2

**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**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial agonist at α4β2* nAChR so partly mimics effects of nicotine eg on dopamine release; partial agonist at mouse 5-HT3 receptors [4]</td>
<td>Occupies α4β2* nAChR in human brain (PET) so partly mimics effects of nicotine</td>
</tr>
</tbody>
</table>

**Brain circuits**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic administration upregulates nAChRs in the cortex, hippocampus, striatum, and thalamus [13]; increases striatal DRD2/3 availability (SPECT) [14]</td>
<td>Thalamus, brain stem, cerebellum, middle frontal gyri, corpus callosum</td>
</tr>
</tbody>
</table>

**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>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]</td>
<td>Occupies α4β2* nAChR in human brain (PET) so partly mimics effects of nicotine</td>
</tr>
</tbody>
</table>

**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

**Neurobiological description**
serotonin reuptake inhibitor and 5-HT1A partial agonist

**Neurotransmitter actions**

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

**Brain circuits**

Preclinical  Preferential activation of cell body 5-HT1A autoreceptors rather than postsynaptic 5-HT1A 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-HT1A agonist

**Clinical**
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-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1A and 5-HT1B 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 |

**References**
**ziprasidone**

Axis 1 **Class**  dopamine  Bifunctional

**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)**

US, Canada, Australia: schizophrenia; monotherapy for the acute treatment of bipolar manic or mixed episodes; adjunct to lithium or valproate for the maintenance treatment of bipolar disorder

**Committee notes**

See next page for more detailed neurobiological description, 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)

**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

**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**

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**Brain circuits**

| Preclinical | Clinical |

**Physiological**

<table>
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<td>Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict</td>
<td>non-selective PAM</td>
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</table>

**References**
zotepine

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
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)

**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**

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**Physiological**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
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</thead>
<tbody>
<tr>
<td>Catalepsy</td>
<td>Blocks central dopamine D2 receptors (PET)</td>
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</tbody>
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**References**