

Pharmacology of Antidepressant Drugs

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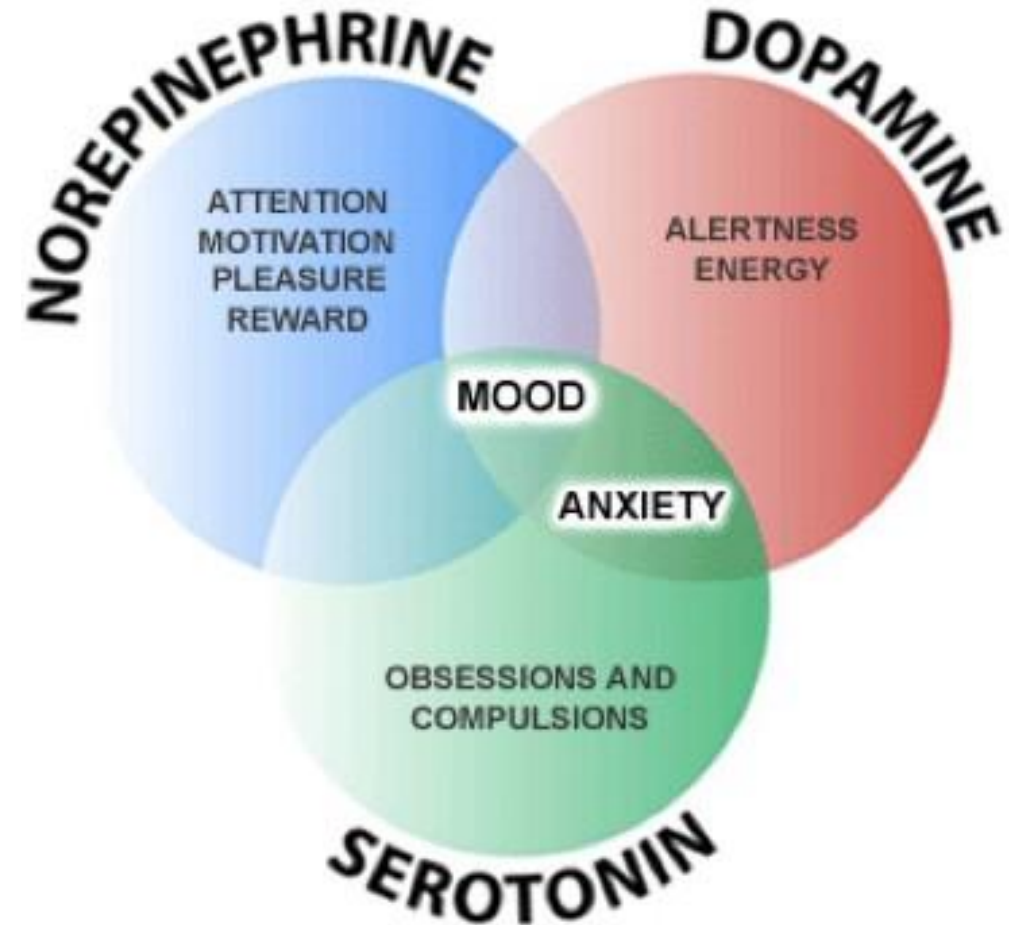
Disclosures

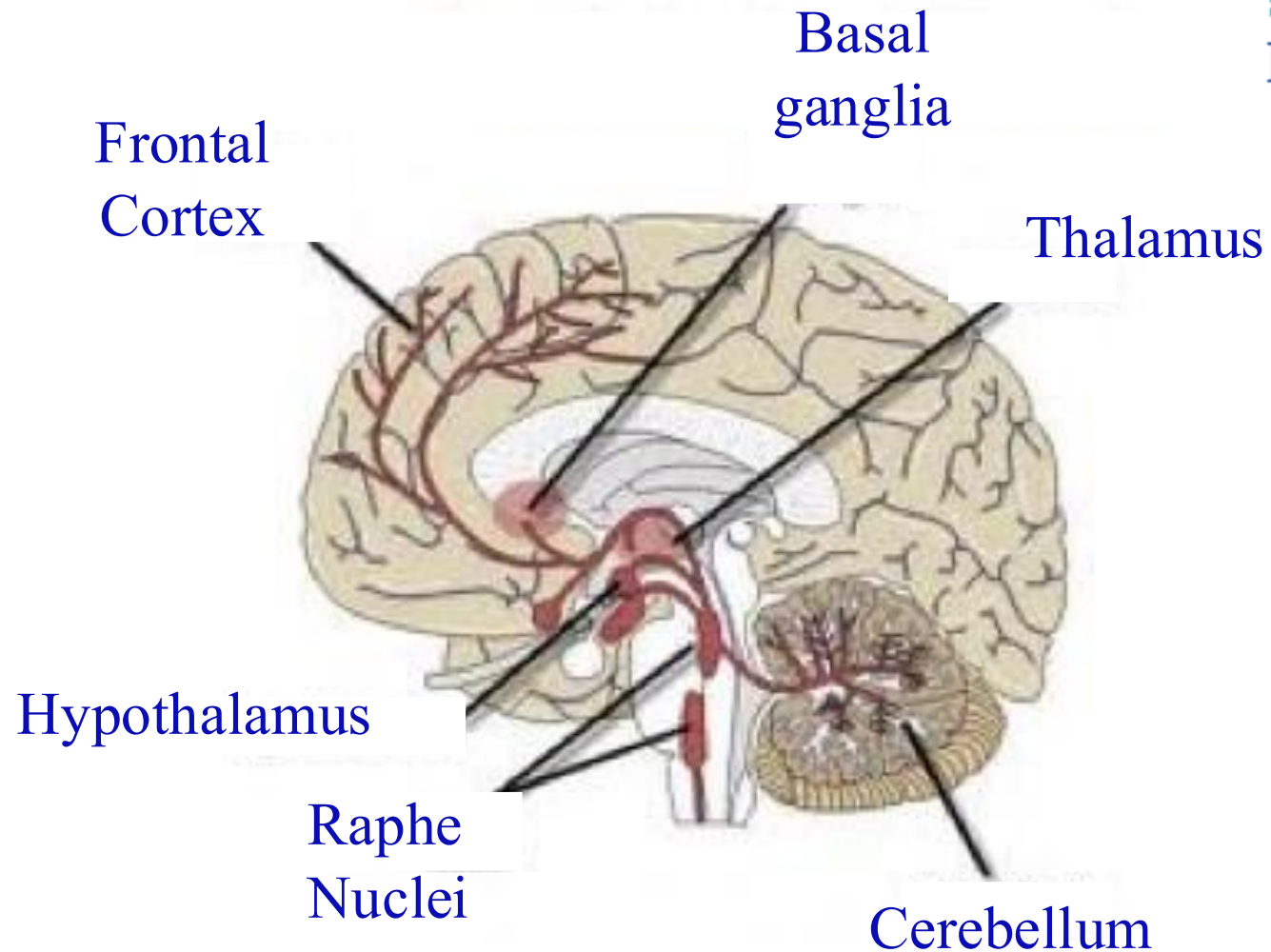
*Neither I nor my spouse has a financial relationship with
a commercial Interest to disclose*

Monoamine Hypothesis of Depression

Three neurotransmitters are involved in
the pathophysiology of depression

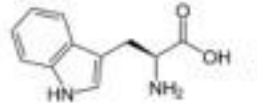
- (1) *Serotonin*
- (2) *Norepinephrine*
- (3) *Dopamine*





Brain Serotonin Pathways

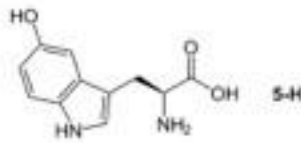
Biosynthesis of Serotonin



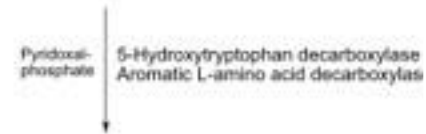
L-Tryptophan



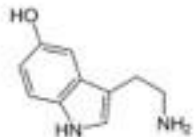
Hydroxylase



5-Hydroxy-L-tryptophan (5-HTP)



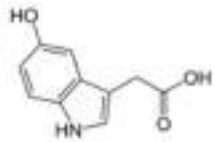
Decarboxylase



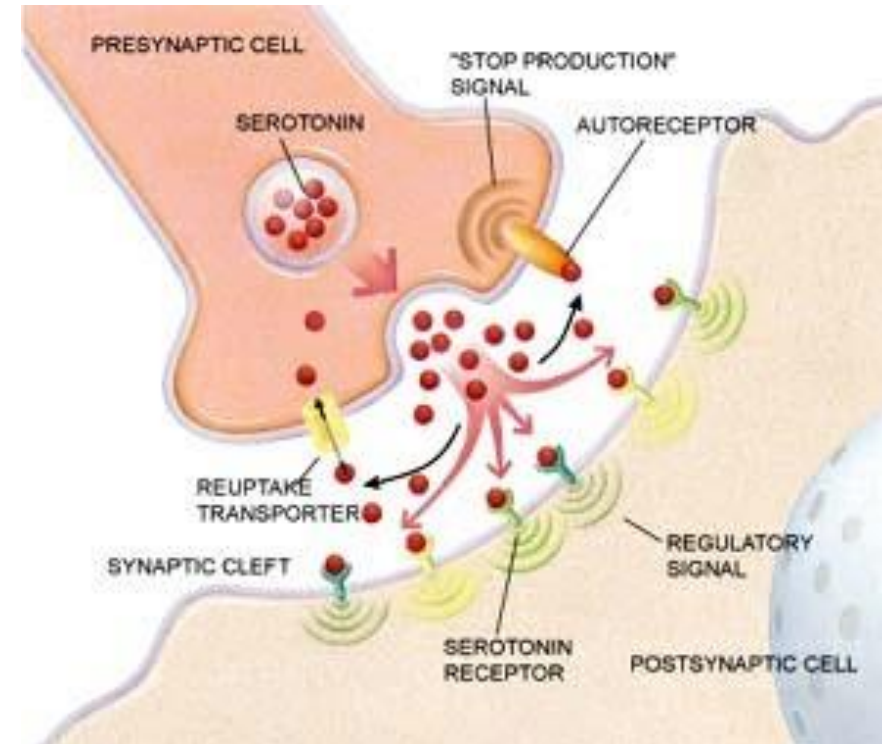
Serotonin (5-HT)

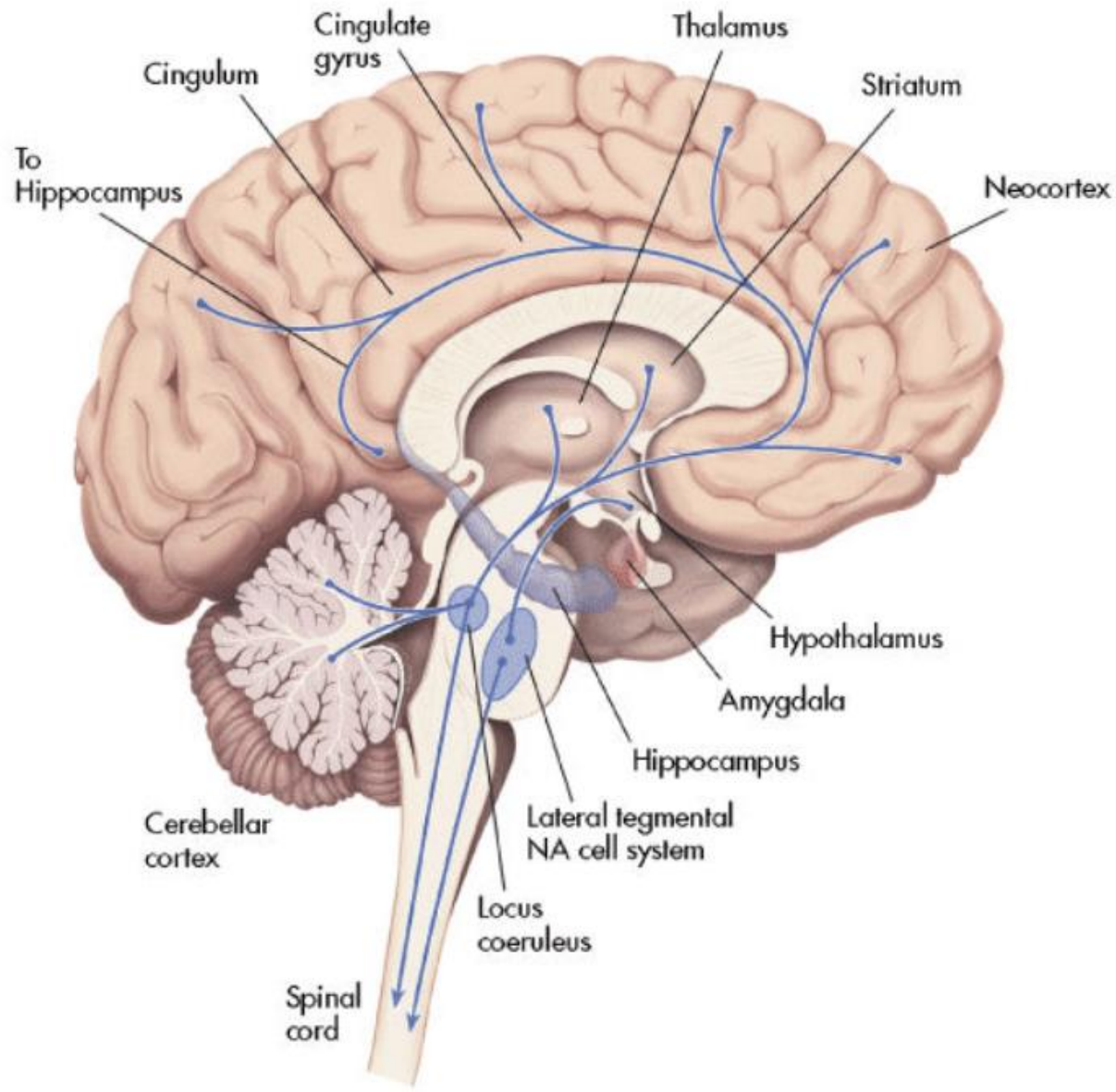


Dehydrogenase



5-Hydroxyindoleacetic Acid (5-HIAA)





Brain Norepinephrine Pathways

Schatzberg 2004, Moret 2011

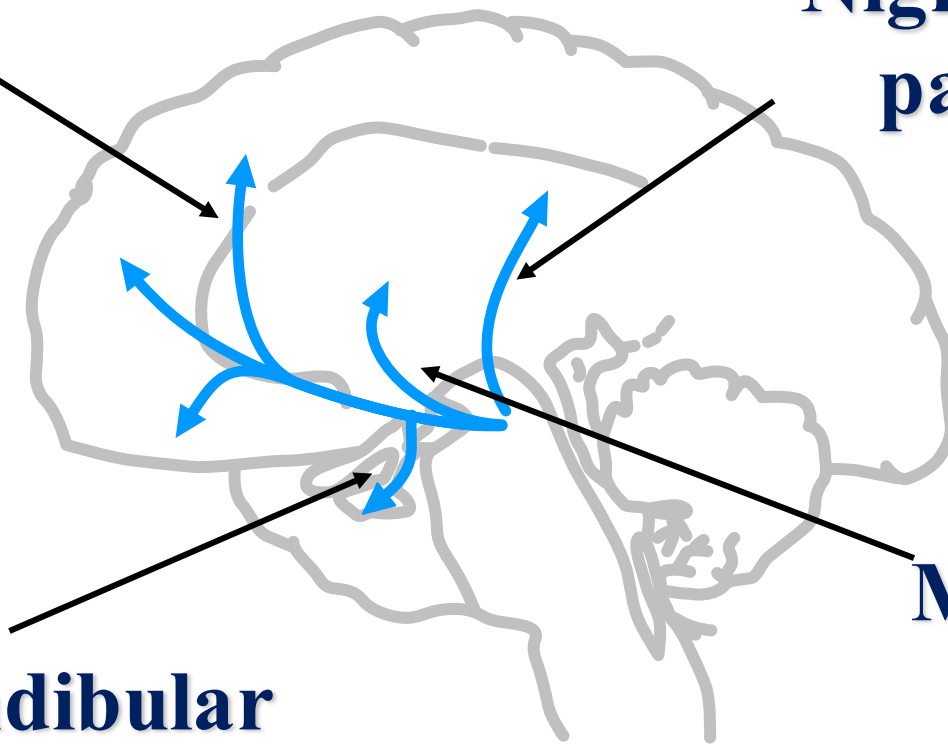
**Mesocortical
pathway**

**Nigrostriatal
pathway**

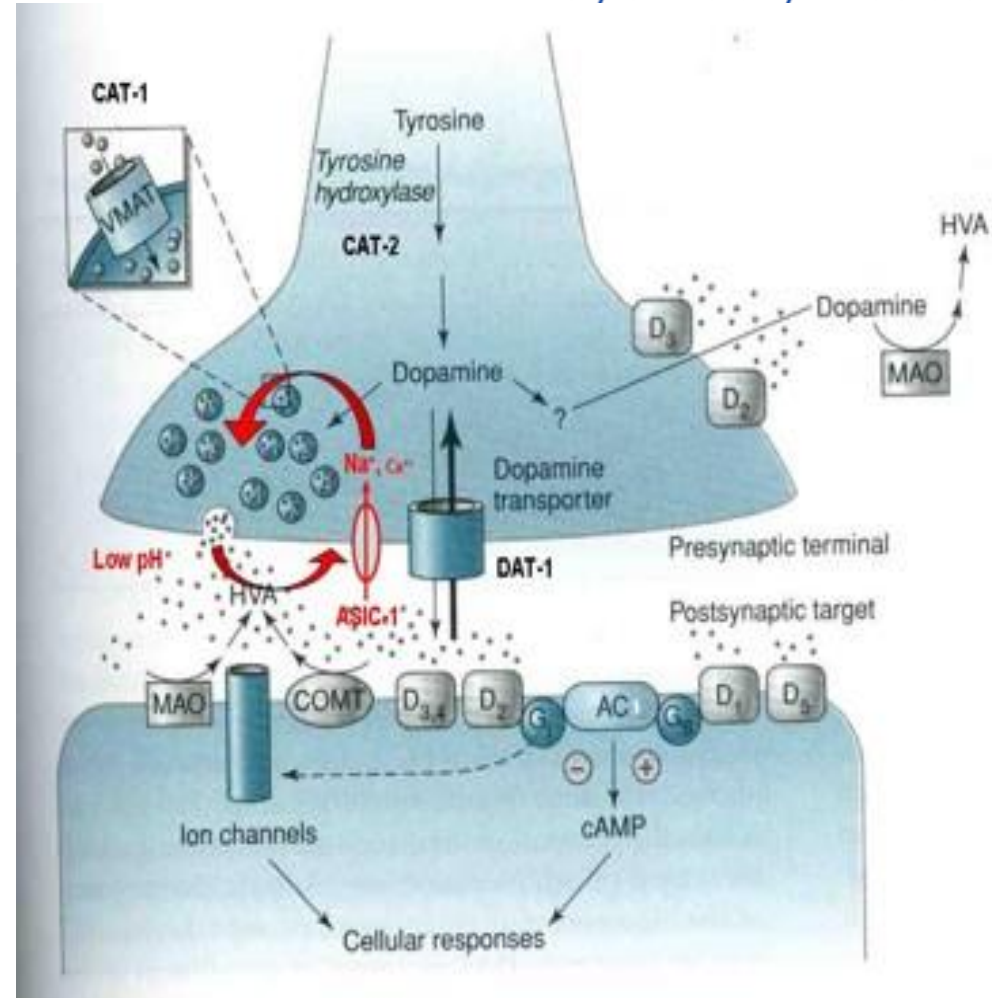
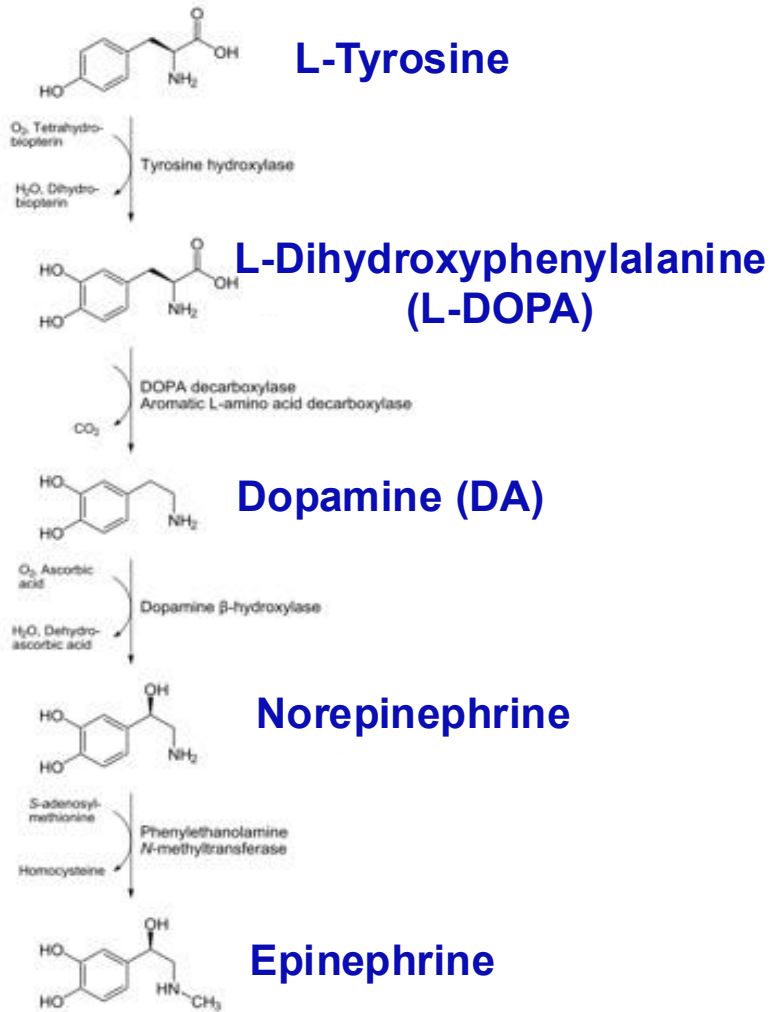
**Brain Dopamine
Pathways**

**Tuberoinfundibular
pathway**

**Mesolimbic
pathway**



Biosynthesis of Dopamine and Norepinephrine



The Journey of Antidepressant Drugs

50s

60s

06

**Isocarboxazid
(1959)**

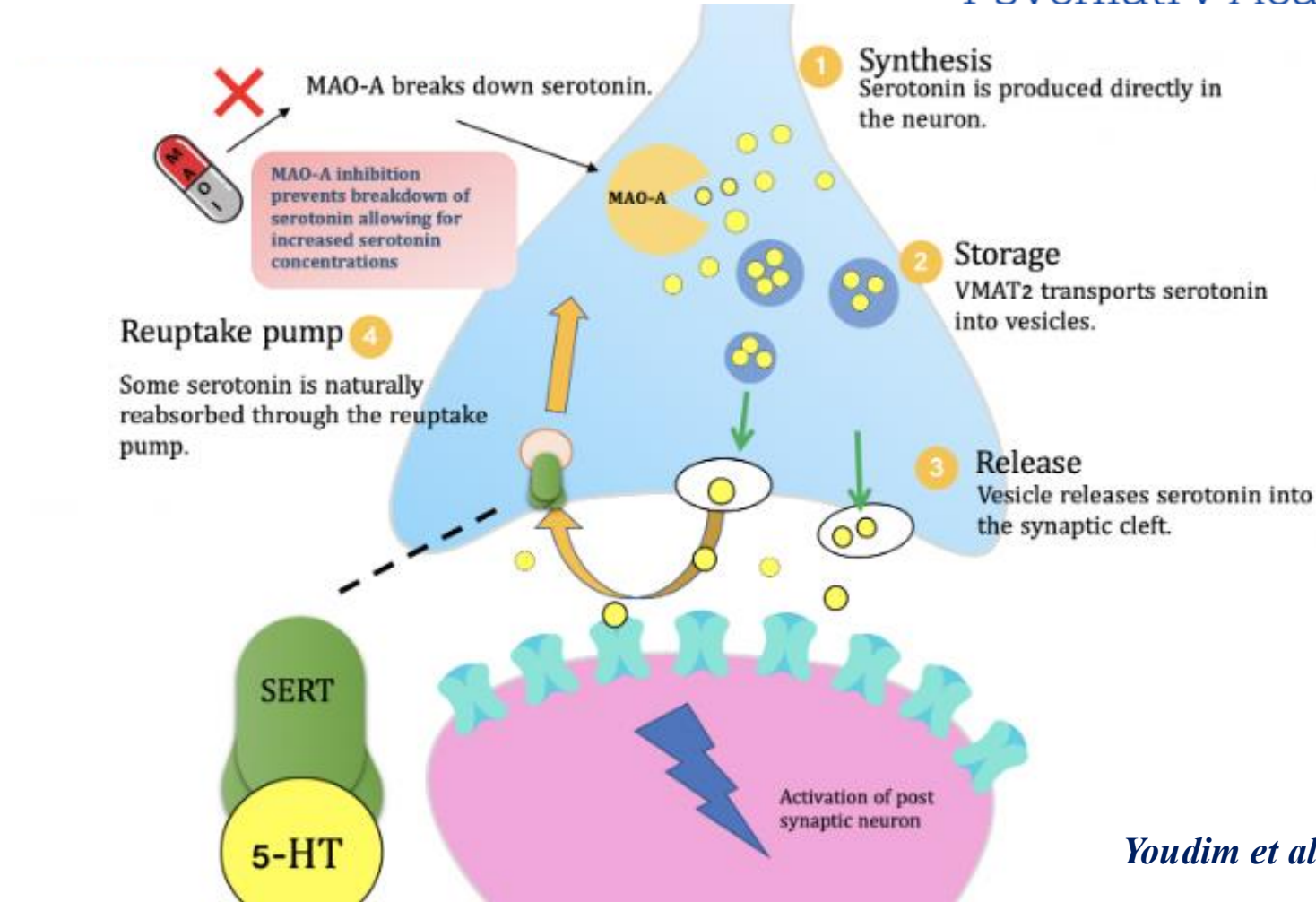
**Phenelzine (1961)
Tranylcypromine (1961)**

**Selegiline (2006)
Transdermal patch**

Monoamine Oxidase inhibitors (MOAIs)

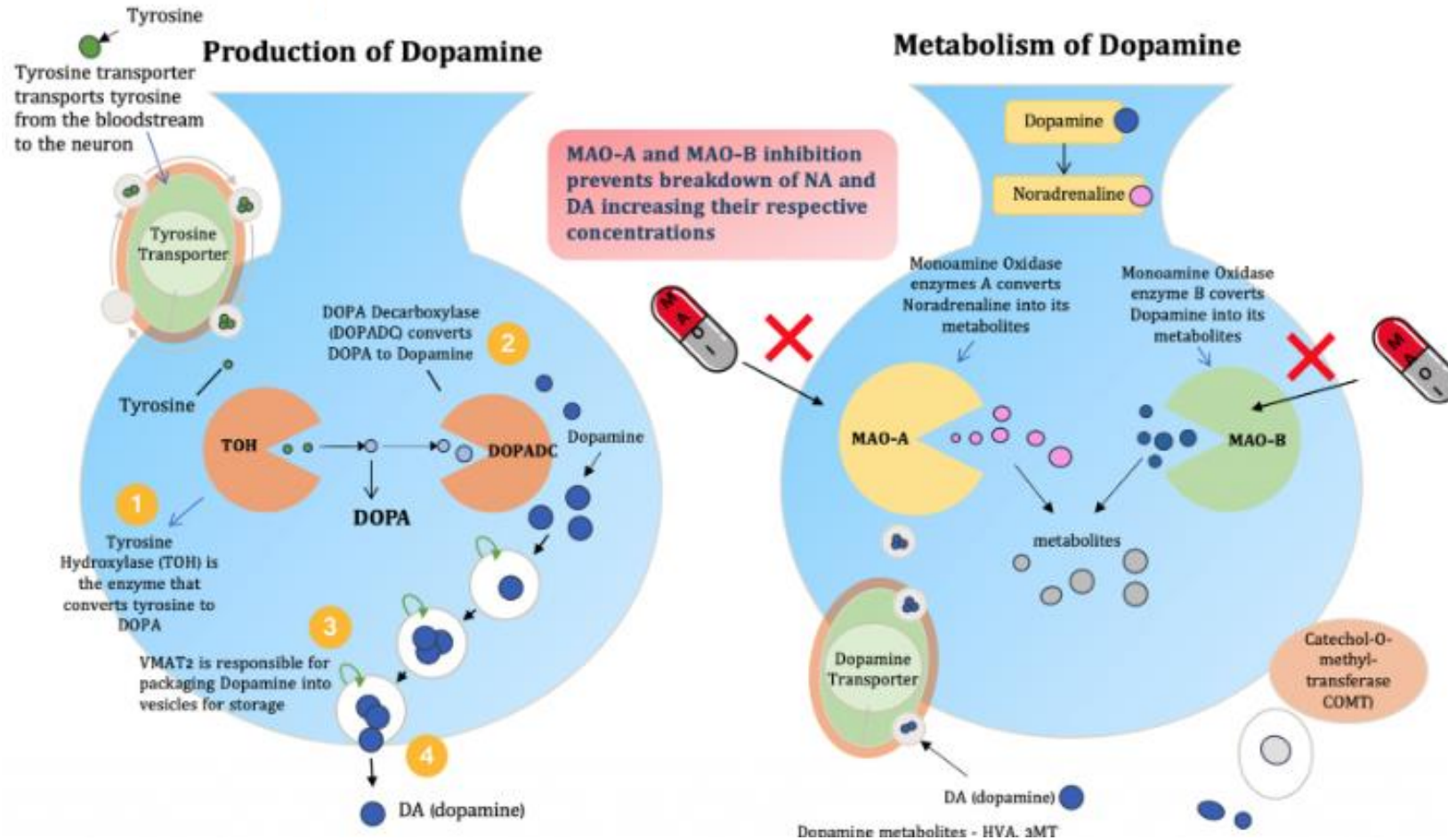
Mechanism of action of MAOIs

Effects of MAOI on Serotonin



Youdim et al. Nature Rev Neurosci 2006; 7:295

Effects of MAOI on Dopamine and Norepinephrine



*Youdim et al. Nature
Rev Neurosci 2006; 7:295*

Adverse Events of MAOIs

Hypertensive Crises!

MAOIs + Tyramine in foods (cheese, meat, fava beans, fermented products, red wine)

➔ Hypertensive Crises

Serotonin Syndrome!

MAOIs + other medications (TCAs, SSRIs, SNRIs, decongestants)

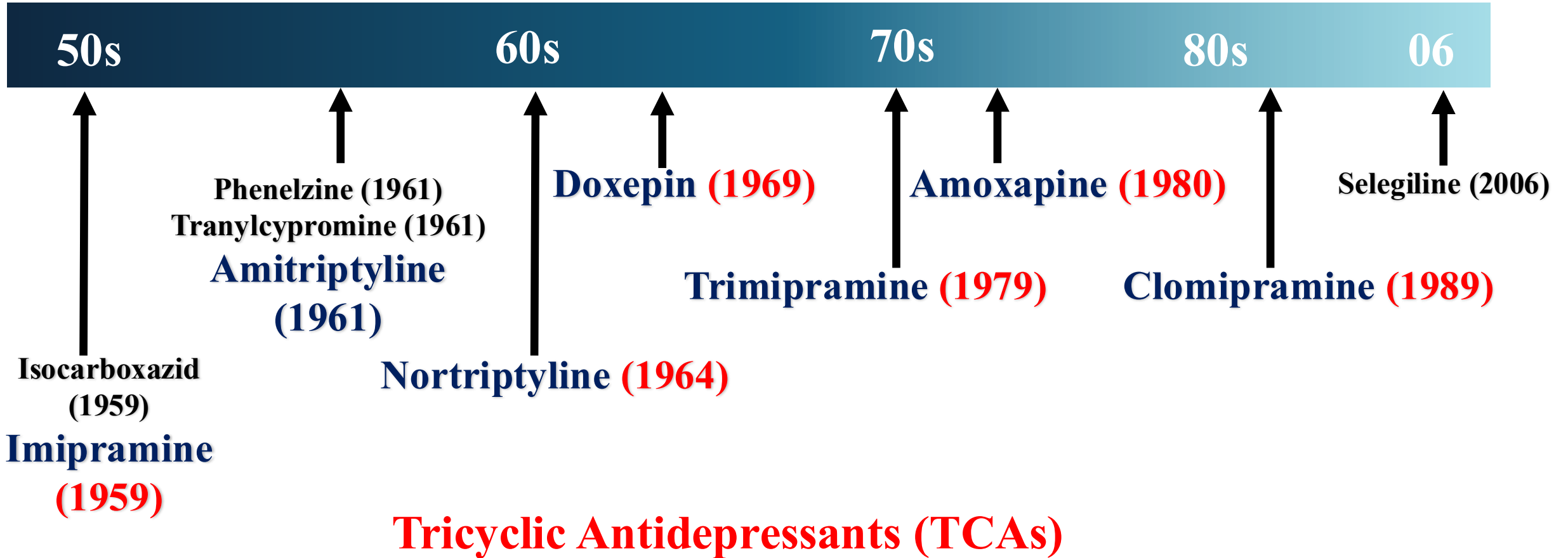
➔ Hypertensive Crises

Symptoms severe hypertension, acute & severe headache, nausea
neck stiffness, palpitations and possibly stroke

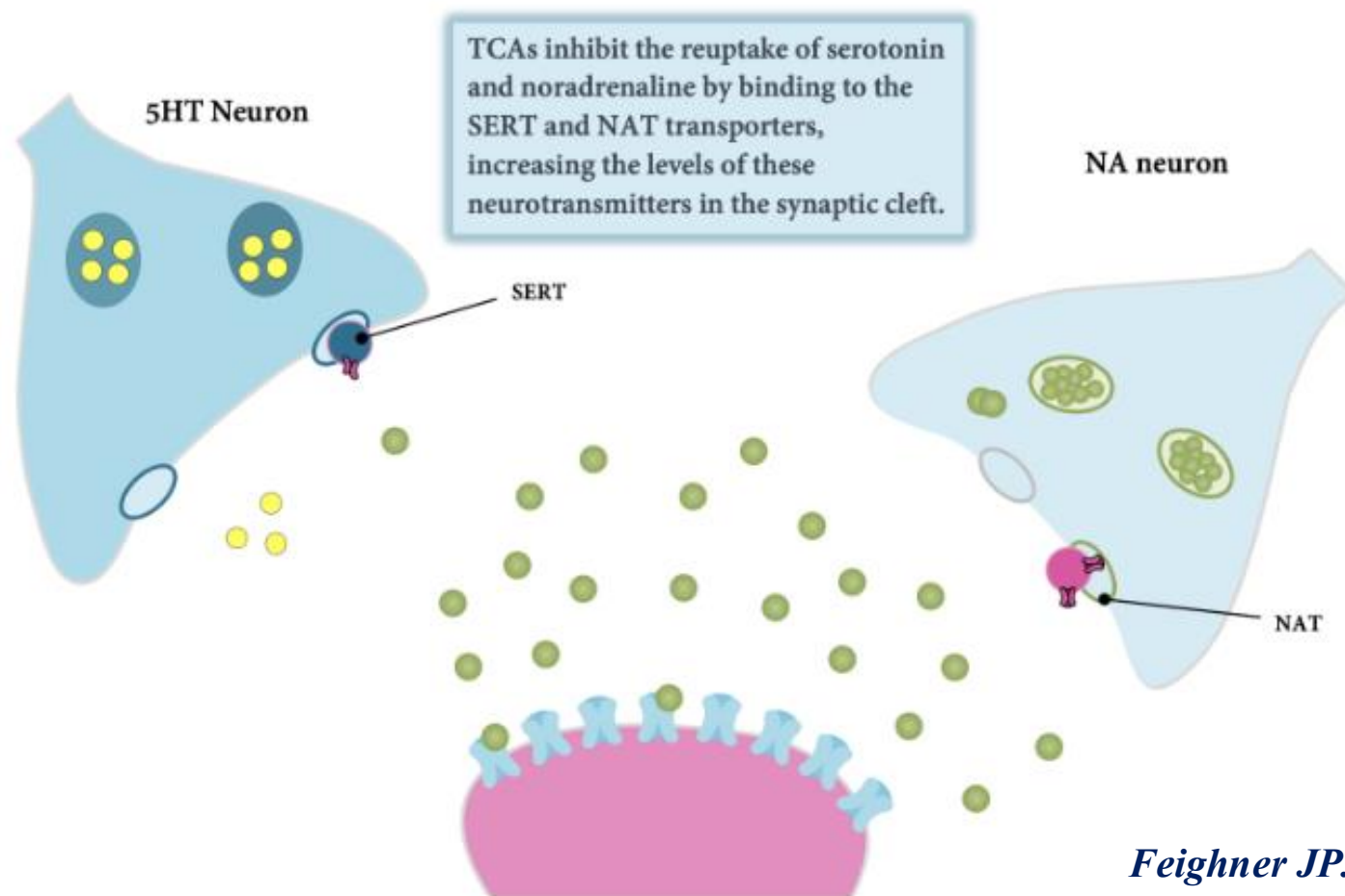
Other side effects: orthostatic hypotension, weight gain, sexual dysfunction, sedation,
dry mouth, constipation, dizziness/headache (especially in early treatment)

Youdim et al. Nature Rev Neurosci 2006; 7:295

The Journey of Antidepressant Drugs



Mechanism of action of TCAs



Feighner JP. J Clin Psychiatry 1999; 60 Suppl 4:4

Adverse Events of TCAs

Cardiovascular side effects

(1) Arrhythmias

APA guidance has recommended a pretreatment ECG in patients >50 years old and in patients with significant cardiac risk factors before starting a TCA.

Avoid combination with anti-arrhythmic drugs

(2) Tachycardia

(3) Orthostatic hypotension

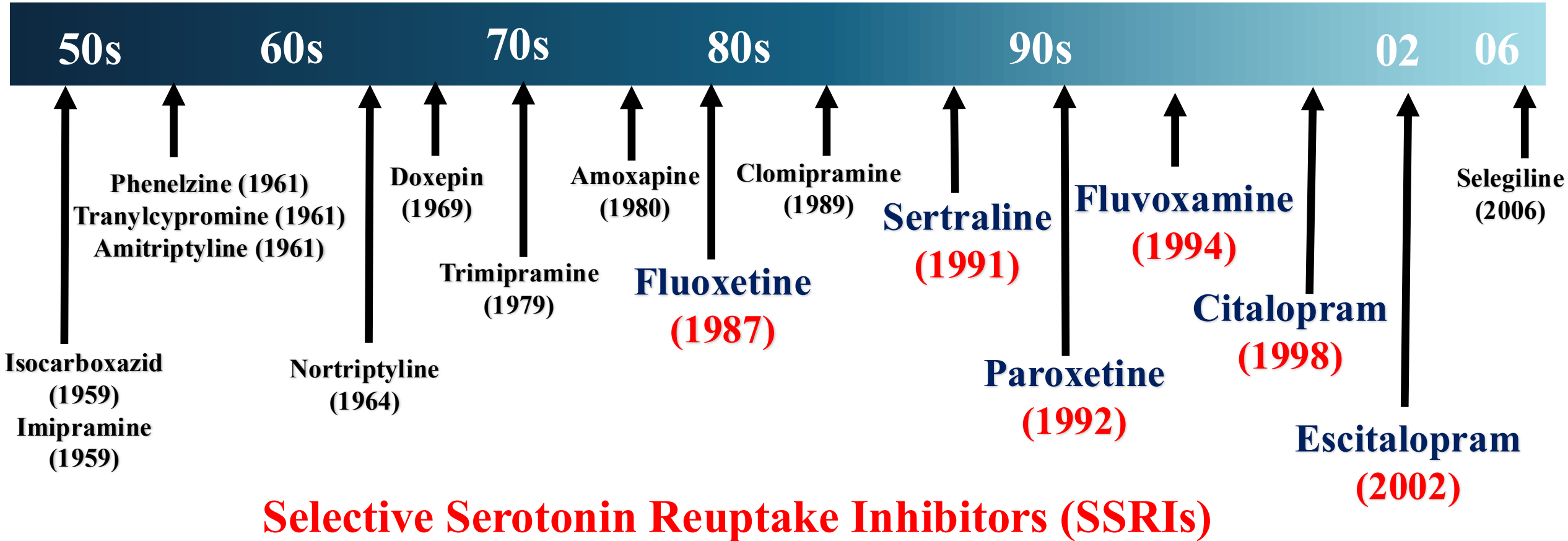
Anticholinergic side effects

Dry mouth, constipation, blurry vision, urinary hesitation.

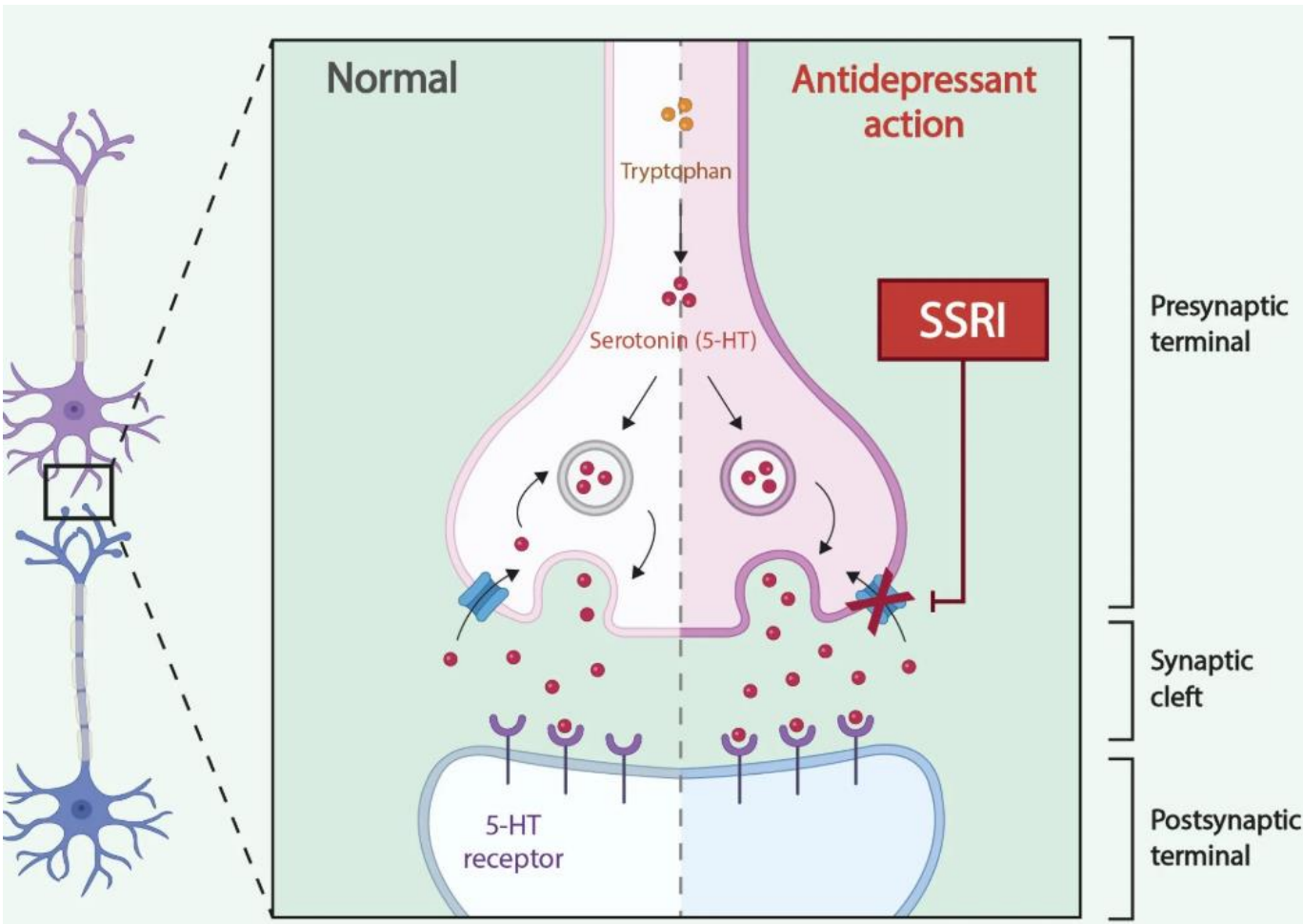
Avoid in patients with cognitive impairment, glaucoma, and Benign Prostatic Hyperplasia (BPH)

Feighner JP. J Clin Psychiatry 1999; 60 Suppl 4:4

The Journey of Antidepressant Drugs



Mechanism of action of SSRIs



- **Most widely prescribed class of antidepressants (over 50% of all antidepressant prescriptions)**
- **Effective antidepressant and anxiolytic agents**
- **Most comparative studies show no clinically meaningful differences in antidepressant efficacy among SSRIs**

Elmarasi & Fuehrlein. Explor Res Clin Soc Pharm 2023; 13:100392

Hansen et al. Ann Intern Med 2005;143:415

Adverse Events of SSRIs

Gastrointestinal: Nausea, vomiting, diarrhea; improves with time

Sexual side effects: ED, delayed ejaculation, anorgasmia

Insomnia: With more activating SSRIs such as fluoxetine

Headache: Common, particularly early in treatment

Weight gain: Paroxetine has greater liability

Serotonin syndrome: Risk increases with other 5-HT drugs, especially MAOIs

Withdrawal Syndrome: Dizziness, flu-like symptoms, insomnia, anxiety

QTc prolongation: Particularly citalopram; dose-dependent

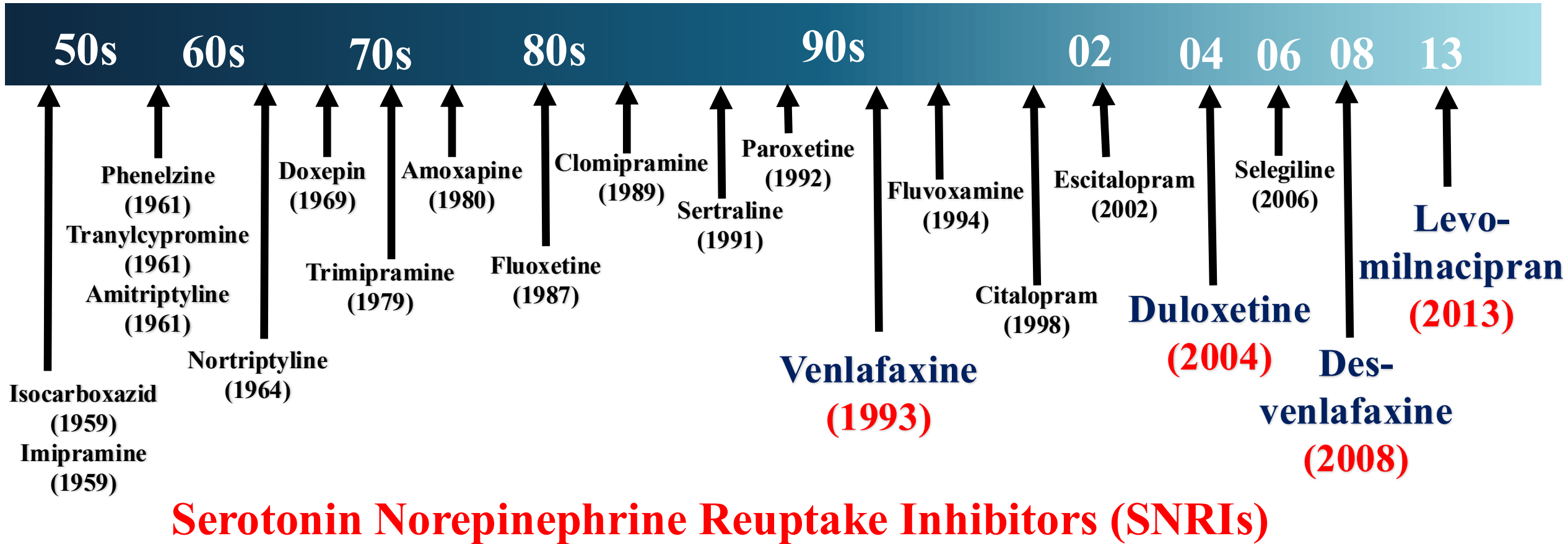
Hyponatremia: Risk increases in older adults and patients taking diuretics

Akathisia “restlessness”: Risk is greatest after treatment initiation or dose escalation

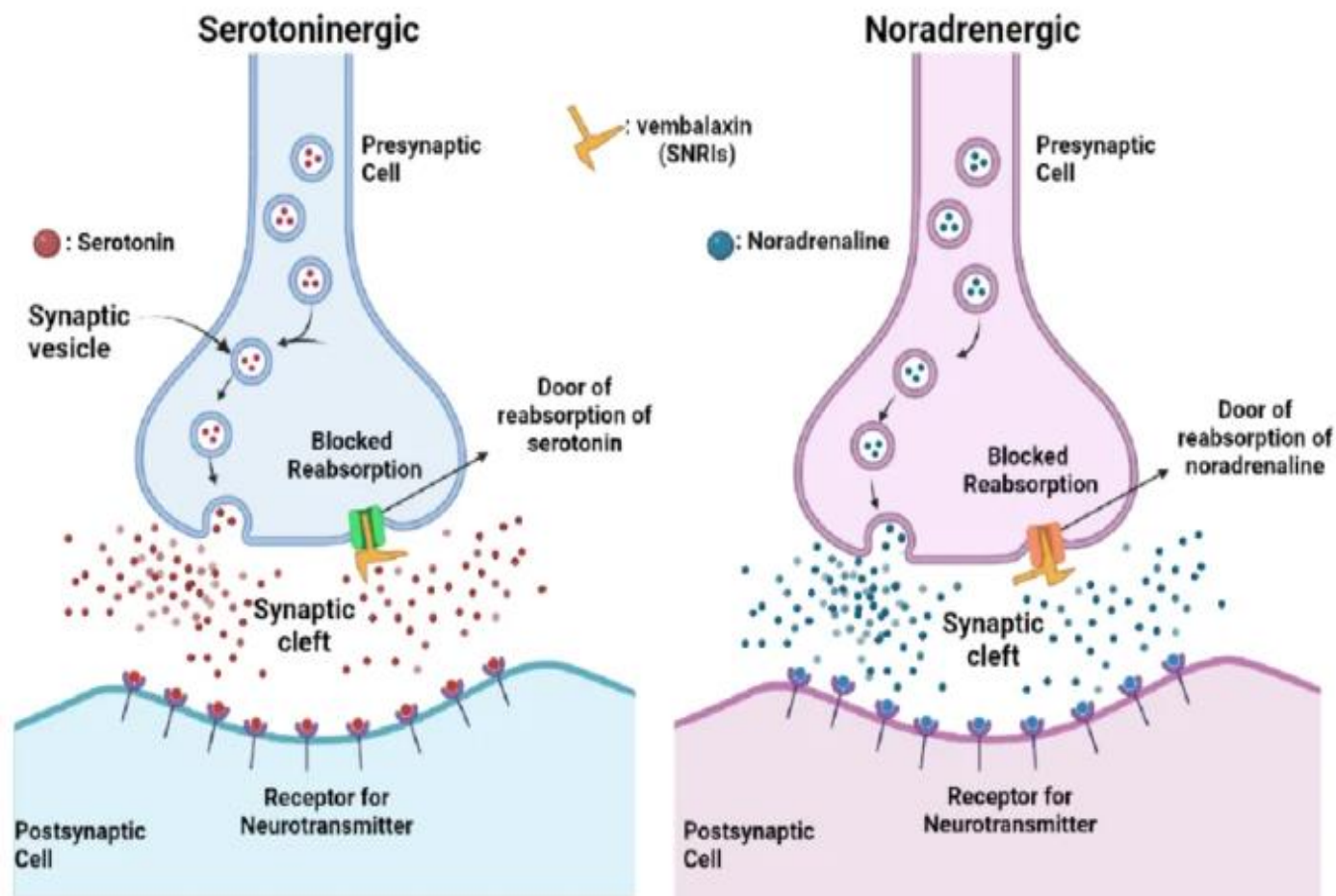


Edinoff et al. Neurol Int. 2021;13(3):387

The Journey of Antidepressant Drugs



Mechanism of action of SNRIs



Venlafaxine: Inhibits 5-HT reuptake at lower doses and NE reuptake at higher doses

Duloxetine: Balanced 5-HT/NE reuptake inhibitor

Desvenlafaxine: Major active metabolite of venlafaxine

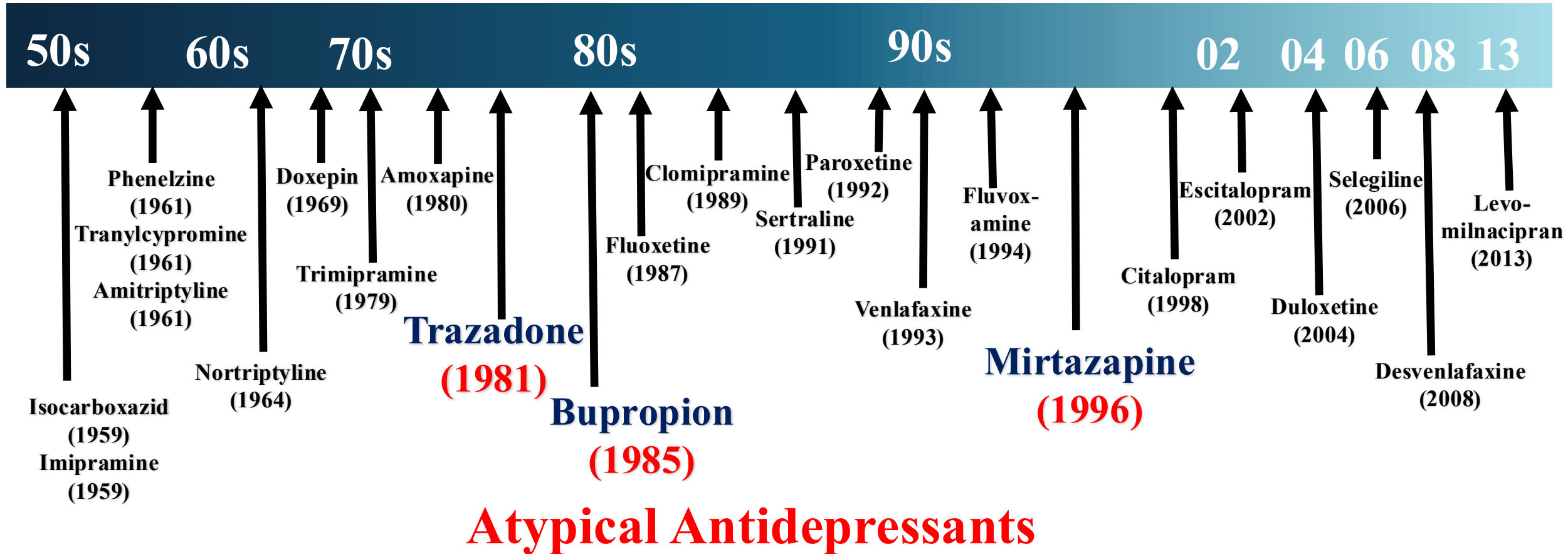
Levomilnacipran: Has greater NE than 5-HT reuptake inhibition

SNRIs share many AEs with SSRIs but have additional noradrenergic effects, particularly at higher doses.

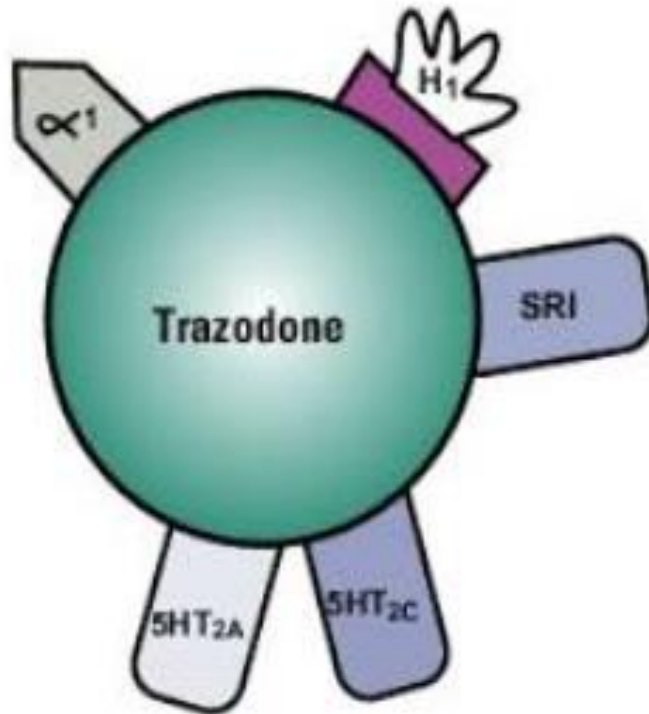
↑ **Blood pressure:** Dose-dependent, especially important with venlafaxine

↑ **Heart rate/palpitations:** Noradrenergic effect

The Journey of Antidepressant Drugs



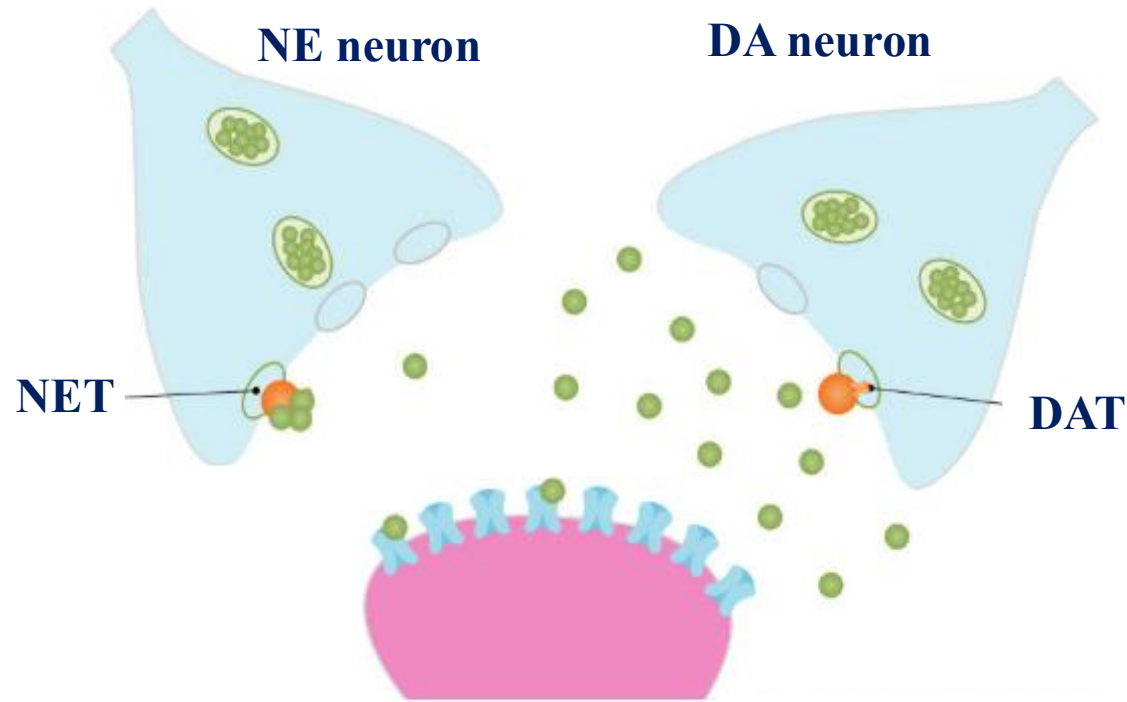
Trazadone



- Classified as a 5-HT antagonist and reuptake inhibitor (SARI)
- It is a potent 5-HT_{2A} receptor antagonist combined with relatively weaker SERT inhibition
- Trazodone also antagonizes H₁-histamine and α_1 -adrenergic Rs, with additional activity at 5-HT_{2C}Rs
- Trazodone exhibits dose-dependent pharmacology:
 - Low doses (25–100 mg):** 5-HT_{2A}, H₁, and α_{21} receptor antagonism predominate, resulting in sedative/hypnotic effects with limited antidepressant activity
 - Higher doses (≥ 100 –400 mg):** SERT inhibition becomes relevant, producing the combined serotonergic actions required for its antidepressant effect

Stahl. CNS Spectr 2009;14:536

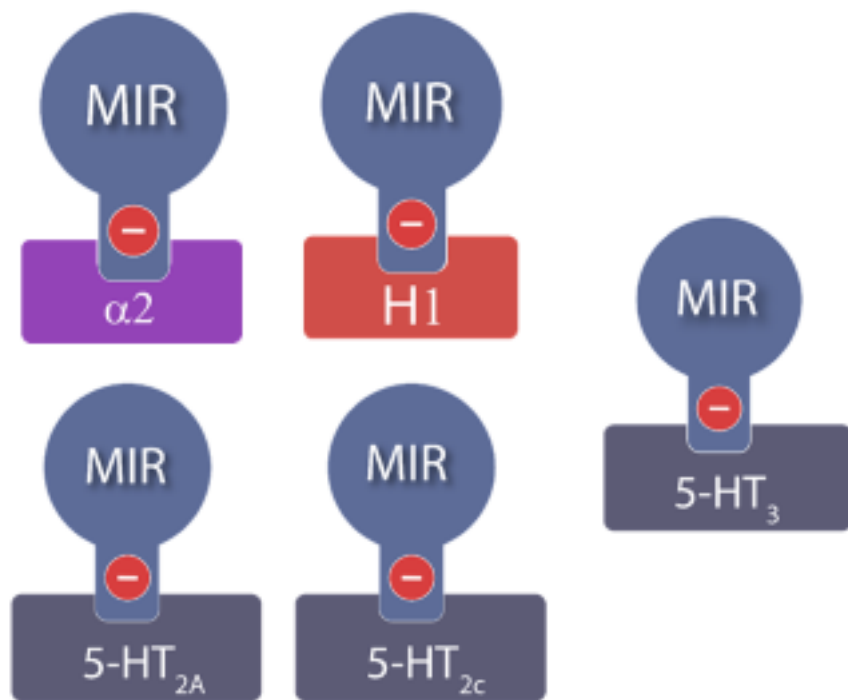
Bupropion



- Atypical antidepressant that acts as a weak DA-NE reuptake inhibitor (NDRI)
- Differs from many antidepressants by having minimal 5-HT activity and no affinity for H, NE or ACh receptors
- Distinguished by low rates of sexual dysfunction and weight gain vs SSRIs/SNRIs and may be activating, improving energy, and fatigue
- Dose-dependent seizure risk (above 450 mg) and potential insomnia/anxiety
- Contraindicated in patients with seizure or eating disorders

Stahl et al. Prim Care Companion J Clin Psychiatry. 2004;6:159

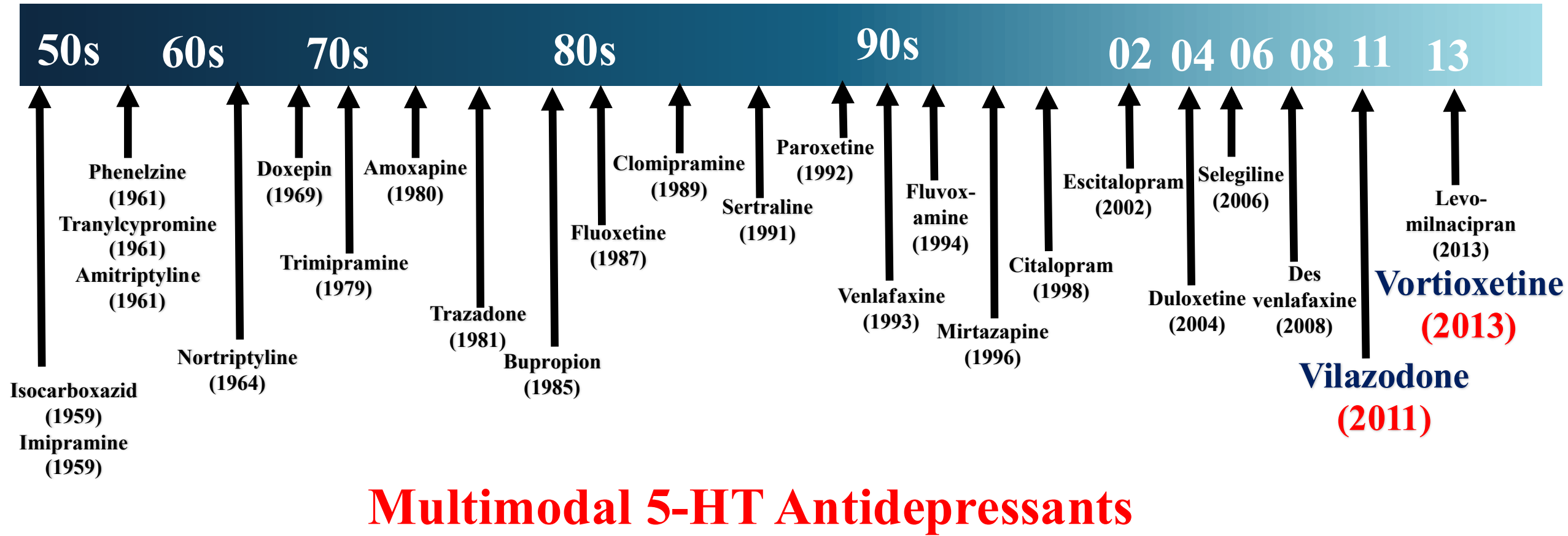
Mirtazapine



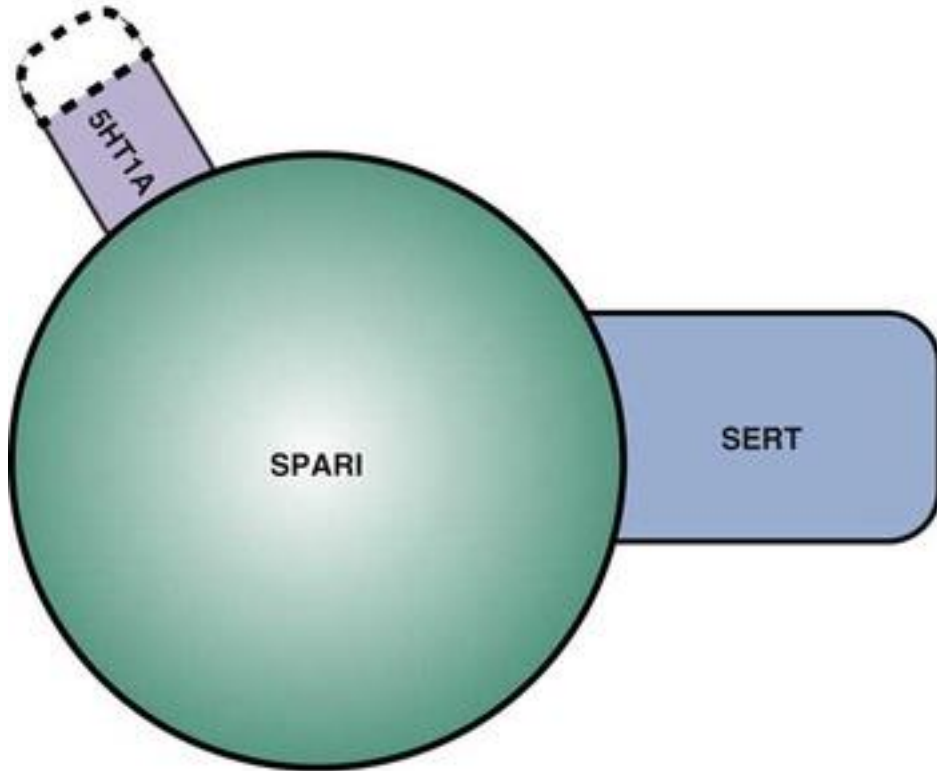
Stimmel et al. Pharmacotherapy. 1997;17:10

- Atypical Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)
- Blocks presynaptic α_2 -adrenergic autoreceptors & heteroreceptors, enhancing NE and 5-HT neurotransmission, while blocking 5-HT_{2A}/5-HT_{2C} and 5-HT₃ receptors
- No affinity for monoamine transporters
- Potent H₁ receptor antagonist. Produces prominent sedation and increased appetite. Useful when depression is accompanied by insomnia or weight loss
- **Key AEs:** somnolence, increased appetite, and weight gain. Causes less nausea and sexual dysfunction than SSRIs/SNRIs

The Journey of Antidepressant Drugs



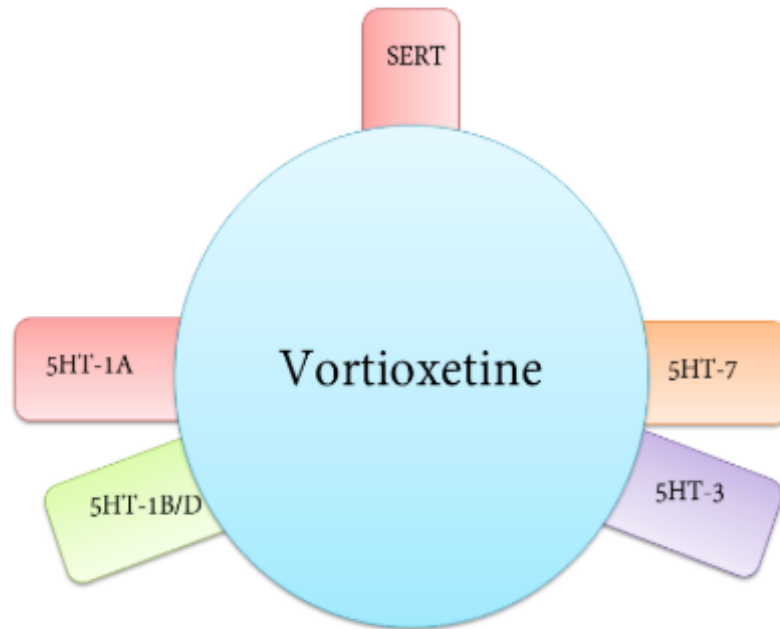
Vilazodone



- Serotonin 5-HT_{1A} Partial Agonist/ Reuptake Inhibitor (SPARI)
- This dual mechanism increases synaptic 5-HT while directly modulating 5-HT_{1A} signaling, distinguishing it from SSRIs
- It has minimal clinically relevant affinity for NET and DAT
- Should be taken with food. Treatment is titrated 10 → 20 → 40 mg/day to reduce GI adverse effects.

Stahl. CNS Spectrums 2014; 19:105

Vortioxetine



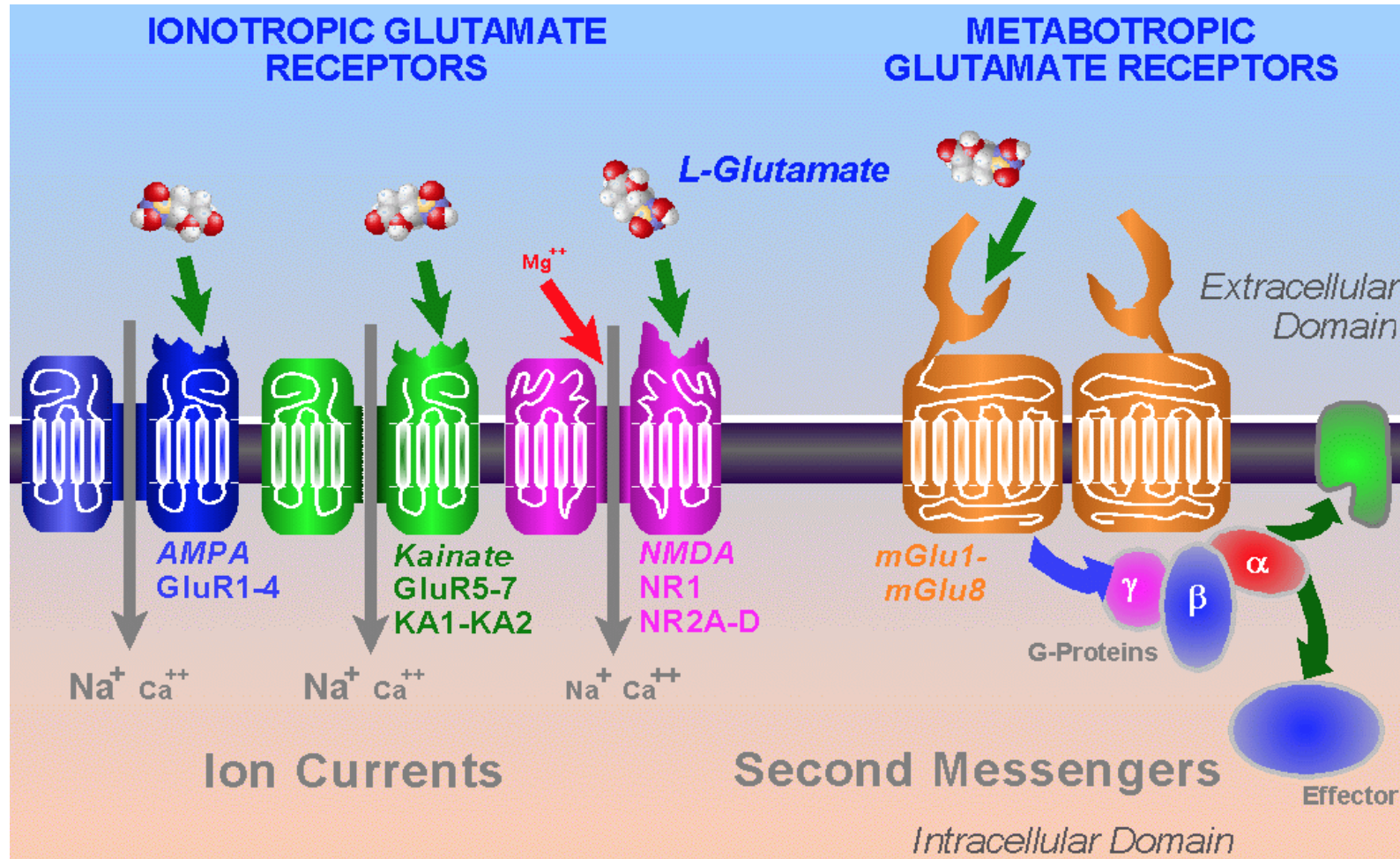
- Combines SERT inhibition with 5-HT_{1A} agonism, 5-HT_{1B/1D} partial agonism, and 5-HT₃/5-HT₇ receptor antagonism, distinguishing it from conventional SSRIs
- Its multimodal actions indirectly modulate six neurotransmitters: Glu, GABA, DA, NE, ACh, H
- Vortioxetine has evidence for improving cognitive symptoms of MDD, including processing speed, attention, and executive function, beyond improvement attributable to depressive symptoms
- Useful in MDD patients with prominent anxiety, particularly when cognitive symptoms are also present

Sowa et al. Pharmacol Rep 2017; 69:595

Novel Antidepressant Drugs: Beyond Monoamine Targets

Gonda, Dome, Neill, Tarazi. CNS Spectrums 2023; 28:6-15

Glutamate Receptor Subtypes

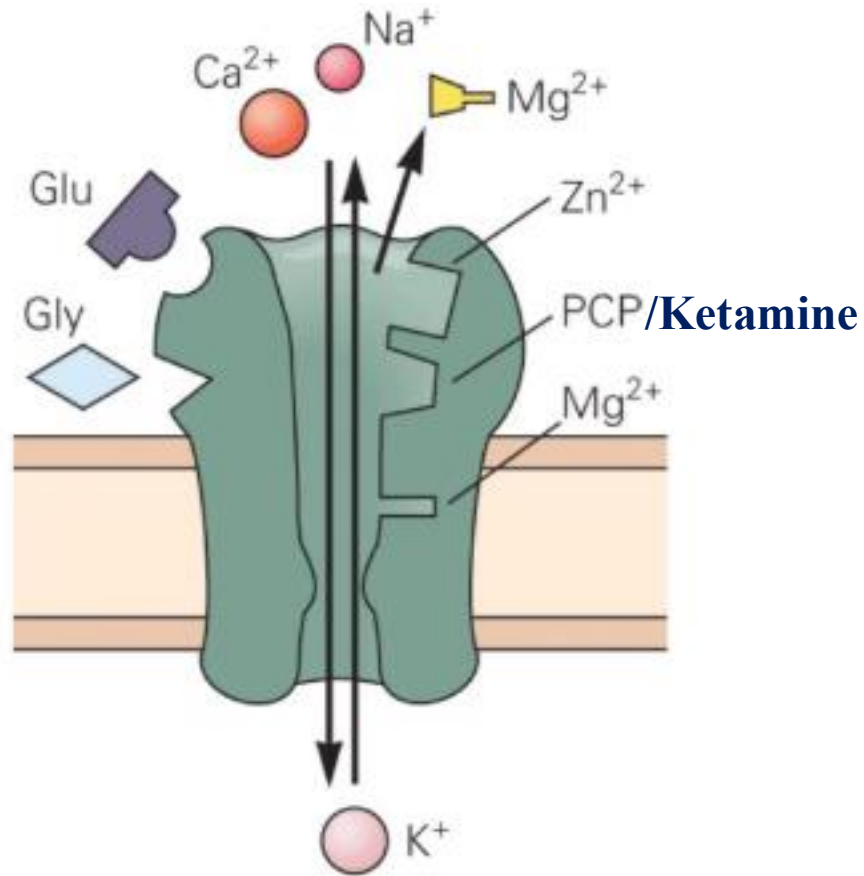


Glu receptors are divided into two major families:

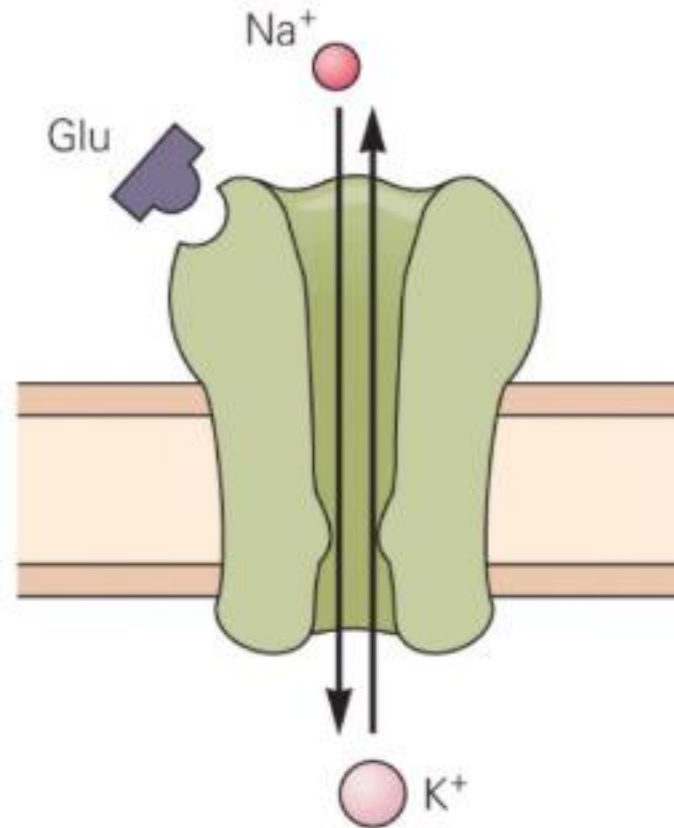
Ionotropic receptors:
NMDA, AMPA, Kainate

Metabotropic receptors:
mGlu1–mGlu8

*Salt. Neurotransmitters in sensory systems.
2017; University College London.*



NMDA Receptors



AMPA Receptors

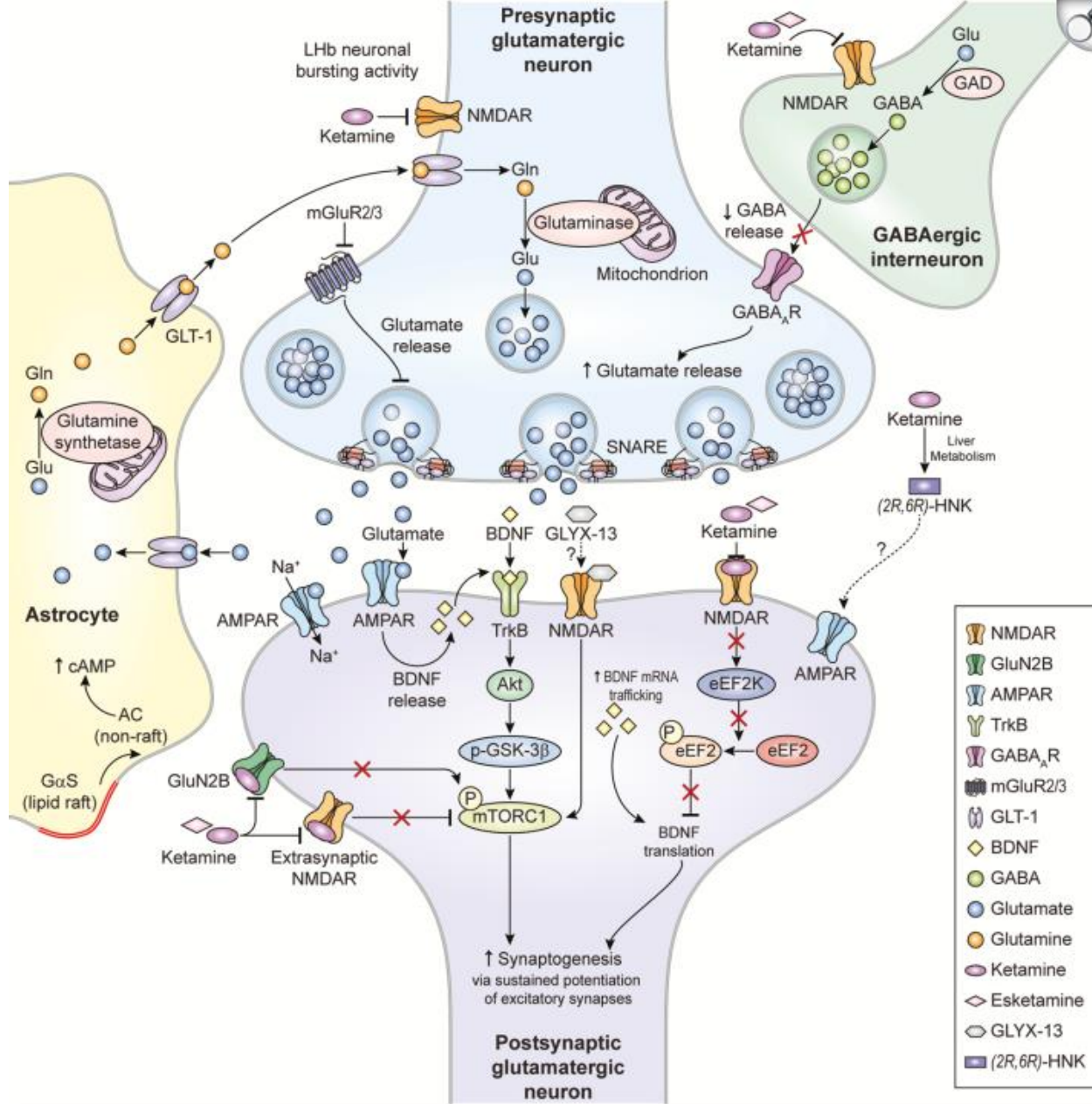
Glutamatergic Hypothesis of Depression

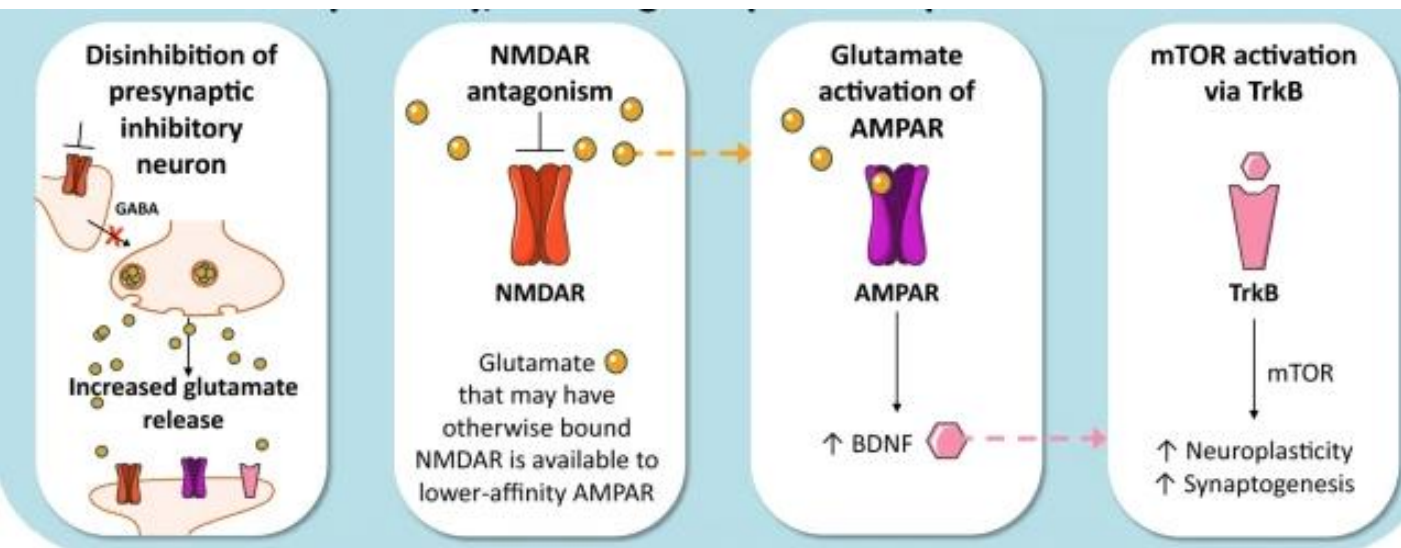
Supporting evidence:

- Significant elevation in blood Glu levels were reported in MDD patients
- PET imaging studies and postmortem tissue analyses have revealed abnormalities in Glu receptor subunit/protein expression in the prefrontal cortex in MDD patients
- Preclinical studies reported that chronic stress–induced Glu dysregulation contributes to dendritic and synaptic loss in the prefrontal cortex and hippocampus; similar Glu and structural abnormalities have also been observed in MDD patients
- In 2000, the first placebo-controlled, double-blind clinical trial of ketamine (potent NMDA-R antagonist) showed significant and rapid improvement in MDD symptoms

Berman et al. Biol Psychiatry 2000; 47:351
Sanacora et al. Neuropharmacol 2012; 62:63

Mechanism of Action of Ketamine

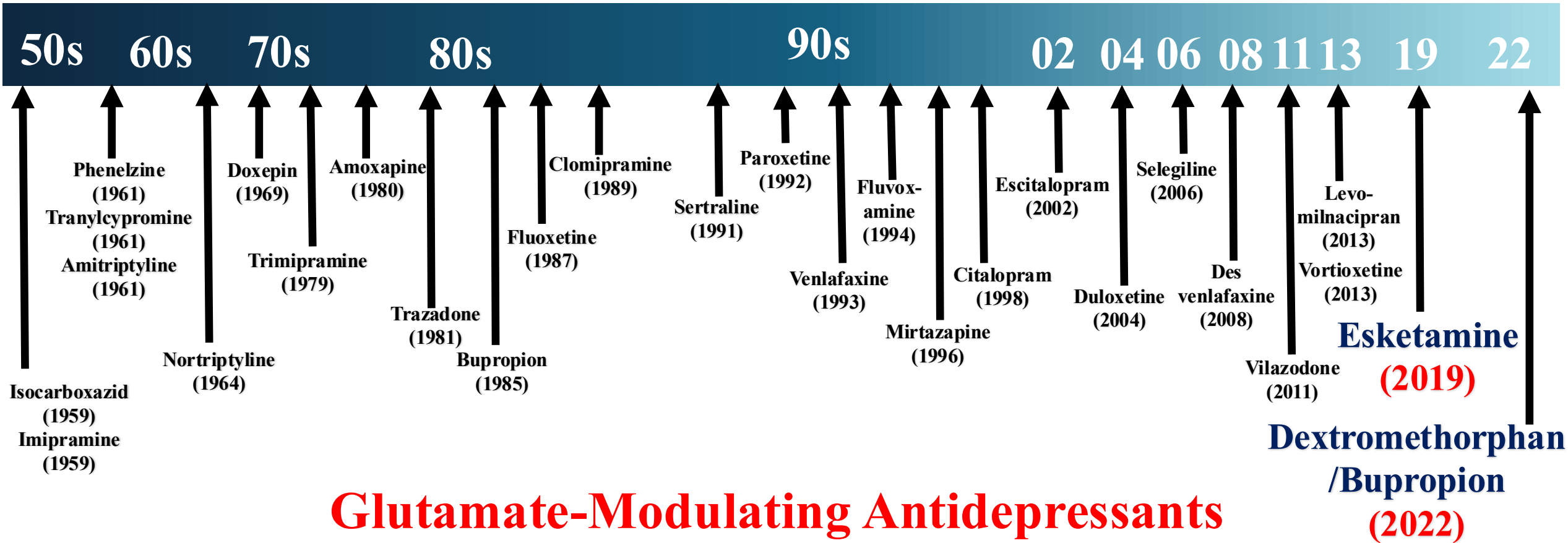
Kadriu et al. *Int J Neuropsychopharmacol* 2019; 22:119



- **Disinhibition of GABA interneurons via NMDA-R blockade leads to disinhibition of pyramidal neurons and consequently increased Glu release**
- **Glu binds and activates AMPA-Rs**
- **Increase expression of hippocampal BDNF**
- **BDNF activates mTOR via TrkB**
- **Increase synaptogenesis and neuroplasticity, resulting in rapid antidepressant effect**

McIntyre & Jain. CNS Drugs 2024; 38:869

The Journey of Antidepressant Drugs



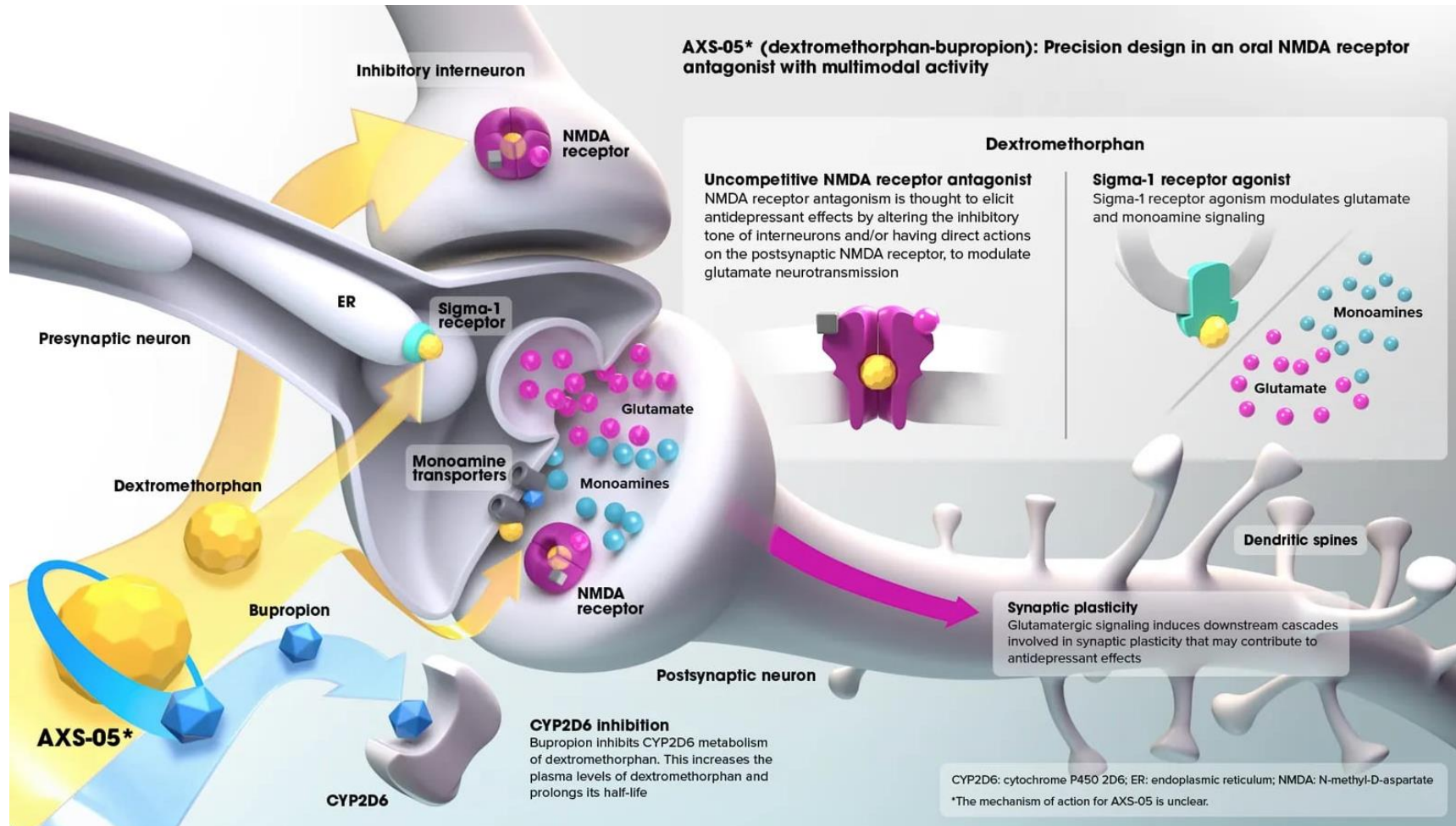
Glutamate-Modulating Antidepressants

Esketamine

- Esketamine is the S-enantiomer of ketamine. Administered as a nasal spray
- Approved in 2019 as adjunctive treatment for TRD. In 2020, FDA approved Esketamine for MDD with acute suicidal ideation or behavior. In 2025, FDA approved Esketamine as monotherapy for TRD
- Esketamine can produce clinically meaningful antidepressant effects much more rapidly than conventional antidepressants
- Esketamine is a Schedule III controlled substance (First scheduled antidepressant) and is available through a restricted REMS program
- Because of risks of sedation, dissociation, respiratory depression, hypertension, and abuse/misuse, administration occurs under HCP supervision, with patients monitored for at least 2 hours afterward



Dextromethorphan-Bupropion



*Axsome Therapeutics, Inc. AXS-05
(dextromethorphan/bupropion)*

Dextromethorphan-Bupropion

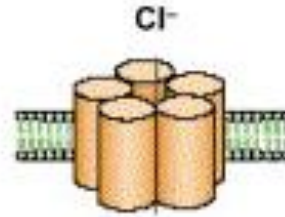
- **First oral Glu-modulating antidepressant. Combines dextromethorphan (NMDA receptor antagonist and sigma-1 receptor agonist) with bupropion.**
- **Bupropion acts as a pharmacokinetic enhancer: By inhibiting CYP2D6, bupropion increases and prolongs dextromethorphan exposure; it also has NE/DA reuptake-inhibiting activity.**
- **In the pivotal MDD study, statistically significant improvement versus placebo was observed as early as Week 1, considerably faster than other conventional antidepressants.**
- **Regimen of treatment: Days 1–3: 45 mg dextromethorphan/105 mg bupropion once daily in the morning; Day 4 onward: 45/105 mg twice daily, with doses separated by at least 8 hours.**
- **It is a non-scheduled drug. Does not require a REMS program, certified treatment center, or post-dose observation. Has a black box warning for an increased risk of suicidal thoughts and behaviors in pediatric and young adult patients**

Akbar et al. CNS Drugs. 2023; 37:867

GABA Receptor Subtypes

GABA_A

- Ligand-gated ion channel



Subunits:
 $\alpha 1-6$, $\beta 1-3$, $\gamma 1-3$, δ , ϵ , θ and π

GABA_B

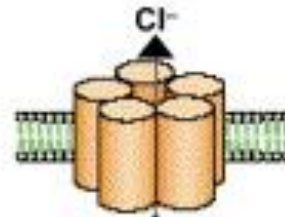
- G protein-coupled receptor



Subunits:
R1a, R1b and R2

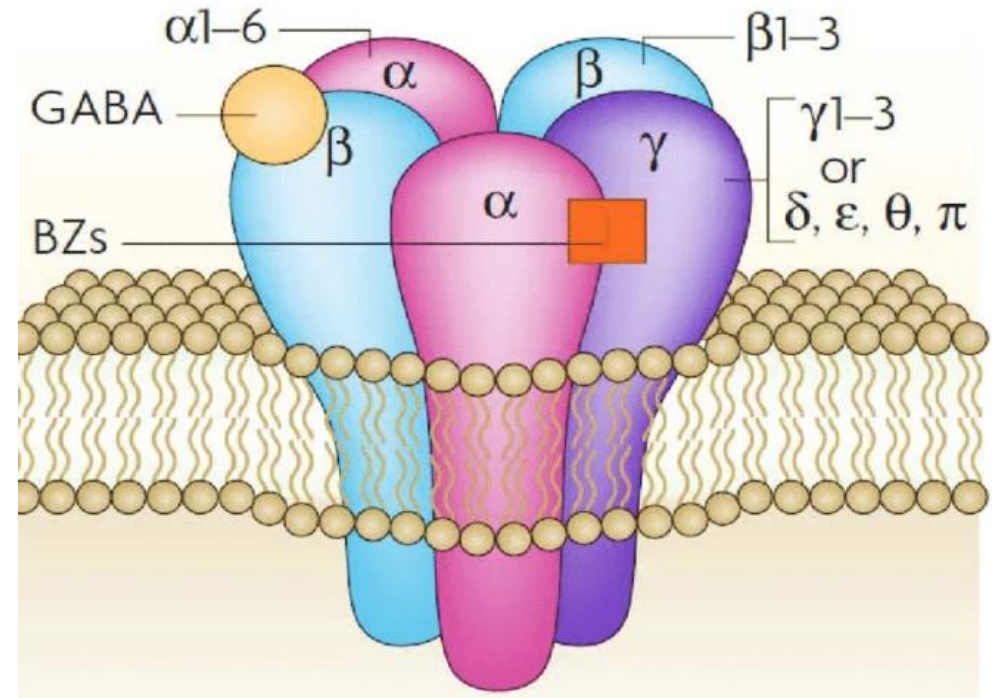
GABA_C

- Ligand-gated ion channel



Subunits:
 $\rho 1-3$

GABA_A Receptors



Bateson. Sleep Med 2006; 7(S1):S3

GABAergic Hypothesis of Depression

Supporting Evidence:

- Proton MRS studies reported significantly reduced cortical GABA concentrations in MDD patients
- Reduced GABA concentrations have also been reported in CSF and plasma samples from MDD patients
- Postmortem and preclinical studies show abnormalities in GABAergic interneurons, including parvalbumin- and calbindin-positive interneurons within corticolimbic circuits implicated in depression
- Chronic stress can reduce GABAergic inhibition in the PFC and hippocampus, increasing neuronal excitability and contributing to HPA-axis dysregulation, an important biological feature of depression.

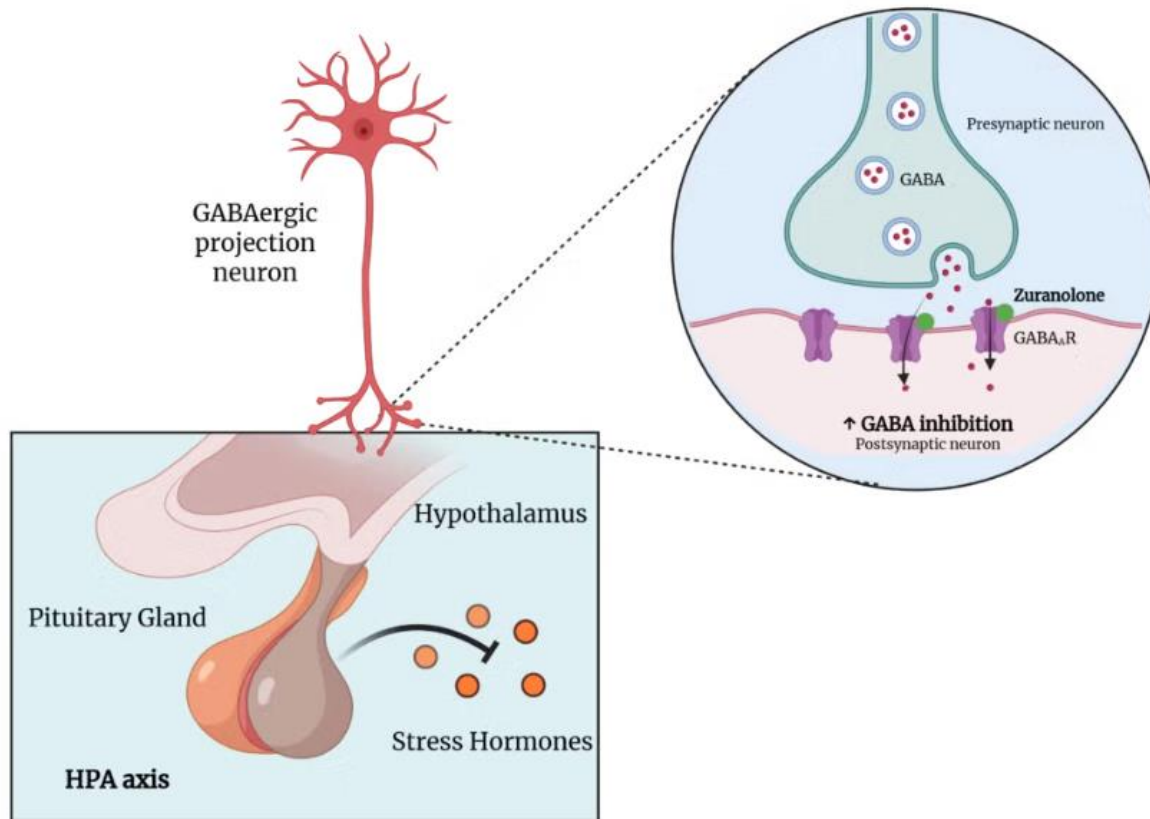
Luscher et al. Mol Psychiatry 2012; 16:383

GABAergic Hypothesis of Postpartum Depression (PPD)

- **Supporting Evidence:**
- Allopregnanolone levels increase during pregnancy and drop rapidly after delivery. This neurosteroid, which is a potent PAM of GABA_ARs, enhances GABA_AR activity and may contribute to changes in mood after childbirth
- Human MRS studies have reported lower GABA levels in women at risk for PPD, with GABA measures negatively associated with depression and anxiety symptoms
- Impaired GABA_AR function can produce postpartum depressive behaviors in animals, while stimulating GABA_A signaling with neurosteroids can reverse them
- Clinical pharmacology provides strong validation: brexanolone and zuranolone, neuroactive-steroid GABA_A PAMs, have showed antidepressant efficacy in PPD

Maguire & Mody. Neuron 2008; 59:207; Gunduz-Bruce et al. J Neuroendocrinol. 2022;34:e13019

Mechanism of action of Zuranolone in PPD



- Zuranolone acts as a positive allosteric modulator (PAM) of GABA_ARs
- Positive allosteric modulation enhances the efficacy of GABA, strengthening inhibitory neurotransmission
- Enhanced GABAergic inhibition may suppress CRH-expressing neurons in the hypothalamus, reducing CRH release
- Reduced CRH signaling decreases downstream ACTH and cortisol release and reduces HPA-axis activity
- Normalization of stress-axis hyperactivity may contribute to the anxiolytic and antidepressant effects of zuranolone

Drinkuth C. MSLS Pipeline Blog. 2024

Glimpse into the Future

Psychedelics!
Psychedelics!
Psychedelics!

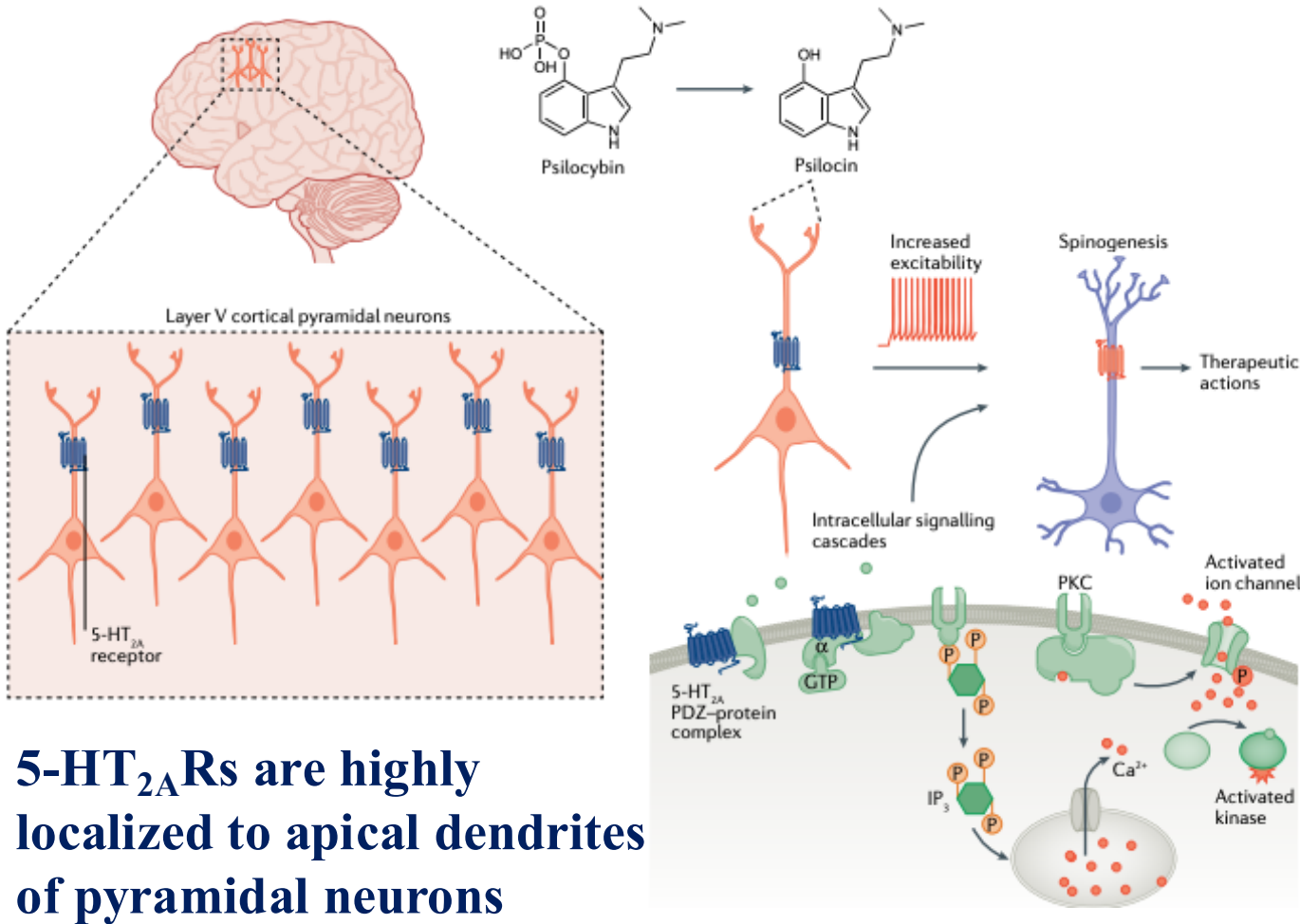


Emerging Psychedelics

Drug	What is it?	Main pharmacology	Route
COMP360	Proprietary synthetic psilocybin	5-HT _{2A} agonism via active psilocin	Oral
DT120 (<i>formerly</i> MM120)	Pharmaceutical LSD/lysergide D-tartrate	5-HT _{2A} partial agonist; broader serotonergic pharmacology	Oral dissolving tablet
BPL-003	Mebufotenin (5-MeO-DMT) benzoate	Predominantly serotonergic 5-HT _{2A} /5-HT _{1A} agonism	Intranasal
GH001	Mebufotenin (5-MeO-DMT)	5-HT _{2A} /5-HT _{1A} agonism	Inhaled
HLP003 (<i>formerly</i> CYB003)	Deuterated psilocin/psilocybin-related serotonergic agonist	Designed primarily around 5-HT _{2A} agonism	Oral
Bretisilocin (GM- 2505; now ABBV- 2505)	Novel short-acting tryptamine psychedelic	5-HT _{2A} agonist + serotonin releaser	IV in clinical development

*McClure-Begley & Roth. Nat Rev Drug
Discov 2022; 21:463–473*
*Sharp & Ippolito Br J Pharmacol. 2026;
doi:10.1111/bph.70050*

Mechanism of action of Psychedelics



- * Stimulation of cortical 5-HT_{2A}Rs is the common pharmacological signature of classic psychedelics
- * LSD activate 5-HT_{2A}Rs directly. Psilocybin is first metabolized to psilocin
- * Activation of 5-HT_{2A}Rs receptor increases neuronal firing and activation of a large number of intracellular signaling cascades
- * This leads to enhancement of synaptic plasticity and spine formation and, ultimately, a potential therapeutic effect

*McClure-Begley & Roth. Nat Rev Drug Discov
2022; 21:463–473*

Clinical Trials with Emerging Psychedelics

Agent	Active compound	Depression indication	Key trial/program	Phase / key design
COMP360	Synthetic psilocybin	TRD	COMP005 / COMP006	Phase 3
DT120	LSD (lysergide tartrate)	MDD	Emerge / Ascend	Phase 3
BPL-003	Intranasal 5-MeO-DMT (mebufotenin) benzoate	TRD	ReConnection-1 / -2	Phase 3
GH001	Inhaled 5-MeO-DMT (mebufotenin)	TRD	GH001-TRD-201 → pivotal program	Phase 2b → Phase 3
HLP003 (CYB003)	Deuterated psilocin analog	Adjunctive MDD	PARADIGM: APPROACH / EMBRACE	Phase 3
Bretisilocin	Short-acting 5-HT _{2A} agonist + 5-HT releaser	MDD	Phase 2 program	Phase 2

Goodwin et al. N Engl J Med 2022;387:1637; Cubala et al. JAMA Psychiatry 2026;83:561

Other Emerging Antidepressants

Drug	Mechanism of Action	Depression Indication	Phase / Key Design
Seltorexant	Selective OX2R antagonist → ↓ hyperarousal, improves sleep	MDD with insomnia; adjunctive	Phase 3; added to SSRI/SNRI
ABX-002 (elunetirom)	CNS-directed thyroid receptor agonist → ↑ neuronal bioenergetics & plasticity	MDD with inadequate response; adjunctive	Phase 2 (AMPLIFY)
ALTO-207	D3/D2 agonist (pramipexole) + 5-HT3 antagonist (ondansetron) → enhances reward/dopamine signaling	TRD; adjunctive	Phase 2b; ~178 patients, 8 weeks
Osavampator	AMPA receptor PAM → ↑ glutamate signaling & synaptic plasticity	MDD with inadequate response; adjunctive	Phase 3

ClinicalTrials.gov NCT06559306 (seltorexant); Autobahn Therapeutics, AMPLIFY (ABX-002); Alto Neuroscience, ALTO-207 Phase 2b (2026); SAVITRI Phase 2 / Neurocrine Biosciences (osavampator)

Thank you!