NbN C&A

NEUROSCIENCE based NOMENCLATURE Child & Adolescent

Nomenclature Taskforce

Joseph Zohar, chair

Celso Arango

Jeremy Veenstra-Vanderweele

Stephen Stahl

Pierre Blier

David Nutt

David Kupfer

Hiroyuki Uchida

Filippo Drago

Alessandro Zuddas

Gil Zalsman

Christoph Correll

ECNP european college of neuropsychopharmacology

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European College of Neuropsychopharmacology
Bolognalaan 28, 3584 CJ Utrecht, The Netherlands
secretariat@ecnp.eu
www.ecnp.eu

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Preface

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

The Neuroscience-based Nomenclature project was launched with exactly this challenge in mind.

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

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

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

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

Joseph Zohar, MD
Taskforce chair

Content

Mission and Scope

In recent years, it has become clear that the established pharmacological nomenclature of psychotropic medications does not reflect contemporary pharmacologic knowledge, nor does it appropriately inform the clinician about neuroscience-based drug prescribing. Moreover, the current nomenclature is confusing to patients, as very often therapists prescribe "antidepressants" for anxiety disorders or "second generation antipsychotics" to depressed patients.

For all of these reasons there is a need to develop a more adequate nomenclature system.

The mission of NbN is to reflect current neuroscience understanding in order to decrease stigma and help clinicians make informed decisions when planning the next "neuropsychopharmacological step".

While NbN reflects the best contemporary knowledge in pharmacology, it does not necessarily can never represent the ultimate scientific truth. The taskforce, however, has decided that it is better to present the most cutting-edge scientific interpretation available than to wait for the definitive scientific conclusion. After all, we need to treat our patients now.

NbN-ca (Neuroscience-based Nomenclature - child and adolescent) aims to bring the clinician a state-of-the-art nomenclature system for the use of psychotropic drugs in children and adolescents, with a focus on the child and adolescent population.

NbN-ca is based on:

1. The need to treat now.
2. Updated insights in neuroscience,reflecting current knowledge and understanding regarding neurotransmitters/molecules/systems being modified plus mode/mechanisms of action.
3. The judgement of the members of the taskforce.
4. The assumption that children are developing and therefore developmental aspects (e.g. liver and kidney function, brain developmental stage) must be considered in use and dosage.

With these considerations, the taskforce formulated a nomenclature that is based on pharmacology and mode of action.

This novel nomenclature provides information regarding four clinically relevant dimensions:

Approved Indications

Based on the recommendations of major regulatory bodies (e.g. FDA, EMA, etc.) for this age group.

Efficacy and Side Effects

Aimed at highlighting situations in which a compound has no formal approval for an indication, yet there is evidence to support its use in additional condition(s), for example well-supported expert guidelines.

In the side effects section, only serious, life-threatening or prevalent side effects are listed

Practical Note

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

Neurobiology

Derived from empirical data.

For those who would like to learn more about the pharmacology discussed, please see the direct link to the relevant site of IUPHAR – our collaborator in this endeavour.

As this is an ongoing process, we recognise that there may be relevant information that is not yet included. Based on your feedback, the response of other colleagues (the “wisdom of clinicians”), and new reports and findings, appropriate updates will be performed.

NbN-ca embeds the current understanding of neuroscience advances in order to provide a comprehensive and coherent naming system for children and adolescent drugs. The taskforce hopes that this novel nomenclature will help clinicians make more informed drug prescribing decisions and that its scientific backing will reduce confusion and decrease stigma.

Seven Important Comments on NbN

1. Medication included

In principle, medications with CNS indications are included. In this book you will find the medications that we were aware of. The taskforce welcomes proposals to include medications that for one reason or another were omitted.

Please check our website: www.ecnp.eu/nomenclature

1a. Fixed combination of medication

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

2. Inclusion criteria for the efficacy section

Positive single, large, RCT , “heavy solid weight” clinical data, and/or well-supported expert guidelines.

3. Inclusion criteria for the side effects section

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

4. The practical note

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

5. Neurobiology

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

6. Affinity

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

7. Uptake inhibitors

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

Nine Specific Nots on NbN-ca

1. The NbN-ca includes the drugs that are often used in children and adolescents even if evidence for efficacy is limited.

2. This book does not include all drugs currently used for children and adolescents, rather the drugs that are most often used. In future editions (and based on your feedback and suggestions) more drugs will be added.

3. For some drugs (mostly older), use (and at times even indication) in children and adolescents is extrapolated from adult populations. Hence the need for special caution in inferring efficacy and safety in children and adolescents..

4. Metabolism changes during puberty can necessitate dosage adjustments. For example, faster hepatic and renal function in children can lead to the use of adult-like dosing regimens despite lower body weights. In children entering puberty, with hepatic and renal function slowing down, clinicians should be vigilant and screen for increased side effects, despite stable doses, and may require downward dose adjustment. Conversely, large increases in body weight may require upward dose adjustments, in the case of otherwise unexplained loss of efficacy in spite of stable dosing.

5. At the initiation of pharmacological treatment for depression frequent clinical assessments are called for, due to the claimed risk of suicidal ideation/behaviours at treatment initiation in patients younger than 25 years, although no increase in suicide rate has been reported.

6. Side effects of drugs for psychosis are more common in children and adolescents than in adults, especially weight gain and sedation. In cases of marked weight gain, it is important to monitor hepatic function to rule out fatty liver-related dysfunction.

7. Low adherence in children and adolescents is a major concern, even more so than in other disorders.

8. Sexual side effects of drugs may be burdensome in adolescents (who tend not to talk about them openly), and are a major cause for low adherence.

9. Safety data of long-term effects of drugs on growth and maturation in children and adolescents are mostly incomplete.

Pharmacological domain & Mode of Action

Pharmacological Domain

- Acetylcholine
- Calcium
- Dopamine
- Glutamate
- Histamine
- Lithium
- Melatonin
- Norepinephrine
- Opioid
- Orexin
- Serotonin

Mode of Action

- Enzyme inhibitor
- Enzyme modulator
- Ion channel blocker
- Neurotransmitters releaser
- Positive allosteric modulator (PAM)
- Receptor agonist
- Receptor antagonist
- Receptor partial agonist
- Reuptake inhibitor

Index

Pharmacology *Index*

Mode of Action *Index*

Medication *Index* (Alphabetically)

Amisulpride

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

Pharmacology

Dopamine

Mode of Action

Receptor antagonist (D2)

Approved Indications

Efficacy

Side Effects

EPS, akathisia, dystonia, galactorrhea, sedation, dizziness, prolactin elevation, QTc prolongation, risk of tardive dyskinesia, NMS.

Practical Notes

Indication extrapolated from old studies in adult population, therefore need to be cautious in inferring efficacy in children and adolescents. Caution regarding EPS and prolactin elevation, QTc prolongation. Renally excreted, ensure adequate renal functioning, but may be given in cases of hepatic enzyme impairment. Safety and efficacy in pediatric population under 12 have not been established.
Doses extrapolated from adults: dose range: 50-1200 mg/day, usual effective doses in adult schizophrenia 400-800 mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, 5-HT7 receptors.

Human

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

Physiological

Preclinical

Human

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

Brain Circuits

Preclinical

Human

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

Amitriptyline

Brand Names: Elavil, Vanatrip

Pharmacology

Serotonin, Norepinephrine

Mode of Action

Reuptake inhibitor (SERT and NET), Receptor antagonist (5-HT2)

Approved Indications

MDD (12+ USA); MDD (16+ UK, Europe)

Efficacy

Side Effects

Similar patterns of side effects with similar or greater frequency/severity than in adults; sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, QTc prolongation, toxic in overdose (potentially lethal).

Practical Notes

Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25 years, although no increased in the suicide rate has been reported.
Doses extrapolated from adults: initiate at 25-50 mg, dose range for adult depression: 75-150 mg/d.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Increase in hippocampus Bcl-2.

Human

Anti-muscarinic effects in healthy volunteers; suppresses REM sleep.

Brain Circuits

Preclinical

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

Human

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

Amphetamine (D) and (D,L)

Brand Names: Adderall, Dexamfetamine, Evekeo, Dyanavel XR

Pharmacology

Dopamine, Norepinephrine

Mode of Action

Reuptake inhibitor (DAT, NET), Releaser (DA, NE)

Approved Indications

ADHD (10+ US, 13+ Europe).

Efficacy

Efficacy at least as high as with methylphenidate, treats inattention and hyperactivity equally well; comorbid oppositional/ disruptive/aggressive behaviors in youth with ADHD (less efficacious than for ADHD symptoms themselves); daytime sleepiness in children with narcolepsy.

Side Effects

Decreased appetite, weight loss, which can lead to slowed growth, insomnia, as well as rebound ADHD symptoms; sometimes blunted affect, dysphoria/irritability; tics may develop or worsen; psychosis may develop or worsen, sometimes dysphoria/ irritability.

Practical Notes

Abuse potential, performance-enhancing use in the absence of ADHD and potential for diversion require attention; measure height and weight regularly; obtain ECG prior to initiation only if structural heart defect or personal or family history indicating risk for cardiac pathology/arrhythmia. Several slow release formulations are available, with longer duration of action (usually once daily) and lower abuse potential. Avoid using prolonged -release preparations after lunch because of insomnia. Consider stopping the drug during holidays if underweight.
Starting dose of 5-10 mg in the morning. Can increase once per week by 5-10 mg total daily dose, typically divided into a morning and afternoon dose.
Maximum suggested daily dose of 30 mg; although some treatment-refractory patients may need higher dose.

Former Terminology

Stimulant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

Increased locomotion, reduced sleep and appetite, sterotypy.

Human

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

Brain Circuits

Preclinical

Human

Improves function of DLPFC in executive tasks.

Aripiprazole

Brand Names: Abilify, Aristada

Pharmacology

Dopamine, Serotonin

Mode of Action

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

Approved Indications

Bipolar Disorder type I, acute and maintenance (10+ USA); schizophrenia; (13+ USA, 15+ Europe); manic episodes in adolescents, for 12 weeks (13+ Europe); irritability/aggression in youth with autistic spectrum disorders (6-17 USA), Tourette's syndrom (6+ USA).

Efficacy

Tic disorder.

Side Effects

Akathisia especially in the beginning of treatment ,nausea, greater prolactin-lowering effects in prepubertal boys than other pediatric populations; weight gain greater in youth than in adults, and greater in those with no or little prior antipsychotic exposure (less than olanzapine, clozapine, quetiapine, risperidone, paliperidone, asenapine); greater sedating properties than in adults; risk of NMS. Chronic insomnia and suicidal behaviour have been reported in children and adolescents.

Practical Notes

Low starting dose and slow titration significantly reduces partial D2- agonist- related side effects, such as restlessness/akathisia risk as well as nausea/vomiting. Based on adult data, could be used as augmentation in unipolar depression, OCD especially with tic-related symptoms, and Tourette syndrome. Depot formulation available in adults (schizophrenia), but not licensed for children and adolescents due to a lack of data on safety and efficacy. When switching from a dopamine anatagonist, tapering off should be started only after steady state is achieved with aripiprazole and this may take a few weeks.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Occupies central D2 receptors (PET).

Physiological

Preclinical

Human

Nausea, Akathisia.

Brain Circuits

Preclinical

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

Human

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

Asenapine

Brand Names: Saphris, Sycrest

Pharmacology

Serotonin, Dopamine, Norepinephrine

Mode of Action

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

Approved Indications

Acute treatment of manic or mixed episodes (10+ USA).

Efficacy

Psychotic symptoms.

Side Effects

Sedation, dizziness, weight gain (more than in adults), EPS, akathisia, dystonia, galactorrhea. Risk of tardive dyskinesia, NMS. Risk of diabetes low but monitoring recommended.

Practical Notes

Mixed data in adolescents with schizophrenia. Rapid onset of effect (within 30 minutes). 24 hour half-life.

Initiate at 2.5 mg sublingually twice a day, may titrate after 3 days, may increase to 5 mg sublingually twice daily, and after an additional 3 days to 10 mg twice a day, as needed and tolerated. Recommended dose: 2.5 to 10 mg sublingually twice a day; maximum dose: 10 mg sublingually twice a day. Sublingual dosing, but less metallic taste and dysgeusia when dissolved in cheek. No food or drink for 10 minutes after the dose.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, 5-HT6, 5-HT7, NE alpha and alpha2 receptors.

Human

Blocks central dopamine D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Striatum, PFC, Pituitary.

Atomoxetine

Brand Names: Strattera

Pharmacology

Norepinephrine

Mode of Action

Reuptake inhibitor (NET)

Approved Indications

ADHD (6+ USA and Europe).

Efficacy

Hyperactivity and inattention symptoms; also effective for comorbid oppositional/disruptive/aggressive behaviors in youth with ADHD, but less so than for ADHD symptoms themselves; ADHD symptoms in autistic spectrum disorder.

Side Effects

Headache, abdominal pain, decreased appetite, sedation. Less weight loss than with stimulants; liver enzyme elevation (see reference to hepatic issues in NbN-ca 9 specific notes). Should only be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

Practical Notes

Second-line or third-line ADHD treatment after stimulants; roughly two thirds of the effect size compared to methylphenidate and amphetamines. Consider if tics are a problem with stimulants. Primarily metabolized by CYP2D6; one quarter of doses to be used in slow metabolizers and in the presence of CYP2D6 inhibitors. Higher doses may be necessary in ultra-rapid metabolizers.

Initial dosing 0.5 mg/kg (max 40 mg) in the morning. Can increase every 2 weeks to recommended target dose of 1.2 mg/kg or 80 mg. Treatment refractory patients may benefit from dosing up to 1.8 mg/kg (max 100 mg), which may be better tolerated in divided dosing with second dose in afternoon.

Former Terminology

Neurobiology

Neurotransmitter Effects

Preclinical

Increases NE and DA in PFC.

Human

Physiological

Preclinical

Human

Increase in BP and HR.

Brain Circuits

Preclinical

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

Human

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

Bupropion

Brand Names: Wellbutrin, Xyban, Buproban

Pharmacology

Norepinephrine, Dopamine

Mode of Action

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

Approved Indications

Efficacy

ADHD as third line treatment.

Side Effects

Mild weight loss, insomnia.

Practical Notes

To reduce risk of insomnia dose twice daily, second dose 8 hours after AM dose and in the afternoon, not in the evening; use extended release formulation, as immediate release formulation is associated with greater risk for seizures. Taper slowly on discontinuation. May be used for smoking cessation in adolescents. Despite supportive adule studies, no randomised placebo-controlled data exist for depression in children and adolesence.

Typically begin at 100-150 mg/day in divided (twice daily) dosing. Increase as high as 450 mg/day. Recommend using extended release formulation, as immediate release formulation is associated with greater risk for seizures.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Increases BOLD signal in hippocampus, amygdala, and prefrontal cortex.

Chlorpromazine

Brand Names: Largactil, Thorazine

Pharmacology

Dopamine, Serotonin

Mode of Action

Receptor antagonist (D2, 5-HT2)

Approved Indications

Severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance (1-12 USA); childhood schizophrenia and autism, agitation and anxiety (1+ Europe).

Efficacy

Psychotic symptoms.

Side Effects

EPS, akathisia, dystonia, galactorrhea, sedation, dizziness, weight gain, hypotension. Risk of tardive dyskinesia, NMS. Greater sensitivity in youth for sedation than in adults.

Practical Notes

Indication for age 1-12 appears to be extrapolated from research among patients older than 18, therefore there is a need to be cautious in inferring efficacy in children and adolescents. Sedation and hypothension are very frequent and may impair academic function. Do not use in children with Reye's syndrome.

Can start at 2.5 mg/kg/d divided dosing. Typically given 12.5-25 mg initially IM for agitation or aggression, with titration up to doses as high as 50 mg IM for refractory agitation.
Under age 5 do not exceed 40mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Blocks central dopamine D2 receptors (PET).

Physiological

Preclinical

Human

Sedative and anticholinergic effects. Increases slow wave sleep.

Brain Circuits

Preclinical

Human

Citalopram

Brand Names: Celexa, Cipramil

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

Efficacy

Depression in children and adolescents.

Side Effects

GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction. May prolong QT interval at dose > 40 mg per day. Must be gradually decreased on discontinuation. For all SRIs: claimed risk of suicidality in patients younger than 25 years (all drugs for depression compared to placebo).

Practical Notes

Pay particular attention to signs of activation in children with developmental disorder or brain injury. Like other SRIs, may be considered in anxiety disorders and OCD. Caution regarding EPS and prolactin elevation, QTc prolongation. Safety and efficacy in pediatric population under 12 have not been established.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

In children <12, start 10 mg daily and titrate every 2 weeks by 5-10 mg daily up to a maximum dose of 40 mg. In adolescents, may start 20 mg daily and titrate every 2 weeks by 10 mg/d to a maximum dose of 40 mg. Adolescents with OCD are sometimes prescribed higher doses.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

Human

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

Brain Circuits

Preclinical

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

Human

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

Clomipramine

Brand Names: Anafranil

Pharmacology

Serotonin, Norepinephrine

Mode of Action

Reuptake inhibitor SERT, NET (metabolite)

Approved Indications

OCD (10+ USA).

Efficacy

Compulsive behaviour and obsessional thoughts, enuresis.

Side Effects

Sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, QTc prolongation, toxic in overdose (potentially lethal).

Practical Notes

Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). Should be more consistently tapered when discontinued in children than in adults. Primarily metabolized by CYP2D6; one quarter of doses to be used in slow metabolizers and in the presence of 2D6 inhibitors, higher doses may be necessary in ultra-rapid metabolizers. Demethylated to a potent NET inhibitor by CYP1A2. Slow release preparations are available in some countries.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideations at treatment initiation in patients younger than 25 years, although no increased suicide rate has been reported.

Doses: Initiated at 25 mg in two doses: dose range from 75 mg to 250 mg in 2 divided doses.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

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

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

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

Human

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

Clonazepam

Brand Names: Antelepsin, Rivotril, Klonopin

Pharmacology

GABA

Mode of Action

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

Approved Indications

Epilepsy.

Efficacy

Acute agitation in adolescents, panic disorder, anxiety, acute mixed or manic episodes, tic disorders.

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit, dizziness.

Practical Notes

Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 19-60 hours. Could be given twice daily. Less likely to produce withdrawal symptoms because of long half-life. For high doses, taper on discontinuation to avoid withdrawal symptoms. May generate behavioural disinhibition particularly in children.

Dosing: 0.25-6 mg.

Former Terminology

Anxiolytic.

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Non-selective PAM.

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

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Human

Broad action across all brain regions.

Clonidine

Brand Names: Catapres, Kapvay

Pharmacology

Norepinephrine

Mode of Action

Receptor agonist (NE alpha-2)

Approved Indications

ADHD (6+ USA) (long-acting formulation).

Efficacy

Second-line ADHD treatment after stimulants; adjunctive to treatment with stimulants; comorbid oppositional/disruptive/aggressive behaviors in children with ADHD, but less effective than for ADHD symptoms themselves.

Side Effects

Hypotension, somnolence, fatigue. Risk of rebound hypertension on abrupt withdrawal, potential for hypotension when administered with beta blockers.

Practical Notes

Roughly two thirds of the effect size in ADHD treatment compared to methylphenidate and amphetamines, roughly equal efficacy for inattention and hyperactivity despite more fatigue, somnolence and sedation than placebo. May be helpful in tic disorders including Tourette. May be helpful in conduct disorder and oppositional defiant disorder. May be combined with stimulants if the latter induce tics. Do not co-administer with beta blockers to avoid severe hypotension. In some countries, available as a long-acting formulation that is dosed once or twice daily. Early signs of toxicity may appear at low doses than in adults. Can also be given adjunctively in the evening only to offset rebound or insomnia associated with stimulants' long-acting formulation.

For children under 40.5 kg, start 0.05 mg at night. Every 3-7 days, may increase by 0.05 mg total daily dose in divided (three or four times daily) dosing to suggested maximum total dose of 0.2 mg/d. In children over 40.5 kg or in adolescents, may start 0.1 mg at night and increase by 0.1 mg total daily dosing to a maximum total dose of 0.4 mg/day. Taper over 2-4 days to avoid rebound hypertension when stopping.

Former Terminology

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Thalamic actions noted on fMRI.

Clozapine

Brand Names: Clozaril, Fazaclo, Leponex

Pharmacology

Dopamine, Serotonin, Norepinephrine

Mode of Action

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

Approved Indications

Schizophrenia (refractory) (16+ Europe).

Efficacy

Psychotic symptoms. Pediatric trials show greater efficacy than haloperidol and regular or high-dose olanzapine in youth with treatment resistant schizophrenia; also established anti-aggressive properties in youth. Anti suicidal effects in schizophrenia.

Side Effects

Sedation, dizziness, weight gain, hypersalivation, tachycardia, hypotension, hyperthermia, EPS (low), galactorrhea (low). Risk of tardive dyskinesia (low), neuroleptic malignant syndrome. Risk of agranulocytosis, monitoring required. Risk of diabetes, monitoring recommended. Hypersalivation and other metabolic effects. Risk of psychosis if abruptly discontinued. Risk of seizures at higher doses (>600 mg). Risk of treatment-emergent obsessive compulsive symptoms. Risk of intestinal blockade -rare but fatal.

Practical Notes

Follow national regulations for registration of patients prescribed clozapine and for WBC/ANC blood testing. Consider drawing blood in afternoon to obtain higher WBC/ANC readings. Clozapine blood levels between 350-450 ng/dL may represent therapeutic window, Tobacco increases metabolism. May have antisuicidal effects, may reduce tardive dyskinesia and be effective for treatment resistant mood disorders. Slow increases recommended when titrating dose; if side effects a problem, slow up-titration. Slow taper for discontinuation to avoid cholinergic symptoms and rebound psychosis.

In adolescents, start 12.5 mg at HS or twice daily, follow adult titration schedule. Consider bedtime dosing instead of twice daily dosing to reduce daytime sedation. Avoid single dose above 450 mg for seizure risk. Beware of myoclonic jerks, dose >/=600 mg/day and single doses above 450mg as risk factors for seizures; if seizures occur, do not stop clozapine if needed, but rather add valproic acid.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha1 and alpha2, H1, ACh M1-4 receptors.

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Human

Sedative and anticholinergic effects.

Brain Circuits

Preclinical

Human

Desipramine

Brand Names: Norpramin

Pharmacology

Norepinephrine

Mode of Action

Reuptake inhibitor (NET)

Approved Indications

Efficacy

Enuresis (low doses).

Side Effects

Sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, QTc prolongation, toxic in overdose (potentially lethal).

Practical Notes

Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). Should be more consistently tapered when discontinued in children than in adults. An active metabolite of imipramine. Primarily metabolized by CYP2D6; one quarter of doses to be used in slow metabolizers and in the presence of CYP2D6 inhibitors, higher doses may be necessary in ultra-rapid metabolizers.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideations at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Not recommended before age 12. Doses extrapolated from adults: initiate at 25 mg in 2-3 divided doses; dose range for adult anxiety or depression is 75-300 mg/d in 2-3 divided doses (single dose should not exceed 150 mg/d).

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Inhibits the tyramine pressor response (NE reuptake inhibition).

Physiological

Preclinical

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

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

Human

Diphenhydramine

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

Pharmacology

Histamine

Mode of Action

Receptor antagonist (H1)

Approved Indications

Efficacy

OTC use in insomnia.

Side Effects

Anticholinergic effects including sedation, dry skin and mucosa, tachycardia, urinary retention, cognitive dulling. May produce delirium in overdose.

Practical Notes

Rapid discontinuation after long-term use can result in cholinergic rebound symptoms. Could be used for treatment of acute extrapyramidal symptoms, parkinsonism and dystonia. May generate behavioural disinhibition particularly in children.

Dosing:12.5-100mg/d. (Available in tablets and liquid)

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Doxepin

Brand Names: Deptran, Sinequan, Silenor

Pharmacology

Norepinephrine, serotonin

Mode of Action

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

Approved Indications

MDD 12+ (USA ,UK, other European countries).

Efficacy

Side Effects

Similar patterns of adverse effects with similar or greater frequency/severity than in adults. Sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, toxic in overdose (potentially lethal).

Practical Notes

Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Is a powerful antihistamine, used in very low doses (3-6 mg) for insomnia and sedation. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). Primarily metabolized by CYP2D6; one quarter of doses to be used in slow metabolizers and in the presence of CYP2D6 inhibitors, higher doses may be necessary in ultra-rapid metabolizers. Should be more consistently tapered when discontinued in children than in adults.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideations at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Doses extrapolated from adults: initiate at 25 mg in 2-3 divided doses; dose range for adult anxiety or depression is 75-300 mg/d in 2-3 divided doses (single dose should not exceed 150 mg/d).

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Very potent H1 inhibitor.

Physiological

Preclinical

Human

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

Brain Circuits

Preclinical

Human

Duloxetine

Brand Names: Cymbalta, Irenka

Pharmacology

Serotonin, norepinephrine

Mode of Action

Reuptake inhibitor (SERT and NET)

Approved Indications

GAD (7+ USA).

Efficacy

Side Effects

Nausea, somnolence, insomnia, dizziness, oropharyngeal pain, cough, sexual dysfunction.

Practical Notes

Gradually decreased on discontinuation.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideations at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Starting dose 30mg/day, increase after 2 weeks by 30mg.
Recommended dose rage is 30-60 mg once daily (up to 60mg/d).

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Decreases 5-HT platelet content.

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

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

Escitalopram

Brand Names: Cipralex, Lexapro

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

MDD 12+ (USA).

Efficacy

OCD, social anxiety disorder (SAD).

Side Effects

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

Practical Notes

Pay particular attention to signs of activation in children with developmental disorder or brain injury. Caution regarding EPS and prolactin elevation, QTc prolongation. Safety and efficacy in pediatric population under 12 have not been established. Reduced clinical response in CYP2C19 ultra-rapid metabolizers.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Suggested starting dose of 5 mg in children under 12, 10 mg in adolescents, with titration every 1-3 weeks up to a maximum of 20 mg. Adolescents with OCD are sometimes prescribed higher doses.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors.

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

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

Human

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

Eszopiclone

Brand Names: Lunesta

Pharmacology

GABA

Mode of Action

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

Approved Indications

Efficacy

Insomnia (short-term use only).

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit.

Practical Notes

Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are largely distinguished by pharmacokinetics unless otherwise indicated. Half-life 5-7 hours. If on higher dose, taper upon discontinuation to avoid withdrawal symptoms.

Dosing: 1-3mg.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Non-selective PAM.

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict.

Human

Slows eye saccades; promotes sleep, anxiolytic.

Brain Circuits

Preclinical

Human

Fluoxetine

Brand Names: Prozac, Sarafem, Selfemra

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

Major depressive episode (moderate to severe) (8+USA) and (8+Europe) if unresponsive to psychological therapy after 4-6 sessions), OCD (7+USA).

Efficacy

Panic disorder.

Side Effects

Similar side effects and safety in youth as in adults. GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction.

Practical Notes

Pay particular attention to signs of activation in children with a developmental disorder or brain injury. Complete inhibition of CYP2D6 and significant inhibition of CYP2C19 - check drug interactions. Long half-life hence effects persist for some days to weeks after discontinuation. Like other SRIs, may be considered in other anxiety disorders (e.g. SAD).

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Initially recommended dose 10mg/d; may increase after 2 weeks to by 20mg10mg/day. Further titration up to 60 mg. Some children are rapid metabolizers and need higher doses and twice daily.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

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

Human

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

Fluvoxamine

Brand Names: Faverin, Luzox

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

OCD (8+ USA and Europe).

Efficacy

Social anxiety disorder and other anxiety disorders.

Side Effects

Similar side effects and safety in youth as in adults. GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction.

Practical Notes

Pay particular attention to signs of activation in children with developmental disorder or brain injury. Inhibits several CYP450 enzymes therefore many drug interactions can occur with other drug classes. Prolongs effect of melatonin, interaction with caffeine and theophylline may cause jitteriness, excessive stimulation, more rarely seizures. gradually decreased on discontinuation.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Start 25-50 mg at night only. Once per 4-7 days, can increase by 25-50 mg total daily dose. Divide doses twice daily once > 50 mg. For children up to 11 years old, can increase up to 200 mg/day. For adolescents, can increase up to 300 mg/day. Adolescents with OCD are sometimes prescribed higher doses.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Decreased 5-HT platelet content.

Physiological

Preclinical

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

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

Human

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

Gabapentin

Brand Names: Neurontin, Gralise, Gabarone, Fanatrex

Pharmacology

Glutamate

Mode of Action

Alpha-2 delta calcium channel blocker

Approved Indications

Epilepsy (3+ USA, 6+ Europe)

Efficacy

Anxiety, post-herpetic neuralgia, chronic pain, alcohol craving and withdrawal symptoms.

Side Effects

Dizziness, somnolence, tremor, nausea, ataxia.

Practical Notes

Similar to pregabalin, less well-absorbed. Excreted by kidney, use lower dose if renal impairment. Possibility of increased sedation if used with lorazepam. More consistent effect if used in higher doses. If higher doses not tolerated, consider switch to pregabalin.

Dosing: Children <12 years old: starting dose: 10-15 mg/kg/d (given in divided doses 2 or 3 times a day).
Effective dose: 25-50 mg/kg/d tid (or bid); adolescents 300-2400 mg/d tid (or bid).

Former Terminology

Anxiolytic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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Physiological

Preclinical

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Human

Increases slow wave sleep.

Brain Circuits

Preclinical

Human

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

Guanfacine

Brand Names: Intuniv, Tenex

Pharmacology

Norepinephrine

Mode of Action

Receptor agonist (NE alpha-2)

Approved Indications

ADHD (6+ USA) and (6+ Europe in children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective) (prolonged release formulation).

Efficacy

Second-line ADHD treatment after stimulants; adjunctive to stimulant treatment; ADHD symptoms in autism, treatment of comorbid oppositional/disruptive/aggressive behaviours in children with ADHD, but less effective than for ADHD symptoms themselves; tic.

Side Effects

Hypotension, somnolence, fatigue. Risk of rebound hypertension on abrupt withdrawal, potential for hypotension when administered with beta blockers.

Practical Notes

Roughly two thirds of the effect size compared to methylphenidate and amphetamines, roughly equal efficacy for inattention and hyperactivity despite more fatigue, somnolence and sedation than placebo. Effective treatment for tics, so a good combination treatment with stimulants if the latter induce tics; some studies suggest utility in conduct disorder, oppositional defiant disorder especially when comorbid with ADHD. Can also be given adjunctively in the evening only to offset rebound or insomnia associated with stimulants' long-acting formulation. Available as a long-acting formulation in some countries, which may better tolerated especially for sedation.

For children <40.5 kg, start 0.5 mg once or twice daily. Once per week, can increase by 0.5 mg total daily dose to 2 mg total daily dose. For children > 40.5 kg and for adolescents, start 0.5 mg once or twice daily and can increase to 4 mg total daily dose. If too sedating, can do bedtime only for 1-2 weeks until sedation has improved.

Former Terminology

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Haloperidol

Brand Names: Haldol, Serenase

Pharmacology

Dopamine

Mode of Action

Receptor antagonist (D2)

Approved Indications

Childhood behavioural disorders, especially when associated with hyperactivity and aggression; Tourette syndrome (3+ USA, Europe); childhood schizophrenia (3+ Europe).

Efficacy

Psychotic symptoms, tics, agitation and aggression.

Side Effects

Sedation, dizziness, prolactin elevation, weight gain, EPS, akathisia, acute dyskinesia. Risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

Indication extrapolated from old studies in adult population, therefore need to be cautious in inferring efficacy in children and adolescents.

For children 3–12 years old, start 0.025-0.05 mg/kg total daily dose in divided (twice or three times daily) dosing. Every 5-7 days, can increase by 0.5 mg/day to anticipated dose of 0.15 mg/kg total daily dose.
For adolescents, start 0.25–0.1 mg/kg/day twice or three times daily.
Can increase to 3-5 mg twice or three times daily. Start with very low doses if possible and titrate slowly. Depot formulation available in adults (schizophrenia), but not licensed for children and adolescents due to a lack of data on safety and efficacy.

Former Terminology

Aantipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, NE alpha1 receptors.

Human

Blocks central dopamine D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Hydroxyzine

Brand Names: Atarax, Vistaril

Pharmacology

Histamine

Mode of Action

Receptor antagonist (H1)

Approved Indications

Anxiety

Efficacy

Agitation, insomnia, anti-emetic.

Side Effects

Anticholinergic effects including sedation, dry skin and mucosa, tachycardia, urinary retention, cognitive dulling. May produce delirium in overdose. Hydroxyzine has very low affinity at muscarinic receptors.

Practical Notes

Discontinuation after long-term use can result in cholinergic rebound symptoms. Tolerance may occur. May generate behavioural disinhibition particularly in children.

Dosing: 50-100mg/d (Available as tablets and liquid, and IM in USA).

Former Terminology

Anxiolytic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to H1, ACh M1-4 receptors.

Human

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

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Imipramine

Brand Names: Tofranil

Pharmacology

Serotonin, Norepinephrine

Mode of Action

Reuptake inhibitor (SERT and NET)

Approved Indications

Relief of nocturnal enuresis in children (6+ USA, UK).

Efficacy

Side Effects

Sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, QTc prolongation, toxic in overdose (potentially lethal). Behavioural changes may occur in children receiving Imipramine for nocturnal enuresis.

Practical Notes

Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). Primarily metabolized by CYP2D6; one quarter of doses to be used in slow metabolizers and in the presence of CYP2D6 inhibitors, higher doses may be necessary in ultra-rapid metabolizers. Partly metabolized to desipramine. Oral solution contains sorbitol: unsuitable for patients with hereditary fructose intolerance.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Doses for enuresis: 6 years to 12 years: initial dose: 25 mg/d; maintenance dose: 50 mg/d; 12 years to 18 years: initial dose: 25 mg/d; maintenance dose: 75 mg/d; (maximum dose: 2.5 mg/kg/d age 6-17). Doses for depression extrapolated from adults: initiate at 25mg, dose range for adult depression: 50-300 mg/d.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Increase in hippocampal BDNF, Bcl-2.

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

Human

Lisdexamfetamine

Brand Names: Elvanse, Vyvanse

Pharmacology

Dopamine, norepinephrin

Mode of Action

Reuptake inhibitor (DAT, NET), releaser (DAT, NET)

Approved Indications

ADHD (6+ USA). ADHD when no response to methylphenidate (6+ Europe).

Efficacy

Side Effects

Loss of appetite, loss of weight, early insomnia, blunted affect, tics might develop or worsen, psychosis may develop or worsen, dysphoria/irritability, headache.

Practical Notes

This is a prodrug to dextroamphetamine, with the same pharmacological effects but slower onset of action, and has less abuse liability (is not active if snorted or injected). Obtain ECG prior to initiation only if structural heart defect or personal or family history indicate risk of cardiac pathology/ arrhythmia. Seems to be similarly effective to d-amphetamine and methylphenidate, but effects may last longer. Capsules may be opened and the contents mixed with yogurt/apple sauce or dissolved in water or juice.

Initial starting dose for children and adolescents of 30 mg in the morning.
Some children may not tolerate this dose and may benefit from a lower dose.
Titrate upward once per week by 10-20 mg to a maximum daily dose of 70 mg.

Former Terminology

Stimulant

Neurobiology

Neurotransmitter Effects

Preclinical

see amphetamine.

Human

Little data.

Physiological

Preclinical

see amphetamine.

Human

Probably as amphetamine.

Brain Circuits

Preclinical

See amphetamine.

Human

Probably as amphetamine.

Lithium

Brand Names: Lithobid, Eskalith

Pharmacology

Lithium

Mode of Action

Enzyme interactions

Approved Indications

Treatment and prophylaxis of mania; treatment and prophylaxis of bipolar disorder (12+ USA, Europe). Treatment and prophylaxis of recurrent depression (UK, other European countries).

Efficacy

Anti-manic; mood stabilizing; used to augment effect of drugs for depression; suicide prevention; anti-aggression.

Side Effects

Weight gain; tremor; parathyroid, thyroid and renal dysfunction.

Practical Notes

Narrow therapeutic window so monitor plasma levels regularly (maintenance: approximately 0.6-0.8 mmol/L; acute mania: 0.9-1.2 mmol/L). Provide detailed information on what increases lithium levels (sweating without adequate fluid replacement, diarrhea, vomiting, concurrent NSAID (non-steroidal anti-inflammatory drugs) and many other drugs, and what reduces lithium levels (increased fluid intake).

Strongly advise the use of contraceptives to sexually active female adolescents to avoid foetal defects. Start at 10 mg/kg total daily dose, divided three or four times daily. May increase by 10 mg/kg total daily dose every 5 days. Maximum suggested 60 mg/kg total daily dose or 2400 mg/d, but adjust dose based on plasma level.

Former Terminology

Mood stabiliser

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Inositol depletion, decreases brain cAMP.

Human

Brain Circuits

Preclinical

Human

Broad action across all brain regions.

Lorazepam

Brand Names: Ativan

Pharmacology

GABA

Mode of Action

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

Approved Indications

Status epilepticus.

Efficacy

As IM or PO (for acute agitation in adolescents, anxiety, panic attack, insomnia).

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit.

Practical Notes

Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life is 12 hours, but metabolized to lorazepam glucuronide, half-life 18 of hours. Can be given in 2 to 4 divided doses. If on high doses, taper upon discontinuation to avoid withdrawal symptoms. May generate behavioral disinhibition, particularly in children.

Dosing: 0.25-6mg.

Former Terminology

Anxiolytic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Non- selective PAM.

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Broad action across all brain regions.

Lurasidone

Brand Names: Latuda

Pharmacology

Dopamine, serotonin

Mode of Action

Receptor antagonist (D2, 5-HT2)

Approved Indications

Schizophrenia (13-17 USA).

Efficacy

Psychotic symptoms.

Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, weight gain (less than olanzapine, clozapine, quetiapine, risperidone, paliperidone, asenapine).
Risk of diabetes (low but monitoring recommended). Risk of tardive dyskinesia, NMS.

Practical Notes

Has to be taken with food (at least 350 kcal, fat content is irrelevant) or plasma levels can drop to <50%. Evening instead of morning dosing results in reduced akathisia rates.

Initiate at 20 or 40mg/d and increase every 3-5 days by 20-40mg. Usual efficacy for psychosis is 40-80mg/d for adolescents.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Improves cognition in marmoset on difficult tasks.

Human

Brain Circuits

Preclinical

Human

Melatonin

Brand Names: Circadin

Pharmacology

Melatonin

Mode of Action

Receptor agonist (Mel1 and Mel2)

Approved Indications

Efficacy

Delayed sleep phase, decreases sleep latency.

Side Effects

Side effects rare.

Practical Notes

Resynchronises circadian rhythm. May improve sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, ADHD, autism and learning difficulties. Typically dosed at bedtime for soporific effects in patients with sleep-onset insomnia but sometimes dosed 2-3 hours before bedtime for patients with delayed circadian rhythms. Available as prolonged release prescription medicine for adults in Europe, with dosing 2-3 hours before bedtime.
Over the counter products can vary significantly in content.
Pharmaceutical grades are available.

Start at 0.5-1 mg and increase by 0.5-1 mg to a typical treating dose of 3 mg.
In patients who benefit from 3 mg but with some continued difficulty, higher doses are sometimes given.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Human

Physiological

Preclinical

Human

Shortens sleep onset latency and advances circadian phase.

Brain Circuits

Preclinical

Human

Methylphenidate D and D,L

Brand Names: Ritalin, Concerta, Metadate CD, Quillivant XR

Pharmacology

Dopamine, norepinephrine

Mode of Action

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

Approved Indications

ADHD (6+ USA and Europe).

Efficacy

Signs and symptoms of ADHD; daytime sleepiness and cataplexy in narcolepsy.

Side Effects

Decreased appetite / weight loss / failure to gain weight (common) which can lead to slowed growth, insomnia, end-of dose ADHD rebound symptoms; sometimes blunted affect, dysphoria/irritability; tics may develop or worsen; psychosis may develop or worsen.

Practical Notes

Abuse potential, performance-enhancing use in the absence of ADHD and potential for diversion require attention; measure height and weight regularly; obtain ECG prior to initiation only if structural heart defect or personal or family history indicating risk for cardiac pathology/arrhythmia.
Several slow-release formulations are available, with longer duration of action (usually once daily) and lower abuse potential. Avoid using slow release formulations after lunch because of insomnia.
Consider stopping the drug during weekends and/or holidays if underweight.

For immediate release preparations starting dose 0.3 mg/kg total dose per day, divided twice or three times per day, or 2.5-5 mg twice daily. Increase by 0.1 mg/kg or 5-10 mg total daily dose. Maximum dose 2 mg/kg total daily dose or 72 mg total daily dose, although treatment-refractory patients sometimes need even higher doses. For sustained release preparations appropriate dose adjustments should be made.

Former Terminology

Stimulant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Occupies DAT and increases DA availability in striatum (PET).

Physiological

Preclinical

Human

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

Brain Circuits

Preclinical

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

Human

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

Mirtazapine

Brand Names: Zipsin, Remeron, Avanza

Pharmacology

Norepinephrine, serotonin

Mode of Action

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

Approved Indications

Efficacy

Side Effects

Weight gain, sedation, especially at beginning of treatment and at lower doses, dry mouth, constipation.

Practical Notes

No advantage over placebo for pediatric depression. Low level of sexual dysfunction. Sometimes given in the evening for insomnia at 7.5-15mg.

Doses: starting dose 7.5 mg increase to 15 mg and titrate every 5 or more days. Maximum suggested dose 45 mg/d.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Binds to cortical H1 receptors (PET).

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

Human

Nortriptyline

Brand Names: Aventyl, Northrilen, Pamelor

Pharmacology

Norepinephrine

Mode of Action

Reuptake inhibitor (NET)

Approved Indications

Nocturnal enuresis (6+ UK).

Efficacy

Side Effects

Sedation, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, QTc prolongation, toxic in overdose (potentially lethal).

Practical Notes

Used to treat core symptoms of ADHD (third or fourth line), usually in children above 12 years old. Drugs for depression with tricyclic structure appear to have no advantage over placebo in efficacy for pediatric depression. Obtain ECG prior to initiation due to QTc prolonging effects. Too rapid discontinuation in children is more likely to cause an anticholinergic withdrawal syndrome than in adults (diarrhea, sweating, etc.). CYP2D6 genotype can affect response to nortriptyline.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

For children 6-12 years old, it is suggested to start with 1-3 mg/kg total per day in divided (three or four times daily) dosing, with a maximum of 150 mg per day. For adolescents > 12 years old, it is suggested to start with 30-50 mg total per day in divided dosing, with a maximum of 150 mg per day. Lower doses are recommended for enuresis.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Human

Suppresses REM sleep.

Brain Circuits

Preclinical

Human

Olanzapine

Brand Names: Zyprexa

Pharmacology

Dopamine, serotonin

Mode of Action

Receptor antagonist (D2, 5-HT2)

Approved Indications

Schizophrenia and manic or mixed episodes within bipolar I disorder (13+ USA); in association with fluoxetine: episodes of depression within bipolar I disorder, (10+, USA).

Efficacy

Psychotic symptoms.

Side Effects

Increased appetite, weight gain, sedation, headache, dizziness, abdominal pain, pain in extremities, fatigue, dry mouth. Risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

A greater magnitude of weight gain (compared with aripiprazole, lurasidone and ziprasidone), and lipid and prolactin alterations have been reported in short-term studies of adolescent patients than in studies of adult patients. Olanzapine is to be avoided as a first-line treatment in treatment-naïve patients. May be given at bedtime only to decrease daytime sedation. Depot formulation available in adults (schizophrenia), but not licensed for children and adolescents due to a lack of data on safety and efficacy. Although olanzapine is sometimes used for anorexia, clinical trials for weight gain and metabolic symptoms are negative.

Dosing begins at 2.5-5 mg daily in adolescent patients, with dose increased in 2.5-5 mg increments up to a typical treating dose of 10 mg daily, with a maximum suggested dose of 20 mg daily. Some treatment-refractory patients are prescribed higher doses.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Human

Sedative and anticholinergic effects. Increases slow wave sleep.

Brain Circuits

Preclinical

Human

Paliperidone

Brand Names: Invega

Pharmacology

Dopamine, Serotonin, Norepinephrine

Mode of Action

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

Approved Indications

Schizophrenia (12+ USA, 15+ Europe).

Efficacy

Improvement in psychotic symptoms.

Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, sexual dysfunction, gynaecomastia, weight gain; risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

Metabolite of risperidone. Can be given safely to patients with elevated liver enzymes as it does not interact with CYP450 system. A greater magnitude of weight gain (compared with aripiprazole, lurasidone and ziprasidone), and lipid and prolactin alterations have been reported in short-term studies of adolescent patients than in studies of adult patients. Sexual side effects may be burdensome in adolescents who tend not to talk about them openly. Depot formulation available in adults (schizophrenia), but not licensed for children and adolescents due to a lack of data on safety and efficacy. The long-term effects of paliperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

For adolescents >50kg dosing follows adult schedule, should start at 3 mg once daily and increase by 3 mg total daily dose every 5 or more days. Max suggested dose 12 mg/d. Adolescents <5kg should not exceed 6mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3, NE alpha1 and alpha2, 5-HT2A, H1 receptors.

Human

Blocks central dopamine D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Paroxetine

Brand Names: Seroxat, Paxil, Brisdelle, Pexeva

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

Efficacy

OCD

Side Effects

GI symptoms, anxiety, changes in sleep early in treatment, sexual dysfunction

Practical Notes

No advantage over placebo for pediatric depression. Possibility of dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be done when using high doses. Complete inhibition of CYP2D6. Short half-life may be particularly problematic in children who may experience withdrawal symptoms with once daily dosing. Must be gradually decreased on discontinuation. Weight neutral. Like other SRIs, may be considered also in anxiety disorders.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Dose: starting dose 10 mg, titrate 10 mg every 5 or more days.
Maximum suggested dose 60mg/d.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

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

Human

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

Brain Circuits

Preclinical

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

Human

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

Perphenazine

Brand Names: Trilafon

Pharmacology

Dopamine

Mode of Action

Receptor antagonist (D2)

Approved Indications

As an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour; Schizophrenia, treatment of symptoms and prevention of relapse; Nausea and vomiting; (14+ UK and other European countries).

Efficacy

Psychotic symptoms.

Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, weight gain; risk of diabetes, tardive dyskinesia NMS.

Practical Notes

Indication extrapolated from old studies in adult population, therefore caution is need in inferring efficacy in children and adolescents.

In children aged >12 years old: initiate at 4 mg and titrate upto 4 to 8 mg three times per day. Regular adult dose for psychosis: 8 to 16 mg given two to three times per day; maximum adult dose: 64 mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Blocks central dopamine D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Pimozide

Brand Names: Orap

Pharmacology

Dopamine

Mode of Action

Receptor antagonist (D2)

Approved Indications

Schizophrenia (12+ UK) Tourette syndrome (12+ USA).

Efficacy

Psychotic symptoms, chorea, tic disorder and Tourette syndrome in children and adolescents.

Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, weight gain; dose-related QTc prolongation; risk of tardive dyskinesia, NMS.

Practical Notes

Indication extrapolated from old studies in adult population, therefore need to be cautious in inferring efficacy in children and adolescents. Should not be taken with inhibitors of CYP 3A4, such as some antibiotics, and antifungal agents, fluvoxamine and nefazodone, because of QTc prolongation. Consideration of dose-related QTc prolongation would generally make its risks outweigh its benefits.

In children aged >12 years old: initial dose 0.05 mg/kg orally at bedtime (1-2 mg/d) ; maximum dose 0.2 mg/kg, not to exceed 10 mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3 receptors.

Human

Blocks central D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Pregabalin

Brand Names: Lyrica

Pharmacology

Glutamate

Mode of Action

Alpha-2 delta calcium channel blocker

Approved Indications

Efficacy

Anxiety, fibromyalgia, neuropathic pain.

Side Effects

Dizziness, sedation.

Practical Notes

Similar to gabapentin. Better absorbed than gabapentin at higher doses. Excreted by kidney, use lower dose if renal impairment. Taper on discontinuation.

Dosing: 25-400mg/d.

Former Terminology

Anxiolytic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Physiological

Preclinical

Human

Increases slow wave sleep.

Brain Circuits

Preclinical

Human

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

Promethazine

Brand Names: Phenergan, Promethegan, Phenadoz

Pharmacology

Histamine, dopamine

Mode of Action

Receptor antagonist (H1, D2)

Approved Indications

Sedation in children > 2year; motion sickness, nausea / vomiting.

Efficacy

Agitation, aggression.

Side Effects

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

Practical Notes

Monitor for excessive sedation, monitor respiratory rate in case of excessive sedation, should be avoided in children with compromised respiratory function (e.g. COPD, sleep apnea). Avoid prolonged sun exposure during treatment.
Promethazine misuse in conjunction with opioids may have serious adverse health effects.
Dosing: 12.5-50mg.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at H1 receptors, also ACh M1-4, 5-HT2, D2 receptors, α7-nicotinic acetylcholine receptor. Inhibits NMDA-mediated membrane currents.

Human

Physiological

Preclinical

Human

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

Brain Circuits

Preclinical

Human

Quetiapine

Brand Names: Seroquel

Pharmacology

Dopamine, serotonin

Mode of Action

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

Approved Indications

Schizophrenia (13+ USA), bipolar mania as monotherapy (10+ USA).

Efficacy

Psychotic symptoms; ADHD symptoms in autistic spectrum disorder.

Side Effects

Sedation, dizziness, weight gain; galactorrhea (low), EPS (low); risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

Although in adults with bipolar depression quetiapine augmentation was effective, studies in the pediatric population were negative. May be useful in irritability and oppositional defiant disorder, and in severe aggression in children with ADHD. A greater magnitude of weight gain (compared with aripiprazole, lurasidone and ziprasidone), and lipid and prolactin alterations have been reported in short-term studies of adolescent patients than in studies of adult patients. Used at low doses for insomnia, but due to weight gain and metabolic abnormalities the clinician may look for safer alternatives. A prolonged release oral formulation is available in some countries. Doses are very heterogeneous with some adolescent patients prescribed doses above 1g/d. Higher doses may be given at night because of sedation and somnolence.

Starting dose 25 mg/d for one or more days, then increase to 50 mg for one or more days, then 50 mg twice daily for one or more days, then increase by 100 mg total daily dose up to a total of 400 mg total daily dose by day 5 or later. Typical total daily dose of 300-450 mg, maximum suggested up to 600 mg (10-12 year olds) to 800 mg

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, 5-HT2, NE alpha1 and alpha2, H1 receptors. Increases 5-HT and NE in frontal cortex, histamine in medial prefrontal cortex, 5-HT in N.Acc.

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Human

Sedative and anticholinergic effects.

Brain Circuits

Preclinical

Human

Risperidone

Brand Names: Risperdal, Belivon

Pharmacology

Dopamine, serotonin, norepinephrine

Mode of Action

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

Approved Indications

Manic or mixed episodes in bipolar disorder (10+ USA, 13+ Europe); schizophrenia (13+ USA, 15+ Europe); Short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children and adolescents with subaverage intellectual functioning or mental retardation (5+ Europe); irritability and aggression in autism (5+ USA).

Efficacy

Psychotic symptoms; irritability and aggression in children with conduct disorder and oppositional defiant disorder with sub-average intellectual functioning; aggression in children with ADHD.

Side Effects

Sedation, weight gain, headache, increased appetite, dizziness, raised prolactin, sexual dysfunction, gynaecomastia, abdominal pain, pain in extremities, fatigue, dry mouth. risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

A greater magnitude of weight gain (compared with aripiprazole, lurasidone and ziprasidone), and greater lipid and prolactin alterations have been reported in short-term studies of adolescent patients than in studies of adult patients. Sexual side effects may be burdensome in adolescents who tend not to talk about them openly. Depot available (schizophrenia), but not licensed for children and adolescents due to a lack of data on safety and efficacy. IM long-acting risperidone is approved from age 13 (USA). Monitor for metabolic syndrome.

Patients >50 kg: starting dose of 0.5 mg once daily; dosage can be individually adjusted by increments of 0.5 mg once daily, every other day, if needed. Optimum total daily dose is 1 mg or higher, often in twice daily dosing. Some patients may benefit from 0.5 mg once daily while others may require 1 mg twice daily. Total daily doses of more than 2 mg are sometimes used in treatment-refractory patients (in adolescents with schizophrenia: 6-8 mg/day not uncommon, but titrate to efficacy or EPS, lowering the dose below EPS threshold). Patients <50 kg: starting dose of 0.25 mg once daily, optimum dose 0.5 mg once or twice daily. Some patients may benefit from 0.5 mg once daily while others may require 1.5 mg total daily dose. For children with conduct disorder and oppositional defiant disorder recommended dose is up to 1.5 mg/d. IM long-acting risperidone is approved from age 13 (USA).

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Sertraline

Brand Names: Lustral, Zoloft

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT)

Approved Indications

OCD (6+ USA and UK).

Efficacy

GAD

Side Effects

Gastrointestinal symptoms, anxiety, change in sleep early in treatment; sexual dysfunction.

Practical Notes

Pay particular attention to signs of activation in children with developmental disorder or brain injury. Weak interaction with CYP 2D6. Only a problem at doses >200mg. Gradually decrease on discontinuation. Like other SRIs may be considered for other anxiey disorders and also for MDD.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Dose: Age 6-12 years, Initially 25 mg once daily. The dosage may be increased to 50 mg once daily after one week then titrated upward with increases of 25-50 mg once per week with maximum dose of 200 mg. Aged 12-18 years, can initiate at 25 or 50mg once daily, increase in steps of 50mg once weekly to 200mg. Higher doses (300 mg/d) are sometimes used for refractory OCD or anxiety symptoms.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

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

Physiological

Preclinical

Human

Decreased REM sleep, increased REM latency.

Brain Circuits

Preclinical

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

Human

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

Trazodone

Brand Names: Molipaxin, Deprax, Desyrel, Oleptro

Pharmacology

Serotonin

Mode of Action

To be determined

Approved Indications

Efficacy

Depression, insomnia in adolescents.

Side Effects

Sedation, dry mouth, dizziness. Rarely priapism. Nasal congestion (in some preparations).

Practical Notes

Widely used in USA in insomnia in adults; low level of sexual dysfunction.

Dosing: For depression 25-150mg. For insomnia 50-100mg.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

Increases extracellular levels of 5-HT in frontal cortex; antagonist at 5-HT2, NE alpha-1 receptors, weak SERT inhibitor, 5-HT1A receptor agonist.

Human

Physiological

Preclinical

Desensitizes cell body 5-HT1A autoreceptors and terminal 5-HT1B autoreceptors; increases 5-HT1A and NE alpha-2 transmission in the rat hippocampus.

Human

Increases slow wave sleep.

Brain Circuits

Preclinical

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

Human

Trifluoperazine

Brand Names: Stelazine, Jatroneural, Modalina, Terfluzine, Trifluoperaz, Triftazin

Pharmacology

Dopamine, serotonin

Mode of Action

Receptor antagonist (D2, 5-HT2)

Approved Indications

Schizophrenia (6+ USA, UK); (low-dose) short-term management of anxiety states, depressive symptoms secondary to anxiety, nausea and vomiting (6+ UK); (higher dose) adjunct in the short-term management of severe psychomotor agitation and of dangerously impulsive behaviour in, for example, learning disability.

Efficacy

Psychotic symptoms.

Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, weight gain, QTc prolongation; risk of diabetes, tardive dyskinesia, NMS.

Practical Notes

Indication extrapolated from old studies in adult population, therefore need to be cautious in inferring efficacy in children and adolescents. Consideration of dose-related QTc prolongation might make its risks outweight its benefits.
May cause less weight gain than other dopaminergic drugs used in psychosis.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D2 and D3 receptors.

Human

Blocks central D2 receptors (PET).

Physiological

Preclinical

Human

Brain Circuits

Preclinical

Human

Valproate

Brand Names: Depakene, Depacon, Stavzor

Pharmacology

Glutamate

Mode of Action

Yet to be determined

Approved Indications

Epilepsy (10+ USA, 1 month+ UK).

Efficacy

Manic and mixed episodes in bipolar disorder.

Side Effects

Sedation, elevated liver enzymes, hair loss, weight gain, mydriasis; risk of premature growth plate ossification in children and adolescents, resulting in decreased height; may increase the chance of polycystic ovary syndrome (PCOS) in girls; considerable risk of foetal abnormalities if given in females who become pregnant.

Practical Notes

Limited data for mania, irritability, aggression. Valproate inhibits CYP2C9, glucuronyl transferase, and epoxide hydrolase and is highly protein bound and hence may interact with drugs that are substrates for any of these enzymes or are highly protein bound themselves. Many interactions with other drugs - check. Monitor liver function before and during therapy. Strongly advise the use of contraceptives in sexually active female adolescents to avoid foetal defects. Once daily slow release preparation is available in some countries. Dose of lamotrigine should be reduced when given with valproate.

Do not use in children <2 because of hepatotoxicity. Age <12 dosing 7.5mg/kg starting dose in 2 divided doses, increasing every 5 days to 60-120mg. Age 12+ start at 300mg twice daily increasing every 3 days or more by 200mg/day. Titrate according to plasma levels, should be 50-100 µg/mL total valproic acid for maintenance.

Former Terminology

Mood stabiliser

Neurobiology

Neurotransmitter Effects

Preclinical

Modulates intracellular signalling.

Human

Physiological

Preclinical

Anti-epilepsy, inositol depletion, decreases brain cAMP.

Human

Brain Circuits

Preclinical

Human

Venlafaxine

Brand Names: Effexor

Pharmacology

Serotonin, norepinephrine

Mode of Action

Reuptake inhibitor (SERT and NET)

Approved Indications

Efficacy

Social anxiety disorder (age 8-17), GAD.

Side Effects

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

Practical Notes

Limited data in depression and in chronic pain in adolescents. Pay particular attention to signs of activation in children with developmental disorder or brain injury. Must be gradually decreased on discontinuation.

It is important to assess more frequently in the beginning of treatment due to the claimed risk of suicidal ideation at treatment initiation in patients younger than 25, although no increased suicide rate has been reported.

Dose 37.5-300mg/d. Effects on norepinephrine transporter at doses of 225mg and above.

Former Terminology

Antidepressant

Neurobiology

Neurotransmitter Effects

Preclinical

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

Human

Decreased 5-HT platelet content.

Physiological

Preclinical

Normalization of 5-HT neuron firing activity, sustained decrease in firing of NE neurons with increased transmission; normalization of decreased GRK2; is a substrate for permeability-glycoproteins.

Human

Decrease in tyramine pressor response at 225 mg/day (NET inhibition), suppresses REM sleep.

Brain Circuits

Preclinical

Human

Decreased glucose metabolism in the orbitofrontal cortex and subgenual anterior cingulate cortex.

Vortioxetine

Brand Names: Brintellix, Trintellix

Pharmacology

Serotonin

Mode of Action

Reuptake inhibitor (SERT), receptor partial agonist (5-HT1A), receptor antagonist (5-HT3)

Approved Indications

Efficacy

Depression.

Side Effects

GI symptoms (especially nausea and vomiting), headache, dizziness.
Low incidence of sexual dysfunction.

Practical Notes

Low level of sexual dysfunction at doses < 15 mg/d.

Dosing: 5-20mg/d.

Former Terminology

Antidepressant.

Neurobiology

Neurotransmitter Effects

Preclinical

Increases 5-HT NE, DA, and ACh in ventral hippocampus and prefrontal cortex, histamine in medial prefrontal cortex, 5-HT in N.Acc. Receptor agonist 5-HT1A, partial agonist 5-HT1B, antagonist 5-HT3, 5-HT7, 5-HT1D.

Human

Lower occupancy of SERT than SSRIs in its lower range of antidepressant efficacy.

Physiological

Preclinical

Human

Suppresses REM sleep.

Brain Circuits

Preclinical

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

Human

Decreased glucose metabolism in the orbitofrontal cortex and subgenual anterior cingulate cortex.

Zaleplon

Brand Names: Sonata, Andante, Starnoc

Pharmacology

GABA

Mode of Action

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

Approved Indications

Efficacy

Insomnia (short-term use only).

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit.

Practical Notes

Very short half-life, can be used during, the night 5 hours or more before driving etc. Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life 1-1.5 hour. If on higher dose, taper upon discontinuation to avoid withdrawal symptoms.

Dosing: 5-10mg.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Alpha-1 subtype selective PAM.

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy.

Human

Sleep-promoting in first few hours after dosing.

Brain Circuits

Preclinical

Human

Ziprasidone

Brand Names: Geodon, Zeldox

Pharmacology

Dopamine, serotonin

Mode of Action

Receptor antagonist (D2, 5-HT2)

Approved Indications

Manic or mixed episodes of moderate severity in bipolar disorder (10+ Europe).

Efficacy

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Side Effects

Sedation, dizziness, EPS, akathisia, dystonia, galactorrhea, weight gain (less than olanzapine, clozapine, quetiapine, risperidone, paliperidone, asenapine); risk of seizures, diabetes, tardive dyskinesia, NMS.

Practical Notes

Negative study for adolescents aged 13-17 with schizophrenia (but positive study in adults with schizophrenia). Less weight gain in comparison with risperidone, olanzapine, or quetiapine. Twice daily dosing , has to be taken with food (at least 500 calories, fat content is irrelevant) otherwise plasma levels can drop to <50%.

Initiate at 20mg /d and increase every 3-5 days by 20mg. Usual efficacy for psychosis 80-160mg/d.

Former Terminology

Antipsychotic

Neurobiology

Neurotransmitter Effects

Preclinical

Antagonist at D1, D2 and D3, NE alpha 1, 5-HT2A, 5-HT2C, 5-HT1B and 5-HT7 receptors, partial agonist at 5-HT1A and 5-HT1D receptors, weak NET and SERT inhibitor.

Human

Blocks central dopamine D2 and 5-HT2A receptors (PET).

Physiological

Preclinical

Human

Sedative and anticholinergic effects, increases slow wave sleep.

Brain Circuits

Preclinical

Human

Zolpidem

Brand Names: Stilnoct, Ambien

Pharmacology

GABA

Mode of Action

Alpha-1 subunit selective benzodiazepine receptor agonist (GABA-A receptor positive allosteric modulator)

Approved Indications

Efficacy

Insomnia (short-term use only)

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit)

Practical Notes

Selective for alpha-1 subtype of GABA-A receptor, relevant to sleep/sedation. Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are distinguished only by pharmacokinetics unless otherwise indicated. Half-life of 2-4 hours. If on higher dose, taper upon discontinuation to avoid withdrawal symptoms.

Dosing: Immediate release: 2.5-10mg/d; continuous release: 6.25-12.5mg/d.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Alpha-1 subtype selective PAM.

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy.

Human

Slows eye saccades; promotes sleep.

Brain Circuits

Preclinical

Human

Zopiclone

Brand Names: Zimovane

Pharmacology

GABA

Mode of Action

Alpha-1 subunit selective benzodiazepine receptor agonist
(GABA-A receptor positive allosteric modulator)

Approved Indications

Efficacy

Insomnia (short-term use only).

Side Effects

Sedation, somnolence, ataxia, muscle relaxation, memory deficit.

Practical Notes

Many different benzodiazepine receptor agonists are licensed worldwide, some in most countries and some in only 1 or 2. They all act in the same way, and are largely distinguished by pharmacokinetics unless otherwise indicated. Half-life of 5-7hours. If on higher dose, taper upon discontinuation to avoid withdrawal symptoms.

Dosing: 3.75-7.5 mg/d.

Former Terminology

Hypnotic

Neurobiology

Neurotransmitter Effects

Preclinical

Binds to GABA-A receptors.

Human

Non-selective PAM.

Physiological

Preclinical

Reduces motor activity and promotes sleep; anti-epilepsy; anticonflict.

Human

Slows eye saccades; promotes sleep, anxiolytic.

Brain Circuits

Preclinical

Human

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Abbreviations

NbN-ca Abbreviations

Pharmacological Domain

A = Agonist
ACh = Acetylcholine
Ca = Calcium
DA = Dopamine
Glu = Glutamate
H = Histamine
Li = Lithium
Mel = Melatonin
NE = Norepinephrine
S = Serotonin
O = Opioid
Or= Orexin

Mode of Action

An = Antagonist
CB = Channel blocker
EI = Enzyme inhibitor
I = Inhibitor
Na= Sodium
NRe = Neurotransmitters Releaser
R = Reuptake
Re = Releaser
RI = Reuptake Inhibitor
RA = Receptor Agonist
RAn = Receptor Antagonist
RPA = Receptor Partial Agonist

Additional Abbreviations

ADHA = Attention Deficit Hyperactivity Disorder
ANC = Absolute Neutrophil Count
ASL = Arterial Spin Labeling
BDNF = Brain-Derived Neurotrophic Factor
BOLD = Blood Oxygen Level Dependent
CAMP = Cyclic Adenosine Monophosphate
DAT = Dopamine ReuptakeTtransporter
ECG = Electrocardiography
EPS = Extrapyramidal Syndrome
GABA = Gamma-Aminobutyric Acid
GAD = Generalized Anxiety Disorder
GI = Gastrointestinal
GMP = Guanosine Monophosphate
HR = Heart Rate
IM = Intramuscular
MAOI = Monoamine Oxidase Inhibitor
MDD = Major Depressive Disorder
N.Acc = Nucleus Accumbens
NET = Norepinephrine Reuptake Transporter
NGF = Nerve Growth Factor
NMDA = N-methyl-D-aspartate Receptor
NMS = Neuroleptic Malignant Syndrome
OCD = Obsessive Compulsive Disorder
OTC = Over The Counter
PAM = Posited Allosteric Modulator
PCOS = Polycystic Ovary Syndrome
PD = Panic Disorder
PFC = Prefrontal Cortex
RCBF = Regional Cerebral Blood Flow
REM = Rapid Eye Movement
RST = Randomized Controlled Trial
SAD = Social Anxiety Disorder
SSRI = Selective Serotonin Reuptake Inhibitor
SERT = Serotonin Reuptake Transporter
SRI = Serotonin Reuptake Inhibitors
TD = Tardive Dyskinesia