acamprosate

Axis 1 **Class** glutamate

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anti-craving in alcohol abstinence after detoxification.

Side effects

Nausea, diarrhoea; caution in pregnancy

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

Maintenance of abstinence in alcohol dependence

Committee notes

See next page for more detailed neurobiological description, references

acamprosate

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

NMDA antagonist, GABA and glutamate modulator

Neurotransmitter actions

Preclinical	Reduces the ethanol-induced dopamine response in N. Accumbens; promotes the release of taurine
Clinical	Glutamate level in anterior cingulate reduced (^{1}H-MRS)

Brain circuits

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

Physiological

Preclinical	Reduces ethanol consumption and ethanol withdrawal in dependent animals; may act as a “partial co-agonist” at NMDA receptors possibly via a spermidine site
Clinical	Glutamate level in anterior cingulate reduced (^{1}H-MRS)

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

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

amisulpride

Axis 1 **Class** dopamine

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

Side effects

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

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

Schizophrenia (UK; France)

Committee notes

See next page for more detailed neurobiological description, references

amisulpride

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

Neurotransmitter actions

Preclinical	antagonist at D2 and D3, 5HT7
Clinical	Blocks central dopamine D2 receptors. no significant binding of amisulpride to 5-HT2A receptors (PET)

Brain circuits

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

Physiological

Preclinical	Blocks apomorphine-induced climbing and spontaneous grooming in mice; potent blockade of apomorphine-induced effects mediated by dopamine autoreceptors (yawning and hypomotility) compared with those mediated by postsynaptic D2 receptors (e.g. gnawing)
Clinical	Blocks central dopamine D2 receptors. no significant binding of amisulpride to 5-HT2A receptors (PET)

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

Preclinical	Partial agonist at D2, D3; 5HT1A partial agonist; weak 5HT2A antagonist
Clinical	Occupies central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	
Clinical	Occupies central dopamine D2 receptors (PET)

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

atomoxetine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

Neurotransmitter actions

Preclinical	Increases NE and DA in PFC
Clinical	

Brain circuits

Preclinical	increases Fos-positive cells in rat PFC but not in NAc or striatum
Clinical	decreases rCBF in midbrain, substantia nigra, thalamus; increase in cerebellum

Physiological

Preclinical	Attenuates stress-induced hyperthermia in rat
Clinical	

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 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

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References

carbamazepine, oxcarbazepine

Axis 1 **Class** glutamate ?Multifunctional

Relevant mechanism ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

Dizziness, somnolence

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

Bipolar disorder (not USA); epilepsy

Committee notes

See next page for more detailed neurobiological description, references

carbamazepine, oxcarbazepine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated sodium and calcium channel blocker

Neurotransmitter actions

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

Brain circuits

Preclinical	
Clinical	

Physiological

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

References

chlordiazepoxide

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

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

Committee notes

See next page for more detailed neurobiological description, references

chlordiazepoxide

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

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	Antidressant effects in rodent models of depression and anxiety
Clinical	Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

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References

clomipramine

Axis 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; recreased activity in amygdala to negative valence stimuli; recreased 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

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

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

Preclinical	Antagonist at D1, D2 and D3, 5HT2, NE alpha1 and alpha2, histamine H1, ACh M1-4
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	
Clinical	Blocks central dopamine D2 receptors (PET)

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**

serotonin, norepinephrine reuptake inhibitor

Neurotransmitter actions

Preclinical Increase in extracellular 5-HT levels in hypothalamus

Clinical

Brain circuits

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

Clinical

Physiological

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

Clinical

References

diazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

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

Committee notes

See next page for more detailed neurobiological description, references

diazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

donepezil

Axis 1 **Class** acetylcholine

Relevant mechanism enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves or slows worsening of dementia symptoms

Side effects

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

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

Mild, moderate, and severe Alzheimer's disease

Committee notes

See next page for more detailed neurobiological description, references

donepezil

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

cholinesterase inhibitor

Neurotransmitter actions

Preclinical	Increases extracellular ACh in all brain regions
Clinical	

Brain circuits

Preclinical	
Clinical	

Physiological

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

References

dosulepin

Axis 1 **Class** serotonin Bifunctional

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

Side effects

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

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

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	
Clinical	Very potent histamine H1 inhibitor

References

duloxetine

Axis 1 **Class** serotonin Bifunctional

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

Side effects

Nausea, somnolence, insomnia, and dizziness, sexual dysfunction

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

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

Committee notes

See next page for more detailed neurobiological description, references

duloxetine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular 5-HT levels in several brain areas.
Clinical	Decreases 5-HT platelet content

Brain circuits

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

Physiological

Preclinical	Normalization of 5-HT neuron firing activity; antidepressant-like activity in behavioral rodent tests
Clinical	Decreases 5-HT platelet content

References

escitalopram

Axis 1 **Class** serotonin

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

escitalopram

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular 5-HT levels in several brain areas
Clinical	Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Brain circuits

Preclinical	Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)
Clinical	Somewhat greater effects on decreased activity in anterior cingulate cortex, most frontal and parietal areas than citalopram

Physiological

Preclinical	Desensitizes cell body 5-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

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References

estazolam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia

Committee notes

See next page for more detailed neurobiological description, references

estazolam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity and promotes sleep
Clinical	non- selective PAM

References

eszopiclone

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia

Committee notes

See next page for more detailed neurobiological description, references

eszopiclone

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical Binds to GABA-A receptors

Clinical

Brain circuits

Preclinical

Clinical

Physiological

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

Clinical

References

flunitrazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

insomnia (France; Japan; Australia)

Committee notes

See next page for more detailed neurobiological description, references

flunitrazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

fluoxetine

Axis 1 **Class** serotonin

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

fluoxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular 5-HT levels in several brain areas.
Clinical	Occupies 80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Brain circuits

Preclinical	Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)
Clinical	Decreased activity in anterior cingulate cortex in responders in MDD

Physiological

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

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References

flupenthixol

Axis 1 **Class** dopamine

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

Side effects

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

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

Schizophrenia

Committee notes

See next page for more detailed neurobiological description, references

flupenthixol

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

Neurotransmitter actions

Preclinical	Antagonist at D1, D2 and D3
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

fluphenazine

Axis 1 **Class** dopamine

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

Side effects

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

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

Schizophrenia

Committee notes

See next page for more detailed neurobiological description, references

fluphenazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

Neurotransmitter actions

Preclinical antagonist at D1, D2 and D3

Clinical

Brain circuits

Preclinical

Clinical

Physiological

Preclinical Catalepsy

Clinical

References

flurazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia

Committee notes

See next page for more detailed neurobiological description, references

flurazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict activity, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

fluvoxamine

Axis 1 **Class** serotonin

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

fluvoxamine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular 5-HT levels in several brain areas; sigma1 agonist; reduces tyrosine hydroxylase in locus coeruleus
Clinical	Decreased 5-HT platelet content

Brain circuits

Preclinical	
Clinical	After treament 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 volunrteers, 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

Preclinical	Binds to Histamine H1, ACh receptors
Clinical	30mg occupies 70% of brain H1 receptors (PET); anticholinergic adverse effects in overdose

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Slows rat reaction times; causes anticholinergic effects similarly to chlorpheniramine and promethazine
Clinical	30mg occupies 70% of brain H1 receptors (PET); anticholinergic adverse effects in overdose

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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

Preclinical	Irreversible MAOI. Increases monoamine levels. Increases 5HTP head twitches
Clinical	Potentiates blood pressure increase to ingestion of tyramine

Brain circuits

Preclinical

Clinical

Physiological

Preclinical

Clinical Potentiates blood pressure increase to ingestion of tyramine

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References

lamotrigine

Axis 1 **Class** glutamate

Relevant mechanism ion channel blocker

Axis 2 and 3 see next page

Axis 4 **Efficacy**

anti-epilepsy; prevention of depressive episodes in bipolar disorder

Side effects

Skin rash, dizziness

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

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

Committee notes

See next page for more detailed neurobiological description, references

lamotrigine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

Voltage-gated sodium channel blocker

Neurotransmitter actions

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

Clinical

Brain circuits

Preclinical

Clinical

Physiological

Preclinical

Clinical

References

lisdexamfetamine

Axis 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

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

lormetazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia

Committee notes

See next page for more detailed neurobiological description, references

lormetazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

loxapine

Axis 1 **Class** dopamine Bifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

loxapine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and and serotonin antagonist

Neurotransmitter actions

Preclinical	Antagonist at D1, D2 and D3, 5HT2, alpha-1 adrenergic receptors
Clinical	Blocks central D2 and 5HT2A receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

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

References

lurasidone

Axis 1 **Class** dopamine Bifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

lurasidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist

Neurotransmitter actions

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

Clinical

Brain circuits

Preclinical

Clinical

Physiological

Preclinical Catalepsy; improves cognition in marmoset on difficult task

Clinical

References

maprotiline

Axis 1 **Class** norepinephrine

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

Side effects

dizziness, somnolence, hyperhidrosis, enuresis

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

major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

maprotiline

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

Neurotransmitter actions

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

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Increase in AMPA subunit expression in hippocampus and striatum
Clinical	

References

melatonin

Axis 1 **Class** melatonin

Relevant mechanism receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Advances circadian phase, decreases sleep latency

Side effects

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

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

Committee notes

See next page for more detailed neurobiological description, references

melatonin

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

melatonin M1 and M2 receptor agonist

Neurotransmitter actions

Preclinical

Clinical

Brain circuits

Preclinical

Clinical

Physiological

Preclinical

Clinical

References

memantine

Axis 1 **Class** glutamate Multifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement in dementia symptoms

Side effects

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

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

Moderate to severe Alzheimer's disease

Committee notes

See next page for more detailed neurobiological description, references

memantine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

NMDA antagonist

Neurotransmitter actions

Preclinical	NMDA antagonist, 5HT3 antagonist
Clinical	Enhances glutamate through presynaptic mechanisms, neuroprotective through blocking glutamate, blocks NMDA receptors in vivo

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Increases intra-sleep wakefulness, effects blocked by D1 antagonist. Normalizes inflammation-induced disruption of neural encoding in hippocampus (rat in vivo)
Clinical	Enhances glutamate through presynaptic mechanisms, neuroprotective through blocking glutamate, blocks NMDA receptors in vivo

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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

Preclinical	Increase in extracellular levels of 5-HT and NE in cortex. Transporter binding approx equal for SERT and NET (primate PET)
Clinical	Small dose-dependent decrease in platelet 5-HT reuptake

Brain circuits

Preclinical

Clinical

Physiological

Preclinical	Increases firing of noradrenaline and 5-HT neurons
Clinical	Small dose-dependent decrease in platelet 5-HT reuptake

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References

mirtazapine

Axis 1 **Class** serotonin ?Multifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

Weight gain; sedation, especially at beginning of treatment

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

mirtazapine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

Neurotransmitter actions

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

Brain circuits

Preclinical	
Clinical	

Physiological

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

References

moclobemide

Axis 1 **Class** norepinephrine Multifunctional

Relevant mechanism enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression, social anxiety disorder

Side effects

May produce orthostatic hypotension; fods 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 phophorylation of extracellular-regulated kinase (ERK); increase of Bcl-2 and Bcl-xL expression in vitro
Clinical	Low potentiation of blood pressure increase to ingestion of tyramine

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References

modafinil

Axis 1 **Class** dopamine ?Multimodal

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Promotes wakefulness

Side effects

Headache

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

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

Committee notes

See next page for more detailed neurobiological description, references

modafinil

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine reuptake inhibitor

Neurotransmitter actions

Preclinical	Effects mediated through dopamine; ablating NAcc core blocks modafinil-induced wakefulness in rat
Clinical	Blocks DA transporters and increases dopamine in brain including NAcc

Brain circuits

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

Physiological

Preclinical	Promotes wakefulness
Clinical	Blocks DA transporters and increases dopamine in brain including NAcc

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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 μ, δ and κ antagonist

Neurotransmitter actions

Preclinical	Selective antagonist for μ opioid receptors, δ opioid receptors and partial agonist at κ 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 μ, δ and κ 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 ?Multimodal

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression including insomnia.

Side effects

Rare cases of hepatotoxicity

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

Major depressive disorder (US)

Committee notes

See next page for more detailed neurobiological description, references

nefazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

Neurotransmitter actions

Preclinical	Antagonist at 5HT2, NE alpha-1 and alpha-2; weak NET and SERT inhibitor
Clinical	No effect on platelet 5HT2

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	
Clinical	No effect on platelet 5HT2

References

nortriptyline

Axis 1 **Class** norepinephrine Bifunctional

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and chronic pain

Side effects

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

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

oxazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Anxiety

Committee notes

See next page for more detailed neurobiological description, references

oxazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity, conflict behaviour, and promotes sleep; anti-epilepsy
Clinical	non- selective PAM

References

paliperidone

Axis 1 **Class** dopamine Bifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

Side effects

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

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

Acute and maintenance treatment of schizophrenia in adults

Committee notes

See next page for more detailed neurobiological description, references

paliperidone

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist

Neurotransmitter actions

Preclinical	Antagonist at D2 and D3, NE alpha1 and alpha2, 5HT2A, histamine H1
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	cCatalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

paroxetine

Axis 1 **Class** serotonin

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

paroxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular 5-HT levels in several brain areas
Clinical	Occupies 70-80% of striatal SERT at clinical dose (PET); decreased 5-HT platelet content

Brain circuits

Preclinical	Decreases activity of brain structures that are inhibited by 5-HT (i.e. locus coeruleus)
Clinical	Reduction to normal of enhanced activity in pregenual anterior cingulate and enhancement to normal of attenuated prefrontal regions

Physiological

Preclinical	Desensitizes cell body 5-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

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity and promotes sleep; anti-epilepsy; anti-conflict
Clinical	non- selective PAM

References

quetiapine

Axis 1 **Class** dopamine Multifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

quetiapine

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Antagonist at D1, D2 and D3, 5HT2, NE alpha1, alpha2, histamine H1. Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex,5-HT in nucleus accumbens
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

ramelteon

Axis 1 **Class** melatonin

Relevant mechanism receptor agonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Advances circadian phase, decreases sleep latency

Side effects

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

Sleep-onset insomnia (USA; Japan)

Committee notes

See next page for more detailed neurobiological description, references

ramelteon

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

melatonin M1 and M2 receptor agonist

Neurotransmitter actions

Preclinical Binds to melatonin M1 and M2 receptors

Clinical

Brain circuits

Preclinical

Clinical

Physiological

Preclinical

Clinical

References

reboxetine

Axis 1 **Class** norepinephrine

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

Side effects

Urinary hesitancy; may produce tachycardia

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

reboxetine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

norepinephrine reuptake inhibitor

Neurotransmitter actions

Preclinical	Increase in extracellular NE increase in cortex, increase in DA in hippocampus
Clinical	Blocks tyramine pressor response (NE reuptake)

Brain circuits

Preclinical	Increase in blood oxygen level-dependent (BOLD) in hippocampus and cortex. Increase in BDNF, Bcl-xL, Bcl-2 expression
Clinical	Increased brain activity in thalamus, dorsolateral prefrontal and occipital cortex to negative emotional stimuli; increases amygdala responses to positive emotional stimuli

Physiological

Preclinical	Increase in NE transmission through terminal, but not cell body, alpha2-adrenergic autoreceptors; antidepressant-like effect in behavioral models
Clinical	Blocks tyramine pressor response (NE reuptake)

References

risperidone

Axis 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

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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

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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

Preclinical	Reduces DA turnover in striatum
Clinical	

Physiological

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

References

sulpiride

Axis 1 **Class** dopamine

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

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

Committee notes

See next page for more detailed neurobiological description, references

sulpiride

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

Neurotransmitter actions

Preclinical	antagonist at D2 and D3
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

temazepam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia

Committee notes

See next page for more detailed neurobiological description, references

temazepam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	
Clinical	non- selective PAM

References

thioridazine

Axis 1 **Class** dopamine Multifunctional

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms.

Side effects

Galactorrhea, sedation, dizziness, weight gain,low EPS, QTc issues. Risk of tardive dyskinesia, NMS

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

Treatment-resistant schizophrenia (US)

Committee notes

See next page for more detailed neurobiological description, references

thioridazine

Axis 2 **Subclass** dopamine, serotonin

Axis 3 **Neurobiological description**

dopamine and serotonin antagonist, other receptors antagonist

Neurotransmitter actions

Preclinical	Antagonist at D1, D2 and D3 , 5HT2, NE alpha1, histamine H1, Ach M1-4
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

tianeptine

Axis 1 **Class** glutamate

Relevant mechanism Yet to be determined

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

Side effects

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

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

Major depressive disorder (some European countries)

Committee notes

See next page for more detailed neurobiological description, references

tianeptine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

Yet to be determined

Neurotransmitter actions

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

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	No net change in 5-HT transmission in the rat brain; reverses depressant-like effect of prenatal stress; increase in BDNF protein in amygdala; reverses reduction of NGF, membrane glycoprotein 6a, G protein alpha q, CREB produced by stress
Clinical	

References

tranylcypromine

Axis 1 **Class** norepinephrine Multifunctional

Relevant mechanism enzyme inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression

Side effects

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

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

tranylcypromine

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

Axis 3 **Neurobiological description**

monoamine oxidase inhibitor type A and type B, dopamine releaser

Neurotransmitter actions

Preclinical	Irreversible MAOI. Increase of extracellular 5-HT and NE in cortex
Clinical	Potentiates blood pressure increase to ingestion of tyramine.

Brain circuits

Preclinical

Clinical

Physiological

Preclinical	Increase in Bcl-2, Bcl-xL, Arc expression; decreased immobility in the guinea pig; reverses clonidine-induced immobility in the forced swim test
Clinical	Potentiates blood pressure increase to ingestion of tyramine.

References

trazodone

Axis 1 **Class** serotonin Multimodal

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression including insomnia.

Side effects

Sedation, dry mouth, dizziness. Rarely priapism

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

trazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

5HT2 receptor antagonist

Neurotransmitter actions

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

Brain circuits

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

Physiological

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

References

triazolam

Axis 1 **Class** GABA

Relevant mechanism positive allosteric modulator

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Anxiolytic; muscle relaxant; anticonvulsant; sleep-promoting

Side effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit

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

Insomnia (not UK, France, Germany)

Committee notes

See next page for more detailed neurobiological description, references

triazolam

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

Axis 3 **Neurobiological description**

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

Neurotransmitter actions

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	Broad action across all brain regions

Physiological

Preclinical	Reduces motor activity and promotes sleep; anti-epilepsy; anti-conflict
Clinical	non- selective PAM

References

trifluoperazine

Axis 1 **Class** dopamine

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improvement of psychotic symptoms, short term anxiety.

Side effects

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

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

schizophrenia; short term anxiety

Committee notes

See next page for more detailed neurobiological description, references

trifluoperazine

Axis 2 **Subclass**

Axis 3 **Neurobiological description**

dopamine D2 antagonist

Neurotransmitter actions

Preclinical	Antagonist at D2 and D3
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References

trimipramine

Axis 1 **Class** serotonin Bimodal

Relevant mechanism receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression. Useful as a bedtime sedative in low doses

Side effects

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

Preclinical	Partial agonist at α4β2* nAChR so partly mimics effects of nicotine eg on dopamine release; partial agonist at mouse 5-HT3 receptors [4]
Clinical	Occupies α4β2* nAChR in human brain (PET) so partly mimics effects of nicotine

Brain circuits

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

Physiological

Preclinical	Attenuates the effects of nicotine; decreases DNMT mRNA, reduces the binding of MeCP2 to GAD67 promoters, and increases the levels of GAD67 in the frontal cortex [15]
Clinical	Occupies α4β2* nAChR in human brain (PET) so partly mimics effects of nicotine

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References

venlafaxine

Axis 1 **Class** serotonin Bifunctional

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

Side effects

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

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

Major depressive disorder; panic disorder; GAD

Committee notes

See next page for more detailed neurobiological description, references

venlafaxine

Axis 2 **Subclass** serotonin, norepinephrine

Axis 3 **Neurobiological description**

serotonin, norepinephrine reuptake inhibitor

Neurotransmitter actions

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

Brain circuits

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

Physiological

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

References

vilazodone

Axis 1 **Class** serotonin Bimodal

Relevant mechanism reuptake inhibitor and receptor antagonist

Axis 2 and 3 see next page

Axis 4 **Efficacy**

Improves symptoms of depression and anxiety

Side effects

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

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

vilazodone

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor and 5-HT1A partial agonist

Neurotransmitter actions

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

Brain circuits

Preclinical	Preferential activation of cell body 5-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	

References

vortioxetine

Axis 1 **Class** serotonin Multimodal

Relevant mechanism reuptake inhibitor

Axis 2 and 3 see next page

Axis 4 **Efficacy**

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

Side effects

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

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

Major depressive disorder

Committee notes

See next page for more detailed neurobiological description, references

vortioxetine

Axis 2 **Subclass** serotonin

Axis 3 **Neurobiological description**

serotonin reuptake inhibitor, 5-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

Preclinical	Binds to GABA-A receptors
Clinical	non- selective PAM

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict
Clinical	non- selective PAM

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

Preclinical	Antagonist at D1 and D2, NE alpha1, 5HT2, histamine H1
Clinical	Blocks central dopamine D2 receptors (PET)

Brain circuits

Preclinical	
Clinical	

Physiological

Preclinical	Catalepsy
Clinical	Blocks central dopamine D2 receptors (PET)

References