Psychiatric Medications Compared By The Efficacies On Various Receptors

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Scale used for binding/functional effect (qualitative, based on typical Ki/IC50 or occupancy at therapeutic levels):
- +++ = strong (≈ Ki ≤ 10 nM or high occupancy/clinically dominant)
- ++ = moderate (≈ 10–100 nM or meaningful at higher doses)
- + = weak (≈ 100–1000 nM or minimal clinical effect)
- – = negligible/none
Action abbreviations:
- I = re-uptake inhibitor (transporters)
- Ant = antagonist
- IA = inverse agonist (Can consider as an agonist)
- A = agonist
- PA = partial agonist / antagonist
- PAM = positive allosteric modulator
Acronyms
- SERT – Serotonin Transporter
- NET – Norepinephrine Transporter
Notes:
• Values are class-typical/consensus qualitative strengths compiled from standard references (e.g., PDSP Ki Database, review texts, FDA labels). Exact Ki varies by assay and source.
• Transporter entries reflect functional inhibition at therapeutic exposure, not just binding affinity.
• Mood stabilizers with non-receptor mechanisms are annotated in 'Mechanism / Notes' and marked '–' across receptor columns unless clinically meaningful.

Tricyclic Antidepressants

Drug	Class	Mechanism Notes	SERT	NET	H1	M1	Alpha1
Amitriptyline	TCA	SERT/NET inhibition; strong H1/M1/alpha1 antagonism	I++	I++	Ant+++	Ant+++	Ant++
Imipramine	TCA	SERT/NET inhibition; anticholinergic	I++	I++	Ant++	Ant++	Ant+
Clomipramine	TCA	SERT>>NET; anticholinergic	I+++	I+	Ant++	Ant++	Ant+
Nortriptyline	TCA	NET>SERT; fewer anticholinergic than amitriptyline	I+	I+++	Ant++	Ant+	Ant+
Desipramine	TCA	NET selective	I+	I+++	Ant+	Ant+	Ant+
Doxepin	TCA	H1 very strong; SERT/NET; anticholinergic	I++	I+	Ant+++	Ant++	Ant+

SSRI - Antidepressants

Drug	Class	Mechanism / Notes	SERT	NET	DAT	5HT2A	5HT2C	M1	Sigma1
Fluoxetine	SSRI	SERT inhibitor; mild 5-HT2C Ant; weak NET/DAT at higher doses	I+++	I+	I+	Ant+	Ant+	–	–
Sertraline	SSRI	SERT inhibitor; weak DAT inhibition	I+++	–	I+	Ant+	Ant+	–	–
Paroxetine	SSRI	SERT inhibitor; mild M1 anticholinergic; NET weak	I+++	I+	–	Ant+	–	Ant+	–
Citalopram	SSRI	Selective SERT inhibitor	I+++	–	–	–	–	–	–
Escitalopram	SSRI	Selective SERT inhibitor (active S-enantiomer)	I+++	–	–	–	–	–	–
Fluvoxamine	SSRI	SERT inhibitor; Sigma-1 agonist	I+++	–	–	–	–	–	A+++

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Dr. O's thoughts on choosing an SSRI for treating depression and anxiety.

- I don't know about you, but when treating this in my office, colleagues often "choose" an agent because they are used to prescribing it and generally "feel" certain agents are more effective than others. I reject that reality and substitute my own.
- By knowing the mechanisms, here is why I would choose some agents based on this chart I made.
- It is important to note that SERT, NET, and DAT reuptake inhibitors are going to increase serotonin, norepinephrine, and dopamine all ALL available receptors in the central nervous system. So although "Fluvoxamine" doesn't have "5HT2A" agonism, doesn't mean it doesn't activate those receptors → IT DOES. Its not a "direct" agonist there, but SERT inhibition will increase serotonin at ALL 5-HT receptors.

1. **Paroxetine**: Anti-muscarinic, SERT, and short half-life→ more sedating, more weight gain, more sexual dysfunction (Dry mucus membranes). May help if insomnia + anxiety are prominent, but often avoided for side effect burden.
2. **Fluoxetine**: Some 5-HT2C antagonism → more activating/energizing. Good for low-energy depression but can worsen anxiety initially. Less weight gain due to small dopamine reuptake, likely in the reward circuit
3. **Sertraline**: Mild dopamine transporter inhibition → may boost motivation/energy. Often favored in depression with anhedonia. Less weight gain due to small dopamine reuptake, likely in the reward circuit
4. **Citalopram/Escitalopram**: Very "clean," highly selective for SERT. Generally best tolerated, often first-line for generalized anxiety disorder. But that high serotonin at all those 5-HT receptors elsewhere will increase weight gain.

SNRI - Antidepressants

Drug	Class	Mechanism / Notes	SERT	NET
Venlafaxine	SNRI	SERT>>NET; NET increases at higher doses	I+++	I+
Desvenlafaxine	SNRI	SERT>NET	I+++	I+
Duloxetine	SNRI	Balanced SERT & NET inhibition	I+++	I++
Levomilnacipran	SNRI	NET>SERT	I++	I+++

Dr. O's thoughts on choosing an SNRI for treating depression and anxiety.

- When I choose an SSRI, I am thinking about the patient as a whole. In these specific cases, I will usually reach for an SNRI vs an SSRI.

1. Pain Syndromes
    - SNRIs (duloxetine) enhance descending spinal noradrenergic pathways → reduce pain transmission.
        - Neuropathic pain (diabetic neuropathy, post-herpetic neuralgia)
        - Fibromyalgia (duloxetine, milnacipran FDA-approved)
        - Chronic musculoskeletal pain (low back pain, OA)
        - SSRIs: Do not significantly impact pain pathways.
2. Low-Energy / Apathy / Fatigue
    - Norepinephrine promotes alertness, drive, and motivation.
        - Patients with depression + low energy, poor concentration, anhedonia
        - SSRIs: Can worsen fatigue or apathy in some patients.
3. Treatment-Resistant Depression
    - Dual-action (5-HT + NE) → broader neurotransmitter coverage.
        - Some studies show SNRIs (duloxetine, venlafaxine) have slightly higher remission rates than SSRIs in moderate-to-severe or refractory depression.
        - SSRIs: Often first-line, but may not be sufficient in resistant cases.
4. Anxiety with Prominent Physical Symptoms
    - Noradrenergic action may help with somatic symptoms (fatigue, pain, concentration issues) beyond serotonin effects alone.
        - Better for: Patients with GAD who also have chronic pain or fatigue (duloxetine).
        - SSRIs: Excellent for pure psychic anxiety, but less benefit for pain/somatic symptoms.
5. Menopausal Vasomotor Symptoms
    - Venlafaxine and desvenlafaxine reduce hot flashes by modulating hypothalamic thermoregulation.
        - SSRIs: Paroxetine is FDA-approved for hot flashes, but SNRIs may be more effective in some cases without paroxetine side effects
6. Migraines
    - TCAs and mechanisms that increase Nor-Epinephrine / Serotonin can much more effectively work on the monoamine hypothesis of migraines
        - SSRIs: Limited effect due to working only on serotonin

Atypical - Antidepressants

Drug	Class	Mechanism / Notes	SERT	NET	DAT	5HT1A	5HT2A	5HT2C	5HT3	5HT7	H1	Alpha1	Alpha2
Vilazodone	SSRI/5-HT1A PA	SERT inhibitor + 5-HT1A partial agonist	I+++	–	–	PA++	–	–	–	–	–	–	–
Vortioxetine	Multimodal SSRI	SERT inhibitor; 5-HT1A agonist; 5-HT3/7/1D antagonist	I++	–	–	A+	Ant+	–	Ant++	Ant++	–	–	–
Trazodone	SARI	5-HT2A/2C antagonist; SERT weak; H1/alpha1 blockade	I+	–	–	–	Ant++	Ant+	–	–	Ant+	Ant++	–
Nefazodone	SARI	5-HT2A antagonist; SERT/NET weak; CYP3A4 inhibitor	I+	I+	–	–	Ant++	–	–	–	–	–	–
Bupropion	NDRI	DAT/NET inhibitor; minimal SERT	–	I++	I++	–	–	–	–	–	–	–	–
Mirtazapine	NaSSA	Alpha2 antagonist; 5-HT2A/2C antagonist; H1 strong	–	–	–	–	Ant++	Ant++	–	–	Ant+++	–	Ant+++

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Dr. O's thoughts on choosing an Atypical Anti-Depressant for treating Depression and Anxiety.

- When I choose an atypical anti-depressant, think about what other things this drug can improve on or how it can be additive to a current SSRI or SNRI.

1. **Bupropion** (Wellbutrin): NDRI (NET + DAT reuptake inhibitor).
   - Stimulating, weight-neutral, and increases motivation/energy.
   - **Good if depression with fatigue, anhedonia, or sexual dysfunction (can counteract SSRI-induced sexual side effects).**
   - **Great smoking cessation agent**
   - Avoid in seizure disorders, eating disorders, or heavy alcohol use.

2. **Mirtazapine** (Remeron): α2-adrenergic antagonist → increases 5-HT + NE release; also H1 histamine antagonist.
   - Very sedating, causes weight gain and increased appetite.
   - Best if **depression with insomnia, low appetite, or underweight patients**.

3. **Vilazodone** (Viibryd): SSRI + 5-HT1A partial agonist (sometimes called "serotonin partial agonist reuptake inhibitor," SPARI).
   - Theoretically **combines SSRI effects with anxiolysis**.
   - May have **less sexual dysfunction** than pure SSRIs.
   - Needs to be taken with food for absorption.

4. **Vortioxetine** (Trintellix): SSRI + 5-HT1A agonist, 5-HT1B partial agonist, 5-HT3/7 antagonist.
   - Multimodal serotonin agent.
   - Reported benefits for **cognition and executive function in depression**.
   - Less sexual dysfunction compared to standard SSRIs.

5. **Trazodone**: SERT inhibitor + 5-HT2A antagonist + strong H1 antagonist.
   - At low doses → used as hypnotic for insomnia (very sedating).
   - Not used alone for depression, but GREAT to use in addition to an SNRI or SSRI in those with **depression and severe insomnia**

6. **Nefazodone**: Similar to trazodone (SERT + 5-HT2 antagonist),
   - Similar to trazodone, but less sedating and less sexual dysfunction.
   - Rarely used today due to black box warning for hepatotoxicity.
   - Historically chosen if SSRI sexual dysfunction was intolerable.

Anxiety Specific Agents

Drug	Class	Mechanism / Notes	5HT1A	H1	GABA_A_BZD
Diazepam	Benzodiazepine	GABA-A benzodiazepine site PAM	–	–	PAM+++
Lorazepam	Benzodiazepine	GABA-A benzodiazepine site PAM	–	–	PAM+++
Clonazepam	Benzodiazepine	GABA-A benzodiazepine site PAM	–	–	PAM+++
Alprazolam	Benzodiazepine	GABA-A benzodiazepine site PAM	–	–	PAM+++
Buspirone	Anxiolytic	5-HT1A partial agonist	PA+++	–	–
Hydroxyzine	Antihistamine (anxiolytic)	H1 antagonist	–	Ant+++	–
Zolpidem	Z-drug hypnotic	GABA-A benzodiazepine site PAM (α1-selective)	–	–	PAM+++
Eszopiclone	Z-drug hypnotic	GABA-A benzodiazepine site PAM	–	–	PAM+++

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Dr. O's thoughts on choosing an Anxiety Specific Medications

When I choose an anxiety medicine, think about what their anxiety is affecting: Sleep? Panic?

1. Diazepam (Valium): Long half-life, active metabolites. Rapid onset.
    1. Good for acute anxiety, muscle spasm, alcohol withdrawal.
    2. Not great for chronic daily use due to sedation, accumulation, and abuse potential.

2. Lorazepam (Ativan): Intermediate onset/half-life, no active metabolites.
    1. Safer in elderly or liver impairment.
    2. Useful for acute agitation, anxiety, status epilepticus.
    3. More sedating than clonazepam.

3. Clonazepam (Klonopin): Long half-life, high potency.
    1. Useful for panic disorder (can be dosed less frequently) and as adjunct in some seizure disorders.
    2. Less sedating than lorazepam but more risk of accumulation.

4. Alprazolam (Xanax): High potency, rapid onset, short half-life.
    1. Strong anxiolysis but highest abuse/rebound risk.
    2. May help panic attacks acutely, but often avoided for long-term due to dependence.

5. **Buspirone** (Buspar): 5-HT1A partial agonist.
    1. Non-sedating, no abuse potential.
    2. Best for generalized anxiety disorder if patient wants to avoid benzos.
    3. Slow onset (takes weeks), not effective for acute anxiety or panic.

6. **Hydroxyzine** (Vistaril/Atarax): Antihistamine with anxiolytic properties.
    1. Sedating, anticholinergic side effects.
    2. Good for acute anxiety when benzos are contraindicated (e.g., substance use history).
    3. Often used short-term or PRN.

7. Zolpidem (Ambien): Z-drug hypnotic, GABA-A α1 selective.
    1. Best for sleep onset insomnia.
    2. Less anxiolytic, more hypnotic. Short half-life, lower next-day sedation risk. Risk of parasomnias (sleep eating, sleep driving).

8. Eszopiclone (Lunesta): Z-drug hypnotic, longer half-life than zolpidem.
    1. Best for sleep maintenance insomnia.
    2. Approved for longer-term use.

Typical Anti-Psychotics

Drug	Class	Mechanism / Notes	SERT	NET	5HT1A	5HT2A	5HT2C	5HT7	D2	D3	D4	H1	M1	Alpha1
Haloperidol	Typical AP	High-potency D2 antagonist; alpha1/H1 mild	–	–	–	Ant+	–	–	Ant+++	–	–	Ant+	–	Ant+
Fluphenazine	Typical AP	High-potency D2 antagonist	–	–	–	Ant+	–	–	Ant+++	–	–	–	–	–
Perphenazine	Typical AP	Mid-potency D2 antagonist; alpha1/H1 moderate	–	–	–	–	–	–	Ant++	–	–	Ant+	–	Ant+
Chlorpromazine	Typical AP	Low-potency D2 antagonist; strong H1/alpha1/M1	–	–	–	Ant+	Ant+	–	Ant+	–	–	Ant+++	Ant++	Ant+++
Thiothixene	Typical AP	High-potency D2 antagonist	–	–	–	–	–	–	Ant+++	–	–	–	–	–

Dr. O's thoughts on choosing a Typical Antipsychotics .

Don't…..Just don't……..unless you really have too.

1. **Haloperidol (Haldol)**: High-potency D2 antagonist.
    1. Strong antipsychotic effect with **low sedation/anticholinergic burden** but high risk of **EPS (rigidity, dystonia, akathisia, tardive dyskinesia)**.
    2. Often chosen for **acute agitation, delirium, Tourette's, and schizophrenia with <u>severe</u> positive symptoms**.

2. **Chlorpromazine (Thorazine)**: Low-potency FGA.
    1. Strong **sedation, anticholinergic, and hypotension effects**, lower EPS risk, but ehhhhh…… why use it?
    2. Historically the first antipsychotic.
    3. Sometimes used in **severe agitation (IM), intractable hiccups, and nausea/vomiting**.
    4. Side effects (orthostasis, weight gain, QTc prolongation) often limit chronic use.

Atypical Anti-Psychotics

Drug	Class	Mechanism / Notes	SERT	NET	5HT1A	5HT2A	5HT2C	5HT7	D2	D3	D4	H1	M1	Alpha1
Clozapine	Atypical AP	D4>D2; 5-HT2A antagonism; H1/M1/alpha1 strong	–	–	–	Ant+++	Ant+++	–	Ant+	–	Ant++	Ant+++	Ant++	Ant++
Olanzapine	Atypical AP	5-HT2A antagonism; D2 moderate; strong H1/M1; metabolic risk	–	–	–	Ant+++	Ant+++	–	Ant++	–	–	Ant+++	Ant+++	Ant++
Asenapine	Atypical AP	5-HT2A Ant strong; D2 Ant; H1 moderate	–	–	–	Ant+++	Ant+	–	Ant++	–	–	Ant+	–	–
Iloperidone	Atypical AP	D2 Ant; strong alpha1 Ant (orthostasis)	–	–	–	Ant++	Ant+	–	Ant++	–	–	–	–	Ant+++
Risperidone	Atypical AP	5-HT2A antagonism; D2 potent; prolactin increase	–	–	–	Ant+++	Ant+	–	Ant++	–	–	Ant+	–	Ant++
Paliperidone	Atypical AP	Active metabolite of risperidone; similar profile	–	–	–	Ant+++	Ant+	–	Ant++	–	–	Ant+	–	Ant++
Quetiapine	Atypical AP	5-HT2A antagonism; weak D2; H1/alpha1 strong; norquetiapine NET I+	–	I+	–	Ant++	Ant++	–	Ant+	–	–	Ant+++	–	Ant++
Lumateperone	Atypical AP	D2 Ant (modest), 5-HT2A Ant strong; SERT modulation	I+	–	–	Ant+++	–	–	Ant+	–	–	–	–	–

Drug	Class	Mechanism / Notes	SERT	NET	5HT1A	5HT2A	5HT2C	5HT7	D2	D3	D4	H1	M1	Alpha1
Ziprasidone	Atypical AP	5-HT2A/2C Ant; 5-HT1A agonist; SERT/NET I+; low H1/M1	I+	I+	A+	Ant+++	Ant++	–	Ant++	–	–	–	–	–
Aripiprazole	Atypical AP	D2/D3 partial agonist; 5-HT1A PA; 5-HT2A Ant	–	–	PA+	Ant++	–	–	PA++	PA++	–	–	–	–
Brexpiprazole	Atypical AP	D2 partial agonist (lower intrinsic activity); 5-HT1A PA; 5-HT2A Ant	–	–	PA+	Ant++	–	–	PA+	–	–	–	–	–
Cariprazine	Atypical AP	D3>D2 partial agonist; 5-HT1A PA	–	–	PA+	–	–	–	PA++	PA+++	–	–	–	–
Lurasidone	Atypical AP	D2 Ant; 5-HT7 Ant; 5-HT1A PA; minimal H1/M1	–	–	PA+	–	–	Ant++	Ant++	–	–	–	–	–

Dr. O's thoughts on choosing an Atypical Antipsychotics .

Yes, use these. But don't overuse them. I don't care what drug commercials say, we probably overprescribe these because of patient's saying that "Abilify is right for me". Choose the one that will produce the effect you are looking for and try to limit side effect profiles.

1. **Clozapine**: Gold standard for **treatment-resistant schizophrenia and for patients with suicidality**.
    a. Unique efficacy for refractory cases.
    b. Risks: agranulocytosis (REMS monitoring), myocarditis, seizures, metabolic syndrome, sialorrhea.
    c. Reserved for last-line use.

2. **Olanzapine**: Very effective, especially in **acute mania and schizophrenia**.
    a. High risk of weight gain, metabolic syndrome, sedation.
    b. Avoid if metabolic risk is high.

3. **Risperidone**: **Broad use** for **schizophrenia, bipolar disorder (acute mania), irritability in autism**.
    a. Higher risk of EPS and hyperprolactinemia (especially at >6 mg/day).

4. **Paliperidone**: Active metabolite of risperidone. Used for **schizophrenia** and **schizoaffective disorder.**
    a. Less hepatic metabolism → good if liver disease.
    b. Side effects similar to risperidone (EPS, prolactin elevation).

5. **Quetiapine**: **Very sedating** → useful for **bipolar depression, insomnia,** and **adjunct in Major Depressive Disorder.**
    a. Low EPS risk. High risk of weight gain, metabolic syndrome, orthostasis.

6. **Lumateperone**: Newer agent. Approved for **schizophrenia** and **bipolar depression**.
    a. **Lower risk of metabolic issues** and EPS. Expensive but well tolerated.

7. **Ziprasidone**: Useful for schizophrenia and bipolar disorder.
    a. **Lower metabolic risk** (weight-neutral).
    b. Risk: QTc prolongation.

8. **Aripiprazole**: **Broad use** in **schizophrenia, bipolar disorder, adjunct in MDD, irritability in autism, Tourette's**.
    a. **Lower metabolic risk**
    b. Weight-neutral and activating.
    c. Can cause akathisia.

9. **Brexpiprazole**: **Similar to aripiprazole** (D2 partial agonist), but more 5-HT activity → **less akathisia, more sedating**.
    a. Approved for **schizophrenia, adjunct in MDD, agitation in Alzheimer's dementia**.
    b. Weight gain risk higher than aripiprazole.

10. **Cariprazine**: D2/D3 partial agonist with high D3 preference.
    a. Great for **bipolar depression, schizophrenia** with **predominant negative symptoms**.
    b. Can cause akathisia/insomnia but relatively weight-neutral.

11. **Lurasidone**: Approved for **schizophrenia** and **bipolar depression**.
    a. Favorable for patients with metabolic concerns.
    b. Weight-neutral, **lower metabolic risk**.
    c. Limitation: akathisia, nausea

Drugs for ADHD

Drug	Class	Mechanism / Notes	SERT	NET	DAT	Alpha2
Amphetamine (mixed salts)	Stimulant	Substrate/releaser at DAT/NET; TAAR1 agonism; VMAT2 interaction	–	I+++	I+++	–
Dextroamphetamine	Stimulant	Same as amphetamine (d-isomer stronger at DAT/NET)	–	I+++	I+++	–
Lisdexamfetamine	Stimulant prodrug	Prodrug of dextroamphetamine; same mechanism	–	I+++	I+++	–
Methylphenidate	Stimulant	DAT/NET reuptake inhibitor	–	I+++	I+++	–
Dexmethylphenidate	Stimulant	d-isomer of methylphenidate; similar mechanism	–	I+++	I+++	–
Atomoxetine	Non-stimulant ADHD (NRI)	Selective NET inhibitor	–	I+++	–	–
Viloxazine ER	Non-stimulant ADHD (SNRI)	NET>SERT inhibition	I+	I++	–	–
Guanfacine ER	Non-stimulant ADHD (alpha2A agonist)	Alpha2A agonist (prefrontal)	–	–	–	A+++
Clonidine ER	Non-stimulant ADHD (alpha2 agonist)	Alpha2 agonist	–	–	–	A+++

Family	Receptor	Coupled G-protein / Ion Channel	Predominant CNS Sites	Core Functions	Drug Examples	Clinical Side Effects
5-HT1	**1A**	Gi → ↓cAMP	Raphe somatodendritic autoreceptor; hippocampus, cortex	Autoinhibition of raphe firing, anxiolysis, antidepressant effects	Buspirone (partial agonist), Vilazodone, Vortioxetine	Agonism may reduce SSRI-induced sexual dysfunction; anxiolysis
5-HT1	1B / 1D	Gi → ↓cAMP	Axon terminals of raphe → basal ganglia, cortex; trigeminal afferents	Presynaptic inhibition, cranial vasoconstriction	Triptans (acute migraine) are 1B/1D agonists	Vasoconstriction (avoid in CAD, stroke risk)
5-HT1	1F	Gi → ↓cAMP	Cortex, trigeminovascular system	Anti-migraine without vasoconstriction	Lasmiditan (ditan)	Dizziness, sedation
5-HT2	2A	Gq → ↑IP3/DAG	Cortex, limbic system, spinal cord	Perception, mood, cognition; modulates sexual response	Atypical antipsychotics (antagonists), psychedelics (agonists)	Sexual dysfunction (↓desire, delayed orgasm), hallucinations if overstimulated
5-HT2	2C	Gq → ↑IP3/DAG	Choroid plexus, hippocampus, substantia nigra	Appetite, mood, inhibition of dopamine release	Mirtazapine (antagonist), lorcaserin (agonist, withdrawn)	Sexual dysfunction, weight gain (via dopamine inhibition), anxiety
5-HT3	3	Ligand-gated cation channel (Na^+/K^+)	Area postrema, GI tract, cortex	Nausea/vomiting reflex, pain processing	Ondansetron (antagonist), setrons	QT prolongation, constipation, headache
5-HT4	4	Gs → ↑cAMP	GI tract, hippocampus	GI motility, learning and memory	Prucalopride (agonist)	Diarrhea, headache, arrhythmia (older agents)
5-HT5	5A	Gi → ↓cAMP	Hippocampus, cortex	Circadian rhythm regulation, cognition	Experimental only	Unknown (not targeted clinically)
5-HT6	6	Gs → ↑cAMP	Striatum, hippocampus, cortex	Learning, memory, cognition	Investigational antagonists for cognition in dementia	Still experimental
5-HT7	7	Gs → ↑cAMP	Thalamus, hypothalamus, limbic system	Circadian rhythm, mood regulation, thermoregulation	Investigational; vortioxetine has activity	Potential antidepressant effects; role in sleep regulation

Family	Receptor	Coupled G-protein / Ion Channel	Predominant CNS Sites	Core Functions	Representative Drugs / Notes
α1	α1A, α1B, α1D	Gq → ↑IP_3/DAG → ↑Ca^{2+}	Cortex, hippocampus, thalamus, locus coeruleus projections	Excitatory tone, attention, arousal, vigilance	Prazosin (antagonist, PTSD/nightmares, HTN); phenylephrine (agonist, decongestant)
α2	α2A, α2B, α2C	Gi/o → ↓cAMP; ↑K^+; ↓Ca^{2+}	Presynaptic auto-receptors in locus coeruleus; spinal cord dorsal horn	Autoinhibition of NE release, analgesia, sedation, blood pressure lowering	Clonidine, guanfacine (agonists, ADHD, HTN); dexmedetomidine (sedation)
β	β1	Gs → ↑cAMP	Cortex, cerebellum, hippocampus	Enhances memory consolidation, arousal, heart rate regulation	Propranolol (antagonist, tremor, performance anxiety, PTSD reconsolidation studies)
β (adrenergic)	β2	Gs → ↑cAMP	Cortex, brainstem, glia	Neurovascular regulation, relaxation of smooth muscle, stress response	Albuterol (agonist, asthma/COPD); propranolol also blocks β2
β (adrenergic)	β3	Gs → ↑cAMP	Hypothalamus, limbic system; mainly peripheral (adipose tissue)	Energy expenditure, thermogenesis, metabolic regulation	Mirabegron (agonist, overactive bladder); metabolic drug interest

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Receptor	Coupled G-protein / Effector	Key CNS / Peripheral Sites	Core Physiologic Roles	Drug Hooks & Seizure Pearls
H_1	**Gq/11 → ↑IP_3 / ↑DAG** → opens non-selective cation channels, depolarises neurons	• Cortex (especially frontal & sensory)• Thalamus• Vestibular nuclei• Vascular endothelium, smooth muscle	• Wakefulness / attention• Capillary permeability, vasodilation• Vestibular balance, nausea	• Diphenhydramine, chlorpheniramine (1st-gen blockers) → sedation; large ODs can provoke seizures (anticholinergic + Na^+-channel block).• Loratadine, cetirizine (2nd-gen) largely periph., minimal CNS effect.• H_1 agonism **raises** threshold; strong antagonism **may lower** it in susceptible patients.
H_2	**Gs → ↑cAMP/PKA**	• Hippocampus & striatum (modest)• Gastric parietal cells	• Facilitates synaptic plasticity (LTP)• Stimulates gastric acid secretion	• Famotidine, ranitidine (blockers) acid-reflux therapy—no meaningful seizure effect.• High H_2 tone has little direct pro- or anti-convulsant impact.
H_3	**Gi/o → ↓cAMP** (presynaptic **auto-receptor**)	• Tuberomammillary neuron terminals across cortex, thalamus, hippocampus• Also acts as hetero-receptor on NE, ACh, 5-HT terminals	• Autoinhibits histamine release ("thermostat" of wakefulness).• Modulates release of other transmitters.	• Pitolisant (H_3 inverse agonist) ↑ cortical histamine, approved for narcolepsy; early RCTs show modest seizure-frequency ↓ in photosensitive & nocturnal epilepsy.• Blocking H_3 **raises** threshold by boosting endogenous histamine
H_4	**Gi/o → ↓cAMP; Ca^{2+} mobilisation**	• Hematopoietic cells (basophils, mast cells, eosinophils)• Minimal CNS expression	• Chemotaxis & cytokine release (immune modulation)	• Orphan in neurology—focus is allergy / inflammation drug development; no documented seizure relevance to date.

Family	Receptor	Coupled G-protein / Ion Channel	Predominant CNS Sites	Core Functions	Representative Drugs / Notes
D1-like	D1	Gs → ↑cAMP	Striatum, cortex, limbic system	Facilitates movement, reward processing, working memory	No highly selective clinical drugs; contributes to levodopa effects in Parkinson's
D1-like	D5	Gs → ↑cAMP	Hippocampus, hypothalamus	Learning, memory, cognition, neuroendocrine regulation	Experimental interest; less targeted clinically
D2-like	**D2**	Gi/o → ↓cAMP; ↑K^+; ↓Ca^{2+}	Striatum, substantia nigra, pituitary	Motor control, reward, inhibition of prolactin release	Antipsychotics (antagonists); dopamine agonists (bromocriptine, pramipexole) for Parkinson's
D2-like	**D3**	Gi/o → ↓cAMP	Limbic regions (nucleus accumbens, olfactory tubercle)	Motivation, reward, mood regulation	Target for some antipsychotics (cariprazine, aripiprazole)
D2-like	D4	Gi/o → ↓cAMP	Prefrontal cortex, amygdala	Attention, cognition, novelty response	Clozapine shows high D4 affinity; role in antipsychotic efficacy debated

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