NEUROTRANSMITTERS

INHIBITORY
induce IPSPs hyperpolarize

Glycine, GABA: ↑Cl^- entry into cell

GABA-A (>20) Cl channels ↑
↳ hyperpolarizes the post-synaptic neuron, inhibiting it from firing

EPSPs + IPSPs > threshold → AP

"STIMULATORY"
induce EPSPs depolarize ↑Na entry into cell

NE
α1AR
α2AR

↳ **Stress response and emotions**
↳ link the Locus Coeruleus w/ the cortex and thalamus
α1 = post
α2 = pre
(if post then like α1)

serotonin
5-HT1
5-HT2,3,4
5-HT5
5-HT6,7

→ **fear/anxiety and emotional processing**
↳ link the Raphe nuclei with the hippocampus and amygdala

Dopamine
D1-like 1,5
D2-like 2,3,4

→ **Addiction/depression and movement disorders**

Mesolimbic pathway: ventral tegmental → nucleus accumbens
involved in reward, motivation
↑ addiction
↓ depression, anhedonia

Nigrostriatal pathway: substantia nigra → striatum
involved in motor control
↑ huntington's
↓ parkinsons

Mesocortical Pathway ventral tegmental → prefrontal cortex
↑ hallucinations, delusions

Histamine
H1 endothelium, nasal mucosa, brain, SM
H2 brain, gastric mucosa, heart, mast cells (allergens)
H3 brain
H4 eosinophils, T-cells, neutrophils

→ **arousal and allergies**
link hypothalamus w/ thalamus and neocortex

AcH
mAChR 1-5
mAChR 2,4
nAChR 1-4

Glutamate
Kainate
AMPA
mGluR1,5
mGluR2-8
NMDA → LTP (learning/memory)

→ **primary excitatory NT**

Inhibit signaling pathway
↳ autoreceptors on presynaptic neuron that inhibit NT release

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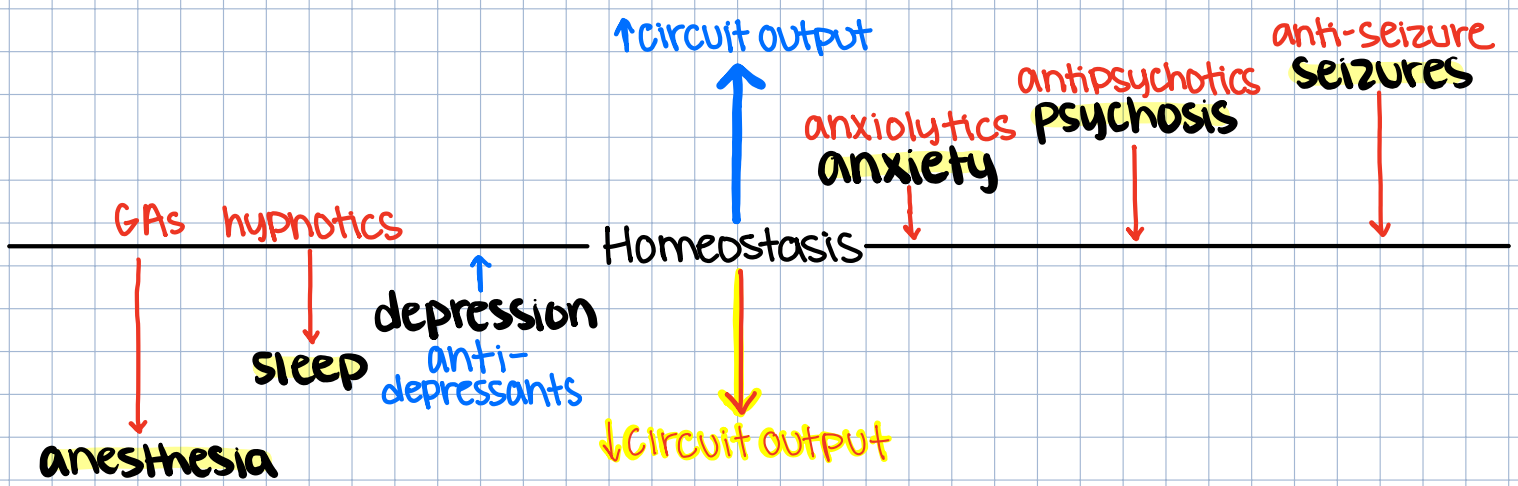
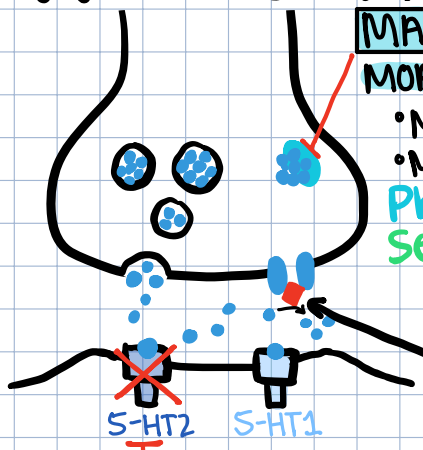
Many psychotherapeutic drugs produce their effects by INCREASING or DECREASING the rate of neuronal circuit input.



ANTI-DEPRESSANTS and ANXIOLYTICS



MAO inhibitors irreversible antagonists of MAO
MOA: inhibit monoamine NT degradation in pre-synaptic neuron
- MAO-A affects ALL monoamines. Present in GIT for tyrosine degradation
- MAO-B only affects dopamine

Phenelzine (A+B) food containing tyrosine → hypertensive crisis
Selegiline (B selective) low dose may avoid food-induced toxicities

SNRIs inhibition of serotonin/NE reuptake
Desvenlafaxine
Duloxetine CYP inhibition
Toxicities: sexual dysfunction

Tricyclics SNRI AND H1, α1, M1-M5 antagonists
Amitriptyline
- sedation
- anticholinergic
- orthostatic hypotension

Serotonin Modulators ATYPICALS

Trazodone 5-HT2/α1 antagonist
Toxicities: somnolence

Mirtazapine 5-HT2/α2 antagonist
↑signaling by ↑NE release
Toxicities: sedation (H1), weight gain

DNRI inhibition of dopamine reuptake
Bupropion
Toxicities: ↑risk of seizures but NO sexual dysfunction

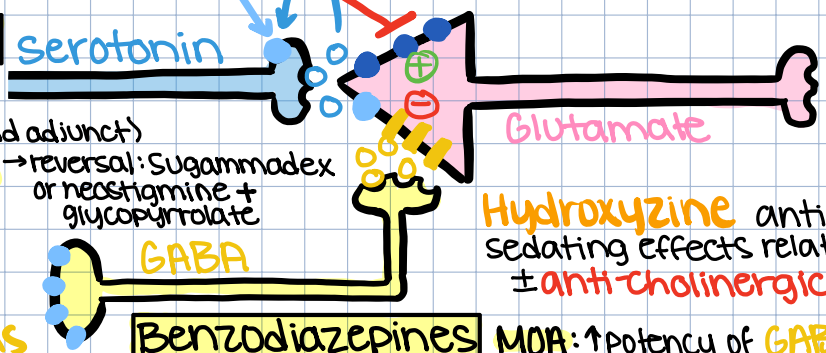
SSRIs inhibition of serotonin reuptake and ↑signaling
PK: long half lives → long time to achieve full effect
↑BDNF expression needed to ↑hippocampus size
Citalopram (35h) prolonged QT → Torsades
Escitalopram (30h)
Fluoxetine (72h)
Sertraline (26h) diarrhea
Paroxetine (20h) pregnancy X
- drug interactions

Toxicities: sexual dysfunction

Buspirone
MOA: Partial agonist of inhibitory 5-HT1 autoreceptor

Depression

Anxiety



General Anesthetics
unconsciousness/amnesia
- contribute to immobility
- may help w/ ANS control (opioid adjunct)

TIVA = GA + opioid + NMBA → reversal: Sugammadex or neostigmine + glycopyrrolate
↳ intraoperative awareness

MOA: $GABA_AR$ positive modulator. ↑Cl^- entry into cell

↑Potency/↓hydrophobicity
- Inhaled: nitrous gas
- Volatile liquids:
  - desflurane airway irritant
  - sevoflurane
  - isoflurane Potent coronary vasodilator

Toxicities: PONV, malignant hyperthermia (dantrolene)

Intravenous:
Etomidate ↓RR
Propofol ↓↓BP and ↓↓RR
↳ anti-emetic effects
Ketamine ↑BP
MOA: glutamate antagonist
Toxicities: emergence reaction dissociative effects → psychosis

Hydroxyzine anti-histamine (H1) w/ sedating effects related to anxiolytic effect
± anti-cholinergic toxicities

Benzodiazepines MOA: ↑potency of GABA at receptors → ↑Cl^- entry into cell → hyperpolarization → ↓rate of fire → anxiolysis
Toxicities: psychomotor impairment, phys/psych dependence
Other uses: insomnia, alcohol withdrawal, anesthesia, seizures

Short Alprazolam, Midazolam, Triazolam
Mod Clonazepam, Lorazepam, Oxazepam, Temazepam
Long Diazepam, Chlordiazepoxide
↳ metabolites

Reversal: FLUMAZENIL
α2-5 receptors mediate anxiolysis for acute anxiety

"Z" drugs
MOA: $GABA_AR$ ⊕ modulators of α1 subunit
- sedation

Hypnotics
- Zaleplon
- Zolpidem
- Eszopiclone
- Ramelteon

MOA: melatonin receptor agonist

ANTI-PSYCHOTICS antagonize multiple receptors in CNS/PNS

Therapeutic Effects:

D2 dopamine antagonism – inhibition of **mesocortical pathway** responsible for positive sx (hallucinations, delusions). D2 receptor **affinity** correlates w/ **effectiveness**

- therapeutic response achieved w/ **60% receptor occupancy**

5-HT2 serotonin antagonism – inhibition of signaling is **prefrontal cortex** → ↑signaling
Contributes to hallucinations and delusions

- anti-hallucinogenic

Toxicities:

Dopamine – extrapyramidal sx, hormonal changes, neuroleptic malignant syndrome

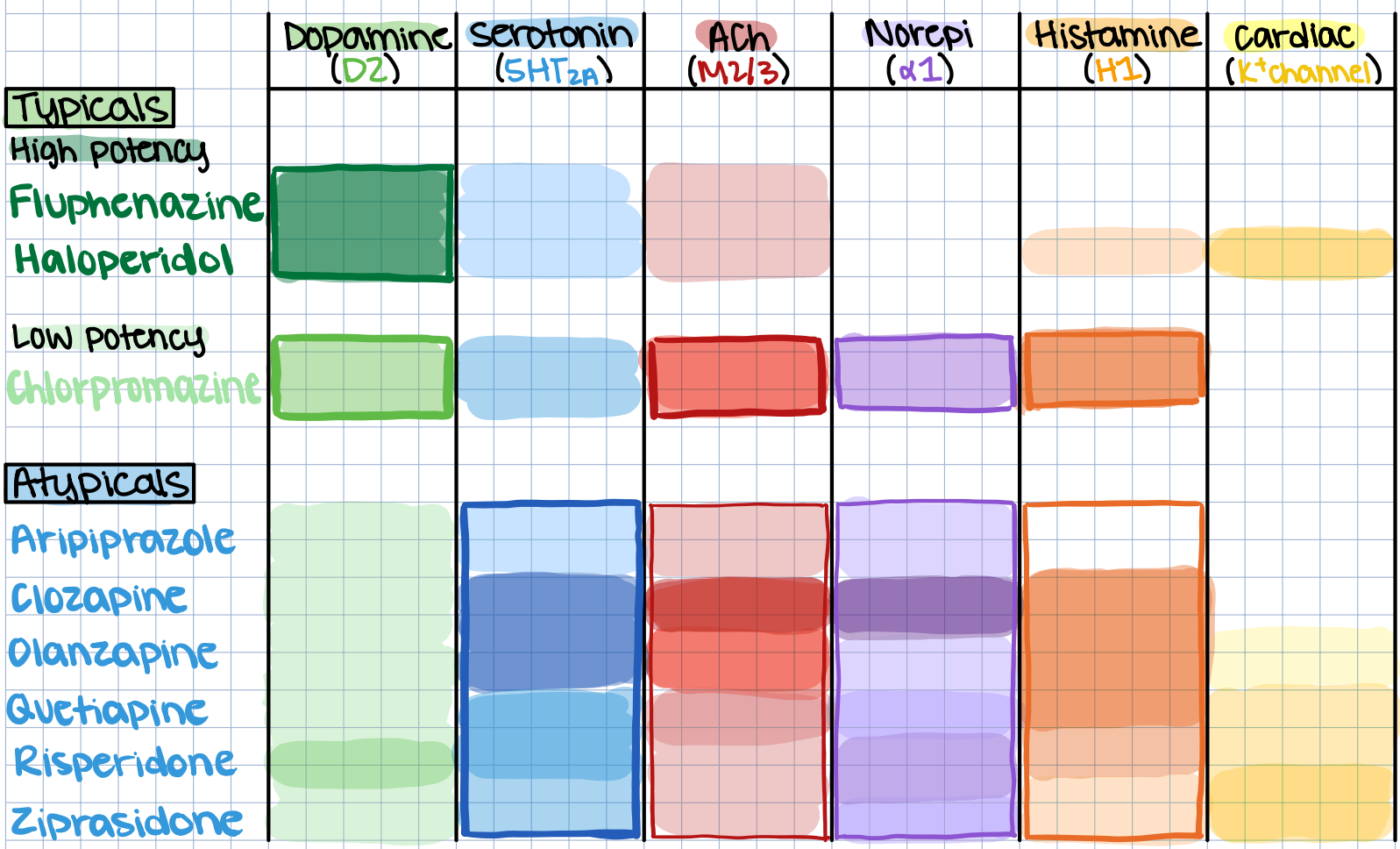
Serotonin – metabolic syndrome (↓HDL, ↑TG, HTN, visceral obesity, insulin resistance)

Acetylcholine – anti-cholinergic/parasympathetic (constipation, blurry vision, etc)

Norepinephrine – orthostatic hypotension

Histamine – sedation (due to inhibition in brain)

Cardiac (K^+ channels) – prolonged QT, sudden death



Clozapine specific → agranulocytosis/neutropenia (potentially fatal)

ANTI-EPILEPTICS

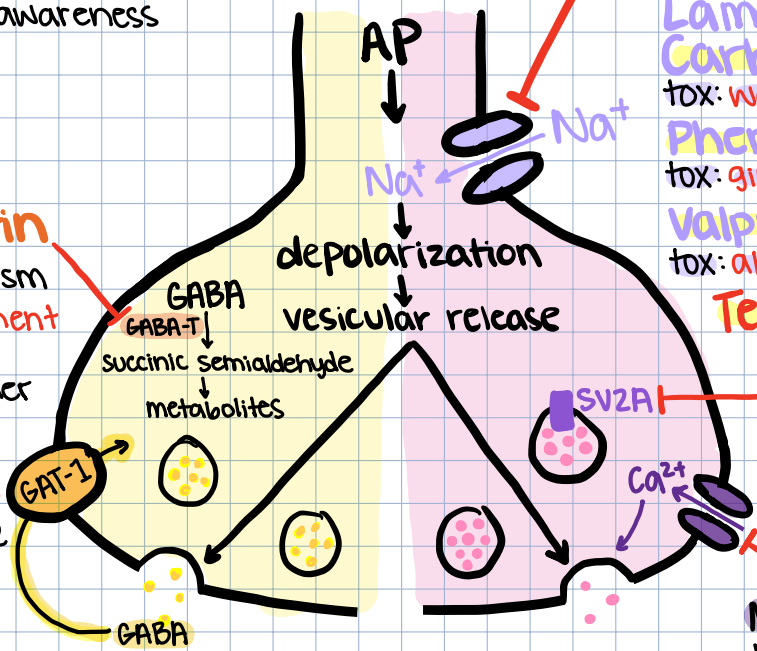
Normal: ordered, nonsynchronous firing

Seizure: disordered, synchronus, and rhythmic firing of populations of brain neurons

Epilepsy: periodic, unpredictable occurrence of seizures

- **PARTIAL** (↓aura)
  - simple → conscious
  - complex → loss of consciousness
- **GENERALIZED:**
  - **Tonic-Clonic:** stiffening, then spasming of limbs/face
    - **Tonic:** ↑muscle tone
    - **Atonic:** abrupt loss of muscle tone
    - **Myoclonic:** rapid, brief muscle contractions
  - **Absence:** lapses in awareness

Mutations in neuron ion channels can promote aberrant depolarization, and initiate seizures



VG Na^+ channel blockers

MOA: Slow the reset of Na^+ channels to resting state to stop AP propagation

- **Lamotrigine**
- **Carbamazepine** → CYP inducer
  - tox: water retention, hyponatremia
- **Phenytoin** → CYP inducer.
  - tox: gingival hyperplasia. zero-order kinetics
- **Valproate** → CYP inhibitor
  - tox: alopecia, weight gain

Teratogenicity

Vigabatrin

MOA: inhibits metabolism

tox: progressive, permanent bilateral vision loss

- used only if failed other therapies

Tiagaban

MOA: inhibits reuptake

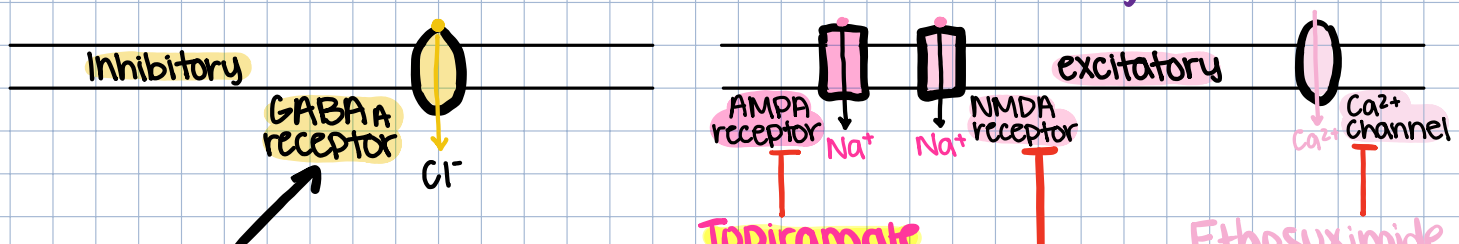
Levetiracetum

MOA: inhibits glutamine release by blocking a vesicle fusion protein

VG Ca^{2+} channel blockers

MOA: ↓Ca^{2+} influx and NT release from presynaptic neuron

- **Gabapentin**
- **Pregablin**



GABA-R positive Modulators

MOA: ↑Cl^- influx and post-synaptic hyperpolarization

- **Benzodiazepines**
  - Clonazepam
  - Diazepam (status epilepticus)
- **Barbituates**
  - Phenobarbital

Topiramate

tox: weight loss, renal calculi (stones)

Felbamate

tox: aplastic anemia, acute liver failure

Ethosuximide

MOA: Slow Ca^{2+}-induced depolarization

- Indicated for absence seizures

Common toxicities

- **Neurologic** - sedation, dizzy, fatigue, ataxia, visual disturbance
- **GI** - nausea / vomiting

NEURODEGENERATIVE PHARMACOLOGY

Dopaminergic nigrostriatal pathway helps to modulate coordination of muscle movement

MOVEMENT SYMPTOMS

HUNTINGTONS

Characterized by ↑dopamine

Dopamine-depleting

Tetrabenazine

MOA: ↓dopamine levels in SN neurons by inhibiting transport of dopamine into presynaptic vesicles

Target: vMAT transporter

Dopamine Antagonist

Aripiprazole

MOA: competes w/ dopamine for binding at receptor

Tox: same as antipsychotic

PARKINSONS

Loss of dopaminergic neurons in SN

Dopamine Precursor

Levodopa

MOA: restores dopamine signaling

can be used in conjunction with:

- **DOC inhibitor**: **Carbidopa**
- **COMT inhibitor**: **Entacapone**, **Tolcapone**

MOA: block the peripheral metabolism of Levodopa, increasing the fraction that reaches the CNS

tox: "wearing off" phenomenon causes dyskinesia as primary tox

interactions: MAOIs

Dopamine agonists

Pramipexol

Ropinirole

MOA: directly substitute for dopamine to restore normal motor control

tox: Suppression of prolactin secretion due to ↑DA in tuberoinfundibular pathway.

Sleep attacks, sedation, somnolence. OCD/ICD

Short term tox:
- N/V
- orthostatic hypotension
- psychosis

MAOB inhibitors

Rasagiline

MOA: block breakdown of dopamine in neurons and increase its release

Dopamine Release Stimulator

Amantadine

MOA: unknown

tox: dizziness, insomnia

Anti-cholinergics

competitive antagonists of ACh

Benztropine

Trihexiphenidyl

MOA: reestablish balance between ACh and DA signaling in striatum

tox: anti-cholinergic → xerostomia, tachy, constipation, urinary retention

- avoid in older patients

COGNITIVE SYMPTOMS

DEMENTIA w LEWY BODIES

Cognitive and neuropsych sx treated with:

Cholinesterase Inhibitors

Donepezil

Galantamine

Rivastigmine

tox: parasympathetic cardiac effects
- various arrythmias

insomnia, vivid dreams, bradycardia, syncope

ALZHEIMERS

60% of dementia cases

Glutamate Antagonist

Memantine

MOA: inhibits neuronal death caused by extra-synaptic glutamate receptors
- amyloid-beta protein blocks glutamate reuptake → excess spills over causing chronic hyperstimulation

OPIOID ANALGESICS

PAIN involves 4 steps:

① **Transduction** → ② **Transmission** → ③ **Perception** → ④ **Modulation**

① Noxious stimulus converted into nerve impulses at pain receptors

② Impulse transmitted to the CNS

③ Pain perceived in the brain

④ descending pathway modulates pain perception

OPIOIDS act on ② and ④

Ascending Pathway: transmit pain signal to brain
Descending Pathway: modulate/inhibit the signal

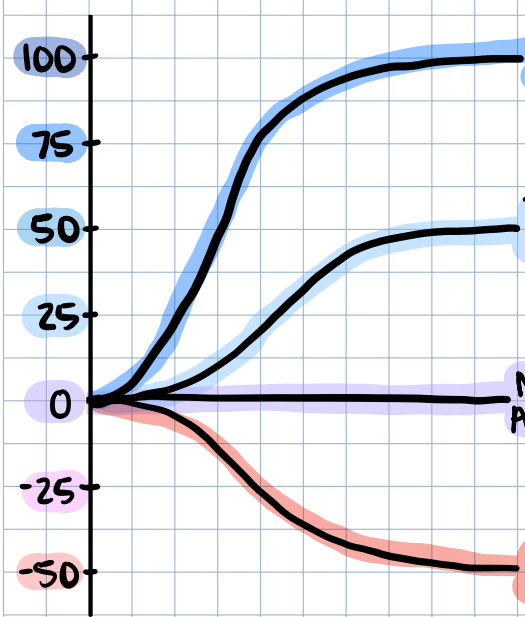
ENDOGENOUS AGENTS

- endorphins → μ opioid receptor
- enkephalins → δ opioid receptor
- dynorphins → κ opioid receptor

found in **CNS** and **peripheral tissues** → GIT

- CNS → brain/spinal cord → **ANALGESIA** (sedation, respiratory distress)
- peripheral tissues → nociceptor neurons → **ANALGESIA**
- GIT → myenteric and submucosal plexus → GI toxicities (constipation)

EXOGENOUS AGENTS



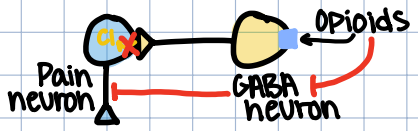
Phenanthrenes	Phenylheptylines	Phenylpiperidines
Morphine, Hydrocodone, Oxycodone, Heroin	Methadone	Fentanyl
Buprenorphine, Nalbuphine	safe for renal impairment	

Full Agonist: Morphine, Hydrocodone, Oxycodone, Heroin
Partial Agonist: Buprenorphine, Nalbuphine
Neutral Antagonist: Methylnaltrexone
- used for OIC

Inverse agonist: Naltrexone, Naloxone
↳ acute overdose

MOA: inhibit ascending
- Inhibit presynaptic Ca^{2+} channels
- Stimulate postsynaptic K^+ efflux

Stimulate descending - bind MOR receptors on GABA neurons and inhibit release of inhibitory GABA at descending pain neurons



PK
- **absorption**: oral well-absorbed but subject to first pass effect
- **distribution**: high volume of distribution from plasma to other tissues
- **metabolism**: converted to polar metabolites cleared primarily by Kidneys
  - some are metabolized into more potent drugs
  - some metabolites have secondary effects (neurotoxic, anti-convulsant)
- **clearance**: renal impairment can ↓clearance of metabolites

Tox:
- **ACUTE** - respiratory distress, sedation, constipation (treat w/ methylnaltrexone)
- **CHRONIC** - withdrawal, tolerance, dependence, hyperalgesia
  - physiologic dependence → produce euphoria by ↑DA in mesolimbic pathway

Treatment of addiction
- Methadone prevents physical withdrawal but clears slowly, easing detox
- Buprenorphine + naloxone = **Suboxone**