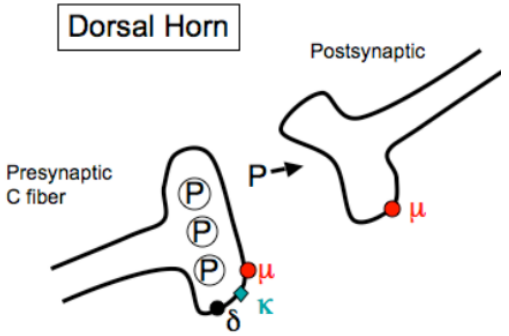
# ENDOGENOUS OPIODS & OPIATE DRUGS

| | Mu (μ) | Delta (δ) | Kappa (κ) |
|---|---|---|---|
| | • Mu 1 – Analgesia<br>• Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence | • Analgesia, spinal analgesia | • Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea |
| **Endogenous Peptides** | | | |
| Enkephalins | Agonist | Agonist | |
| β-Endorphin | Agonist | Agonist | |
| Dynorphin A | Agonist | | Agonist |
| **Agonists** | | | |
| Morphine | Agonist | | Weak agonist |
| Codeine | Weak agonist | Weak agonist | |
| Fentanyl | Agonist | | |
| Meperidine | Agonist | Agonist | |
| Methadone | Agonist | | |
| **Antagonists** | | | |
| Naloxone | Antagonist | Weak Antagonist | Antagonist |
| Naltrexone | Antagonist | Weak Antagonist | Antagonist |




Stimulation presynaptically = ↓$Ca^{2+}$
Stimulation postsynaptically = ↑$K^{+}$

**Opioid analgesics** — Morphine, fentanyl, codeine, loperamide, methadone, meperidine, dextromethorphan, diphenoxylate, pentazocine.

**MECHANISM** — Act as agonists at opioid receptors (μ = morphine, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission—open $K^{+}$ channels, close $Ca^{2+}$ channels → ↓ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.

**CLINICAL USE** — Pain, cough suppression (dextromethorphan), diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).

**TOXICITY** — Addiction, respiratory depression, constipation, miosis (pinpoint pupils), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltrexone (opioid receptor antagonist).

**Green** = Kaplan, Deja. First Aid, or Tulane

# OPIATES

Metabolized by the liver & excreted via kidneys – ***use with caution in hepatic or renal failure patients***

**WITHDRAWAL SIGNS:** Pain & irritability, hyperventilation, dysphoria & depression

| DRUG | INDICATIONS | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|---|
| **MORPHINE**<br>Prototypical narcotic analgesic | **Severe pain** | Long duration of action<br>Active metabolite: **morphine-6-glucuronide**<br>Metabolism: glucuronidation | **TOXICITY TRIAD: COMA, RESPIRATORY DEPRESSION (CYANOSIS), MIOSIS**<br>***RESPIRATORY DEPRESSION is the main cause of death in OD!!!!!***<br>***ACUTE TOXICITY TREATMENT: NALOXONE + RESPIRATORY SUPPORT***<br>**Depression of cough reflex & respiratory drive – DO NOT GIVE PATIENTS $O_2$**<br>**ADDICTION**<br>Postural HTN + fainting when standing<br>Urinary retention<br>**Constipation –** *weak opiates can be used to treat diarrhea!*<br>Nausea & vomiting<br>**Bronchoconstriction** – ***Contraindicated in pts w/ impaired lung function***<br>Flushing of skin, itching, urticarial<br>**Can ↑ ICP** – ***Contraindicated in patients with head injuries***<br>***Contraindicated in pregnancy*** *– except Meperidine is used in labor!* |
| CODEINE | Antitussive<br>*Often combined w/ aspirin* | **Demethylated to morphine**<br>****HIGH ABUSE LIABILITY**** | |
| Heroin | Limited clinical use, except in terminally ill patients (abuse) | High lipid solubility | |
| **METHADONE** | **Treating opiate dependence** | Similar to morphine; ↑oral efficacy<br>**BLACK BOX: respiratory distress & QT prolongation/Torsades de Pointes** | |
| **MEPERIDINE (DEMEROL)** | **Acute, severe pain**<br>**Labor** – *no respiratory distress in neonate* | Short duration of action<br>Active metabolite: normeperidine<br>***Mydriasis, tachycardia, seizures***<br>***Contraindicated in MAOI or SSRI*** | |
| **FENTANYL** | **Anesthesia**<br>**Severe, chronic pain** | **High potency**<br>No histamine release! | |

# MIXED DRUGS: Agonist-Antagonist or Partial Agonist

| | | | |
|---|---|---|---|
| BUTORPHANOL | | **Psychotomimetic effect (K – Kappa Krazy)** | Reduced abuse liability & certain side effects (↓respiratory depression) |
| PENTAZOCINE | Partial mu agonist, K agonist | Psychotomimetic effects (K)<br>*Not recommended in acute MI* (↑BP) | |
| **BUPRENORPHINE** | Potent analgesic | Some abuse liability<br>***Naloxone may not work in OD*** | |

# SPECIAL PURPOSE OPIOIDS

| | | | |
|---|---|---|---|
| **LOPERAMIDE**<br>(Imodium) | **Anti-diarrheal** | Very little crosses BBB – *minimal analgesia or abuse potential* | |
| **DEXTROMETHORPHAN** | **Anti-tussive** | No analgesia or respiratory depression<br>Little abuse potential | *Produces less constipation than codeine!*** |

# OPIATE ANTAGONISTS: Competitive blockade of Mu receptor; "silent antagonists"

| | | | |
|---|---|---|---|
| **NALOXONE** | **Acute opiate OD** (IV) | Short duration of action | |
| **NALTREXONE** | **Maintenance drug for addicts in treatment programs** | Undergoes 1st pass metabolism<br>Long acting & ↑oral bioavailability | |
| **NALMEFENE** | **Acute opiate OD** | Longer half life than Naloxone | |

**Green** = Kaplan, Deja. First Aid, or Tulane

# GENERAL ANESTHETICS

| | |
|---|---|
| **Inhaled anesthetics** | Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, $N_2O$. |
| MECHANISM | Mechanism unknown. |
| EFFECTS | Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand). |
| TOXICITY | Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), expansion of trapped gas in a body cavity ($N_2O$). Can cause malignant hyperthermia—rare, life-threatening hereditary condition in which inhaled anesthetics (except $N_2O$) and succinylcholine induce fever and severe muscle contractions. Treatment: dantrolene. |

| | |
|---|---|
| **Intravenous anesthetics** | |
| **Barbiturates** | Thiopental—high potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by rapid redistribution into tissue (i.e., skeletal muscle) and fat. ↓ cerebral blood flow. |
| **Benzodiazepines** | Midazolam most common drug used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat overdose with flumazenil), anterograde amnesia. |
| **Arylcyclohexylamines (Ketamine)** | PCP analogs that act as dissociative anesthetics. Block NMDA receptors. Cardiovascular stimulants. Cause disorientation, hallucination, bad dreams. ↑ cerebral blood flow. |
| **Opioids** | Morphine, fentanyl used with other CNS depressants during general anesthesia. |
| **Propofol** | Used for sedation in ICU, rapid anesthesia induction, short procedures. Less postoperative nausea than thiopental. Potentiates $GABA_A$. |

B. B. King on OPIOIDS PROPOses FOOLishly.

**Anesthetics—general principles**

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.
Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$

MAC = Minimal Alveolar Concentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (e.g., skin incision).
Examples: nitrous oxide ($N_2O$) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.

## GENERAL ANESTHESIA: *analgesia, amnesia, muscle relaxation*

↓ Surgical stress – *evokes HPA axis & sympathetic system*
**↓BP, ↓baroreceptor control, & ↓central sympathetic tone**
**MECHANISM OF ACTION:** increase threshold for firing to ↓neuronal activity
**3 STAGES:**

1. **INDUCTION**: Blood→Brain; **IV**
2. **MAINTENANCE**: Lungs→Blood→Brain; **Inhalation**
3. **RECOVERY**: time from discontinuing drug to consciousness & regaining reflexes

**Pre-anesthetic Medications:**

1. Relieve anxiety – **benzodiazepine (MIDAZOLAM)**
2. Prevent allergic reactions – **anti-histamines**
3. Prevent nausea & vomiting – **antiemetics**
4. Provide analgesia – **opioids (FENTANYL)**
5. Prevent bradycardia & secretions – **atropine**, **glycopyrrolate**

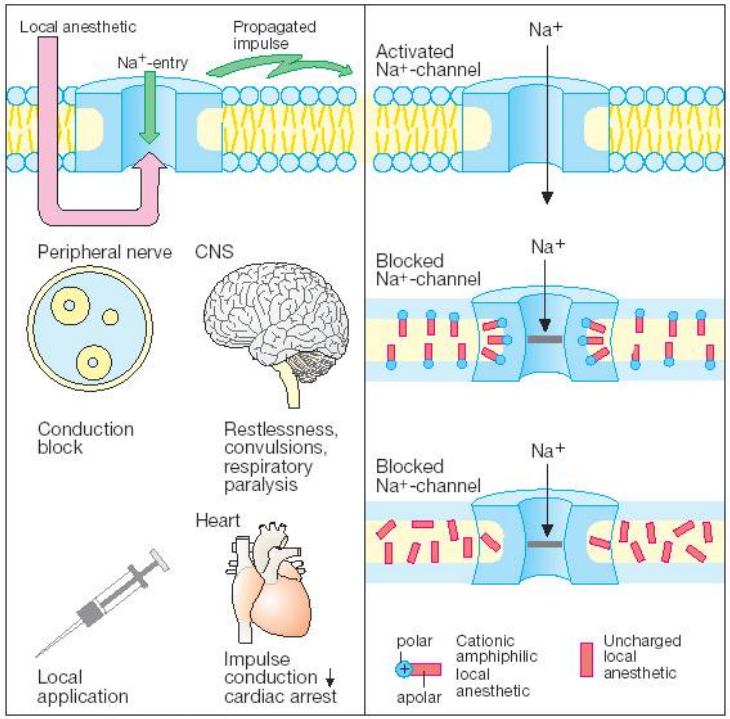
Other adjuncts: **Neuromuscular blockers (PANCURONIUM, SUCCINYLCHOLINE)** to relax jaw/neck/airway muscles for laryngoscopy & intubation

| DRUG | INDICATION | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|---|
| **INTRAVENOUS DRUGS:** *Rapid induction; high lipophilicity; recovery mainly by* ***redistribution*** | | | |
| **THIOPENTAL** | **CAN be used in HEAD INJURY!** | Ultra-short acting **Barbiturate**<br>**LOC in ~20sec; lasts 10-20min** | ***Contraindicated in acute intermittent porphyria*** |
| METHOHEXITAL | | ↑potent than Thiopental; quicker & shorter acting | |
| **PROPOFOL** | **DOC FOR ANESTHESIA INDUCTION+SEDATION**<br>Sedation in ICU<br>**Anti-emetic!** | IV sedative-hypnotic agent<br>Produces **euphoric** feeling | Bradycardia, hiccups<br>**PROPOFOL INFUSION SYNDROME:** rare, but can be fatal; prolonged→ ***acidosis + rhabdomyolysis*** |
| **ETOMIDATE** | **Patients with CAD or CV dysfunction** | **LACKS ANALGESIC EFFECT<br>Quicker than Thiopental | ***VERY LITTLE CV & RESPIRATORY DEPRESSION<br>Rapid injection – s**uppresses steroidogenesis** |
| **KETAMINE** | ****CHILDREN****<br>**ASTHMATICS** – *respiration not depressed*<br>Burn dressing or trauma surgery | Short acting, NON-barb; **blocks NMDA receptors**<br>**DISSOCIATIVE** anesthesia<br>**↑HR, CO, & BP** – ***contraindicated in IHD or HTN*** | **Adults: HALLUCINATIONS, VIVID DREAMS, ↑ICP** |
| DEXMEDETOMIDINE | Short term sedation in **non-intubated** patients | α2 agonist | |
| **INHALATION DRUGS:** *Maintenance*<br>**BLOOD:GAS PARTITION COEFFICIENT:** determines the rate of induction & recovery of inhalation anesthetics; **LOW coefficient=FAST induction & recovery (NITROUS OXIDE)**<br>**OIL:GAS PARTITION COEFFICIENT:** measures lipid solubility; **↑lipid solubility = ↑potency = ↓MAC**<br>**MINIMUM ALVEOLAR CONCENTRATION (MAC):** measure of **POTENCY; LOW MAC=HIGH POTENCY;** MAC values are additive & lower in the elderly | | | |
| **NITROUS OXIDE**<br>*Non-halogenated gas* | Component of balanced anesthesia for surgery<br>Used as a **CARRIER** or **ADJUVANT (SECOND GAS EFFECT)** | Safest inhalation anesthetic<br>**↓BLOOD:GAS & ↑MAC** | Pneumothorax<br>**MEGALOBLASTIC ANEMIA (Vitamin B12 def)**<br>**DIFFUSION HYPOXIA:** treat w/ 100% $O_2$ |
| **HALOTHANE** | **CHILDREN**<br>**Preferred in ASTHMATICS** (dilates bronchus) | Potent anesthetic (↓MAC), weak analgesic | Vagomimetic: bradycardia<br>**SENSITIZES HEART TO EPI – ARRYTHMIAS**<br>**HEPATITIS**<br>**MALIGNANT HYPERTHERMIA – Tx: DANTROLENE** |
| ENFLURANE | | Greater potentiation of muscle relaxants | Doesn't cause arrhythmias!<br>Seizures – ***contraindicated in epileptics***<br>**PUNGENT SMELL – breath holding** |
| **ISOFLURANE** | **BENEFICIAL IN PATIENTS WITH IHD (MI)** – *dilates coronary vasculature, ↑blood flow, ↑$O_2$ supply to heart*<br>Preferred in Neurosurgery – *doesn't provoke seizures* | | No seizures or arrythmogenicity<br>Absence of liver & kidney toxicity |
| **DESFLURANE** | **OUTPATIENT surgical procedures** | | Same as Isoflurane^<br>**PUNGENT** |
| **SEVOFLURANE** | **CHILDREN** – *absence of pungency & airway irritancy*<br>**ASTHMATICS** – *bronchodilation* | | Nephrotoxicity – *unstable compound* |

**Green** = Kaplan, Deja. First Aid, or Tulane

# LOCAL ANESTHETICS

| | |
|---|---|
| **Local anesthetics** | Esters—procaine, cocaine, tetracaine.<br>Amides—lIdocaIne, mepIvacaIne, bupIvacaIne (amIdes have 2 I's in name). |
| MECHANISM | Block $Na^+$ channels by binding to specific receptors on inner portion of channel. Preferentially bind to activated $Na^+$ channels, so most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form. |
| PRINCIPLE | Can be given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration.<br>In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic.<br>Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers.<br>Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure. |
| CLINICAL USE | Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides. |
| TOXICITY | CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine). |




**A. Effects of local anesthetics**

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**LOCAL ANESTHESIA:** *reversible loss of sensory perception (pain)*

**MOA:** Blocks generation & conduction of impulse by blocking recently inactivated **$Na^+$ channel**

*Smaller nerve fibers & myelinated nerve fibers are more sensitive than larger or unmyelinated fibers

**ADDITION OF VASOCONSTRICTOR (EPINEPHRINE) prolongs DOA & ↓systemic toxicity

NOTE: EPI is contraindicated in tx body extremities, i.e. finger before suturing

**LONG-ACTING:** *Bupivacaine, Etidocaine, Ropivacaine, Tetracaine*

**INTERMEDIATE:** *Lidocaine, Mepivacaine, Prilocaine, Cocaine*

**SHORT-ACTING:** *Procaine, Chloropracine*

***Most serious toxic reaction: Convulsions**

| DRUG | INDICATION | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|---|
| **ESTER-LINKED:** *Short duration of action, less intense analgesia, increased risk of hypersensitivity; only 1 i* | | | |
| COCAINE | **Topical**<br>**OCULAR & TRACHEOBRONCHIAL ANESTHESIA (ENT)** | *Only local anesthetic that causes *vasoconstriction* | |
| PROCAINE | *Not popular anymore* | Low potency, slow onset, short DOA | |
| **TETRACAINE** | **TOPICAL USE**<br>**Spinal anesthesia (+ EPI)** | Better than Procaine | |
| BENZOCAINE | Topical use only | | |
| **AMIDE:** *Longer duration of action, intense analgesia, decreased risk of hypersensitivity; two i's* | | | |
| LIDOCAINE | **Infiltration, Spinal, Epidural, & Topical Anesthesia**<br>**REGIONAL NERVE BLOCK**<br>**Anti-arrhythmic agent** | Rapid onset<br>More intense & **longer DOA** than Procaine | Drowsiness, **TINNITUS**, dizziness, twitching, dysgeusia **(distorted sense of taste)** |
| BUPIVACAINE | **PROLONGED Anesthesia**<br>**Labor, Post-op period in obstetrics**<br>**Infiltration, Spinal, Epidural Anesthesia** | Potent! | ***CARDIOTOXICITY*** |
| ETIDOCAINE | Regional blocks, epidural anesthesia<br>*Limited role in OB* | | SAME CARDIOTOXICITY AS BUPIVACAINE |
| **MEPIVACAINE** | *Not used in OB – toxic to neonates* | Longer DOA than Lidocaine | |
| **PRILOCAINE** | **Regional block** | Differences from Lidocaine:<br>*Can be used withOUT vasoconstrictor*<br>*Large Vd → low CNS toxicity* | **METHEMOGLOBINEMIA** – *accumulation of metabolite orthotoluidine* |
| **ROPIVACAINE** | **PERIPHERAL BLOCKS!**<br>**Epidurals for labor & post-op obstetrics** | | **LESS CARDIOTOXICITY THAN BUPIVACAINE** |

| Sodium Channel Toxins | |
|---|---|
| Tetradotoxin (puffer fish)<br>Saxitxin (red tide) | Block *activated* $Na^+$ channels in both cardiac & nerve cell membranes → **↓$Na^+$ influx** |
| Ciguatoxin (exotic fish)<br>Batrachotoxin (frogs) | Bind to *activated* $Na^+$ channels & prevent inactivation → prolong $Na^+$ influx |

# SKELETAL MUSCLE RELAXANTS – Neuromuscular Blocking Agents: $N_M$ Receptor Blockers

| | |
|---|---|
| **Neuromuscular blocking drugs** | Muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor. |
| **Depolarizing** | Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.<br>Reversal of blockade:<br>▪ Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.<br>▪ Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—antidote is cholinesterase inhibitors.<br>Complications include hypercalcemia, hyperkalemia, malignant hyperthermia. |
| **Nondepolarizing** | Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium—competitive antagonists—compete with ACh for receptors.<br>Reversal of blockade—neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors. |

| **Dantrolene** | |
|---|---|
| MECHANISM | Prevents release of $Ca^{2+}$ from the sarcoplasmic reticulum of skeletal muscle. |
| CLINICAL USE | Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs). |

| **Baclofen** | |
|---|---|
| MECHANISM | Inhibits $GABA_B$ receptors at spinal cord level, inducing skeletal muscle relaxation. |
| CLINICAL USE | Muscle spasms (e.g., acute low back pain). |

| **Cyclobenzaprine** | |
|---|---|
| MECHANISM | Centrally acting skeletal muscle relaxant. Structurally related to TCAs, similar anticholinergic side effects. |
| CLINICAL USE | Muscle spasms. |

**NICOTINIC BLOCKERS: Peripheral-acting – Block NM transmission**; have no effect on CNS; & used for *short surgical procedures*

- *Highly polar, thus administered IV; do not cross BBB or placenta*

| DRUG | INDICATION | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|---|
| **NON-DEPOLARIZING (COMPETITIVE):** *Curare-derivatives* | | | Tx toxicity w/ **Neostigmine** (↑ACh) |
| **MOA:** block $N_M$ receptors at NMJ by competing with ACh; *causes **flaccid-paralysis*** | | | |
| **DRUG INTERACTIONS:** Cholinesterase inhibitors overcome action; inhaled anesthetics & aminoglycosides & $Ca^+$ channel blockers enhance blockade | | | |
| **TUBOCURARINE** | **-Adjuvant drugs in anesthesia during surgery**<br>**-Facilitate intubation, laryngoscopies, endoscopies**<br>***Minimizes risk of pulmonary aspiration***<br>**-Used to control ventilation** | Long-acting | **↑HISTAMINE – ↓BP, flushing, bronchospasm** |
| **PANCURONIUM** | | Long-acting | Tachycardia → arrhythmias |
| **VECURONIUM** | | Intermediate-acting | |
| ROCURONIUM | | Intermediate-acting | |
| **ATRACURIUM** | | Intermediate-acting<br>*Inactivated in plasma by Hoffman elimination*<br>****SAFE IN HEPATIC OR RENAL PATIENTS**** | Metabolite **Laudanosine → seizures**<br>↑HISTAMINE – ↓BP, flushing, bronchospasm |
| MIVACURIUM | | Short-acting<br>*Metabolized by plasma cholinesterase* | ↑HISTAMINE – ↓BP, flushing, bronchospasm |
| **DEPOLARIZING (NON-COMPETITIVE)** | | | |
| **MOA:** opens $Na^+$ channels initially causing depolarizing block (**Phase 1 – *fasciculations***) following by desensitizing block (**Phase 2 – *flaccid paralysis***) | | | |
| **SUCCINYLCHOLINE (Suxamethonium)** | Used in **emergencies** – *fast acting* | Short DOA:<br>*Rapid metabolism by pseudocholinesterase* | **MALIGNANT HYPERTHERMIA (Tx: Dantrolene)**<br>*-Causes abnormal release of $Ca^{2+}$ from stores*<br>**POST-OP MUSCLE PAIN**<br>**Prolonged Apnea (paralysis of diaphragm)**<br>**Hyperkalemia** – *don't give to pts w/ burns, nerve damage, NM disease, or head injury → cardiac arrest*<br>Bradycardia, ↑Intraocular or intragastric pressure |

**NICOTINIC BLOCKERS: Direct-acting/Central-acting– Inhibit postsynaptic reflex in CNS**; used for *chronic spastic conditions*

| DRUG | INDICATION | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|---|
| **DIRECT** | | | |
| **DANTROLENE** | Hemiplegia, paraplegia, cerebral palsy<br>**DOC IN MALIGNANT HYPERTHERMIA** | Blocks the release of $Ca^{2+}$ from SR of skeletal muscle by binding to **Ryanodine Receptor (RyR)** | |
| **BOTULINUM TOXIN A** (Botox) | **Chronic migraine, Strabismus, Blepharospasm, Cervical dystonia, Anal fissure, Hyperhidrosis** | Toxin A degrades **SNAP-25** blocking vesicle fusion & release of ACh → *flaccid paralysis* | **Respiratory paralysis** |
| **CENTRAL: Spasmolytic Drugs** | | | |
| **MOA:** produce selective action in cerebrospinal axis – *act as skeletal muscle relaxants*; depress spinal & supraspinal polysynaptic reflexes involved in regulation of muscle tone | | | |
| **BACLOFEN**<br>**GABA-B receptor agonist** | Reduce ↑muscle tone associated with nervous system disorders:<br>**CP, MS, spinal cord injury, & stroke** | Hyperpolarization → ↑K efflux & ↓$Ca^{2+}$ influx<br>**Reduces release of excitatory NT & Substance P** | **Sedation**<br>↑Frequency of seizures in epileptic patients |
| TIZANIDINE<br>α2 agonist | | Reduces spasticity by ↑presynaptic inhibition of motor neuron | |

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# TREATMENT OF EPILEPSY

**Epilepsy drugs**

| | PARTIAL (FOCAL) | | GENERALIZED | | | | | |
|---|---|---|---|---|---|---|---|---|
| | SIMPLE | COMPLEX | TONIC-CLONIC | ABSENCE | STATUS EPILEPTICUS | MECHANISM | SIDE EFFECTS | NOTES |
| **Ethosuximide** | | | | * ✓ | | Blocks thalamic T-type $Ca^{2+}$ channels | GI, fatigue, headache, urticaria, Stevens-Johnson syndrome. EFGHIJ—Ethosuximide causes Fatigue, GI distress, Headache, Itching, and Stevens-Johnson syndrome | Sucks to have Silent (absence) Seizures |
| **Benzodiazepines (diazepam, lorazepam)** | | | | | ** ✓ | ↑ $GABA_A$ action | Sedation, tolerance, dependence, respiratory depression | Also for eclampsia seizures (1st line is $MgSO_4$) |
| **Phenytoin** | ✓ | ✓ | * ✓ | | *** ✓ | ↑ $Na^+$ channel inactivation; zero-order kinetics | Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, peripheral neuropathy, megaloblastic anemia, teratogenesis (fetal hydantoin syndrome), SLE-like syndrome, induction of cytochrome P-450, lymphadenopathy, Stevens-Johnson syndrome, osteopenia | Fosphenytoin for parenteral use |
| **Carbamazepine** | * ✓ | * ✓ | * ✓ | | | ↑ $Na^+$ channel inactivation | Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome | 1st line for trigeminal neuralgia |
| **Valproic acid** | ✓ | ✓ | * ✓ | ✓ | | ↑ $Na^+$ channel inactivation, ↑ GABA concentration by inhibiting GABA transaminase | GI, distress, rare but fatal hepatotoxicity (measure LFTs), neural tube defects (e.g., spina bifida), tremor, weight gain, contraindicated in pregnancy | Also used for myoclonic seizures, bipolar disorder |
| **Gabapentin** | ✓ | ✓ | | | | Primarily inhibits high-voltage-activated $Ca^{2+}$ channels; designed as GABA analog | Sedation, ataxia | Also used for peripheral neuropathy, postherpetic neuralgia |
| **Phenobarbital** | ✓ | ✓ | ✓ | | | ↑ $GABA_A$ action | Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression | 1st line in neonates |
| **Topiramate** | ✓ | ✓ | ✓ | | | Blocks $Na^+$ channels, ↑ GABA action | Sedation, mental dulling, kidney stones, weight loss | Also used for migraine prevention |
| **Lamotrigine** | ✓ | ✓ | ✓ | ✓ | | Blocks voltage-gated $Na^+$ channels | Stevens-Johnson syndrome (must be titrated slowly) | |
| **Levetiracetam** | ✓ | ✓ | ✓ | | | Unknown; may modulate GABA and glutamate release | | |
| **Tiagabine** | ✓ | ✓ | | | | ↑ GABA by inhibiting reuptake | | |
| **Vigabatrin** | ✓ | ✓ | | | | ↑ GABA by irreversibly inhibiting GABA transaminase | | |
| **Stevens-Johnson syndrome** | Prodrome of malaise and fever followed by rapid onset of erythematous/purpuric macules (oral, ocular, genital). Skin lesions progress to epidermal necrosis and sloughing. | | | | | | | |

* = 1st line; ** = 1st line for acute; *** = 1st line for prophylaxis.

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## **Epilepsy:** Recurrent seizures

- **Too much neuronal excitation:** Inward $Na^+$ & $Ca^{2+}$ currents *mediated by* ***↑glutamate & aspartate;*** **Too little neuronal excitation:** Inward $Cl^-$ & outward $K^+$ currents; ***not enough GABA activity***
- **TOXICITY:** drowsiness, cognitive impairment, confusion, poor concentration
- ****MOST ANTI-EPILEPTICS ARE METABOLIZED BY CYP450 ENZYMES**

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **VG $Na^+$ CHANNEL BLOCKERS** | | | |
| – Limit the sustained repetitive firing of neurons by promoting **INACTIVATED state of VG-$Na^+$ channels** | | | |
| – **1ST LINE TREATMENT OF TONIC-CLONIC + PARTIAL SEIZURES: PHENYTOIN, CARBAMAZEPINE, VALPROIC ACID** | | | |
| **PHENYTOIN** | Blocks $Na^+$ channel<br>↑GABA inaction: ↓$Ca^{2+}$ influx<br>**ZERO ORDER KINETICS; Narrow TI**<br>**INDUCER OF CYP450** | **Generalized TONIC-CLONIC + PARTIAL Seizures**<br>IV: *Alternative in Status epilepticus* | **GINGIVAL HYPERPLASIA**<br>**HIRSUITISM** (coarse facial features)<br>Nystagmus, **Diplopia & Ataxia,** ↓Vitamin D absorption<br>**TERATOGEN: Fetal Hydantoin Syndrome**<br>***Contraindications: Sinus brady, AV/SA block, Stokes-Adams*** |
| **CARBAMAZEPINE (Tegretol)** | Blocks $Na^+$ channel<br>**INDUCER OF CYP450 (↓levels of Phenytoin)** | **Generalized TONIC-CLONIC + PARTIAL Seizures** | **APLASTIC ANEMIA,** Diplopia, ataxia<br>***Contraindications: hepatic failure, AV block, MAO-I use*** |
| **VALPROIC ACID (Depakote)** | **Block $Na^+$ channels**<br>**↑GABA-mediated inhibition**<br>↑$K^+$ currents<br>***Blocks T-type $Ca^{2+}$ channels in thalamus***<br>Blocks NMDA-receptor<br>**INHIBITOR OF CYP450** | **ALL EPILEPTIC SEIZURES – *Broad Spectrum***<br>Short term tx MANIC episodes<br>Prophylaxis for migraine headaches | **BLACK BOX WARNING: HEPATOTOXICITY, SPINA BIFIDA, & PANCREATITIS**<br>**WEIGHT GAIN**<br>***Contraindications: hepatic failure & pregnancy*** |
| **LAMOTRIGINE** | Blocks $Na^+$ channel | Partial seizures & Absence Seizures<br>Bipolar disorder – *maintenance therapy* | **SKIN RASHES** – Stevens Johnson Syndrome, Toxic necrolysis |
| TOPIRAMATE | Blocks $Na^+$ channels<br>↑GABA activity & glutamate antagonism<br>Inhibition of carbonic anhydrase | Monotherapy for **partial** onset or primary generalized tonic-clonic seizures | Cognitive impairment, confusion, dizziness, ataxia, HA<br>Agitation, Emotional Lability, nausea, anorexia, weight loss<br>Acute angle-closure glaucoma |
| **GABA ENHANCERS** | | | |
| – **↑GABA**-mediated synaptic inhibition by a presynaptic or postsynaptic action | | | |
| **LORAZEPAM**<br>**DIAZEPAM** | Potentiate GABA: ↑frequency of $Cl^-$ channel opening | **IV: DOC *Status epilepticus***<br>Febrile seizure (Diazepam rectal or IV) | *Drowsiness, ataxia, confusion*<br>***Contraindicated in glaucoma & pregnancy*** |
| PHENOBARBITAL | Potentiates GABA<br>Inhibits $Na^+$ & $Ca^{2+}$ channels & blocks excitatory AMPA-R<br>**INDUCER OF CYP450** | Long term management of Simple Partial Seizures, Tonic-Clonic Seizures<br>IV: *Alternative in Status epilepticus* | Sedation (hyperactivity in kids), Ataxia, cognitive impairment<br>***Contraindicated in patients with porphyria, pregnancy, breast feeding*** |
| GABAPENTIN | | | |
| STIRIPENTOL | ↑GABA & Inhibits **lactate dehydrogenase**<br>**INHIBITOR OF CYP450** | Adjunct: Refractory tonic-clonic seizures | |
| **Absence Seizures** | | | |
| – Inhibit **VG-$Ca^{2+}$ channels** responsible for **T-type $Ca^{2+}$ currents** | | | |
| – **1ST LINE TREATMENT: ETHOSUXIMIDE, VALPROIC ACID** | | | |
| **ETHOSUXIMIDE** | Blocks T-Type $Ca^{2+}$ channels in thalamus<br>**VALPROATE: ↑Plasma ethosuximide** | **Absence seizures ONLY** | Headache, dizziness, Parkinsonism<br>**BONE MARROW DEPRESSION** |

**Green** = Kaplan, Deja. First Aid, or Tulane

# TREATMENT OF PARKINSON'S DISEASE

**Parkinson disease drugs** — Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.

| STRATEGY | AGENTS |
|---|---|
| Dopamine agonists | Ergot—Bromocriptine<br>Non-ergot (preferred)—pramipexole, ropinirole |
| ↑ dopamine availability | Amantadine (↑ dopamine release and ↓ dopamine reuptake); also used as an antiviral against influenza A and rubella; toxicity = ataxia, livedo reticularis. |
| ↑ L-DOPA availability | Agents prevent peripheral (pre-BBB) L-dopa degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine.<br>▪ Levodopa (L-dopa)/carbidopa—carbidopa blocks peripheral conversion of L-DOPA to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of peripheral L-dopa conversion into dopamine (e.g., nausea, vomiting).<br>▪ Entacapone, tolcapone—prevent peripheral L-dopa degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. |
| Prevent dopamine breakdown | Agents act centrally (post-BBB) to block breakdown of dopamine → ↑ available dopamine.<br>▪ Selegiline—blocks conversion of dopamine into 3-MT by selectively inhibiting MAO-B.<br>▪ Tolcapone—blocks conversion of dopamine to DOPAC by inhibiting central COMT. |
| Curb excess cholinergic activity | Benztropine (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia). |

**BALSA:**
Bromocriptine
Amantadine
Levodopa (with carbidopa)
Selegiline (and COMT inhibitors)
Antimuscarinics

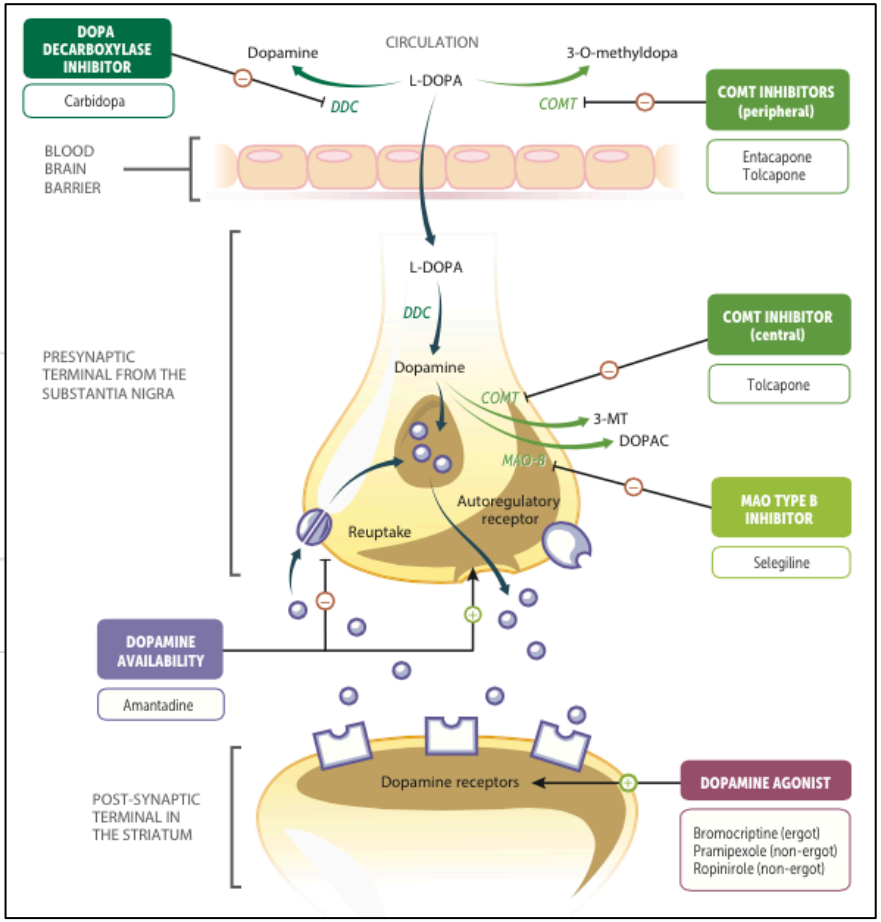
**Park** your Mercedes-**Benz**.

**L-dopa (levodopa)/carbidopa**

| | |
|---|---|
| MECHANISM | ↑ level of dopamine in brain. Unlike dopamine, L-dopa can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-dopa to ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects. |
| CLINICAL USE | Parkinson disease. |
| TOXICITY | Arrhythmias from ↑ peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration ("on-off" phenomenon), akinesia between doses. |

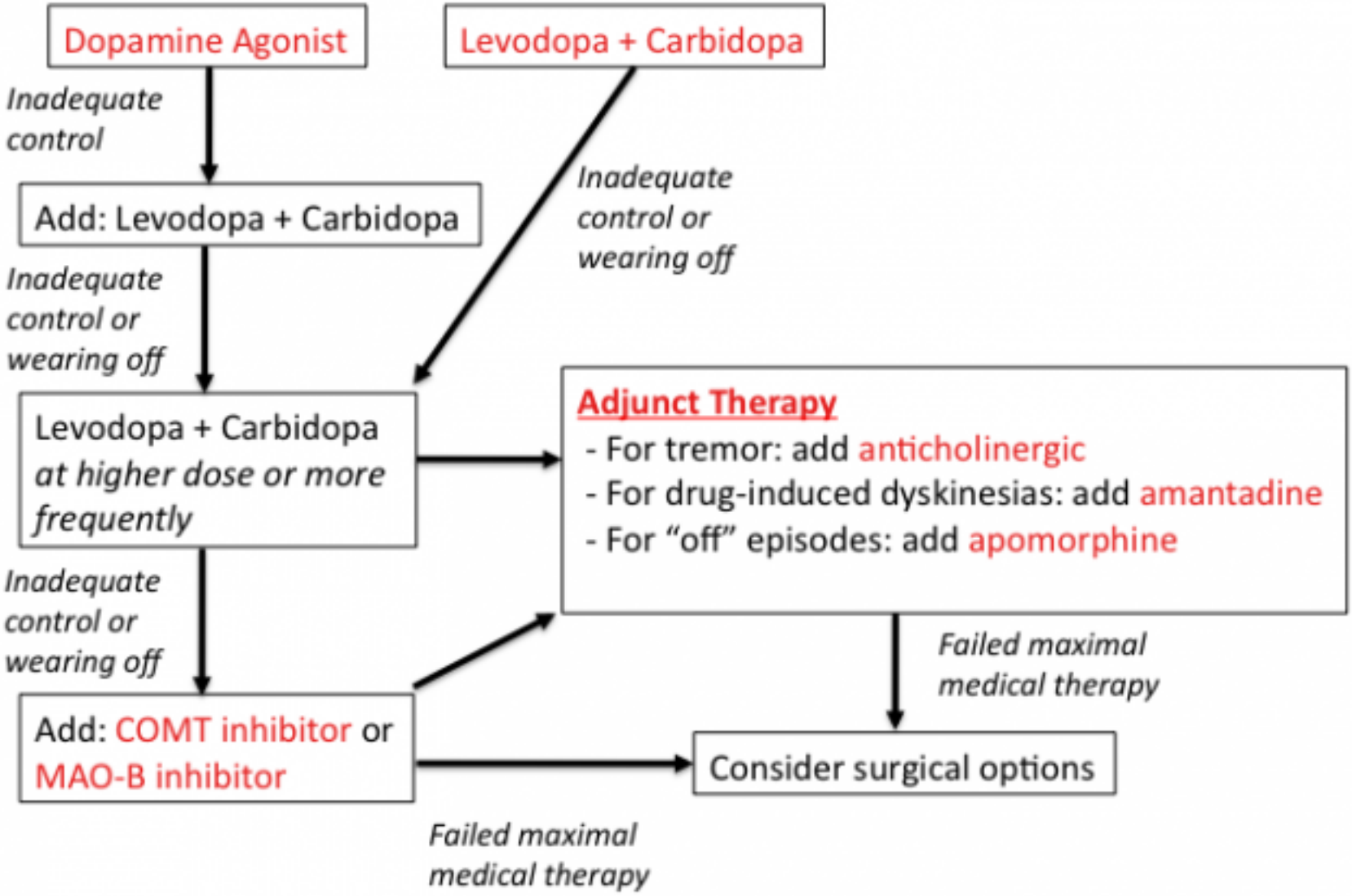
**Selegiline**

| | |
|---|---|
| MECHANISM | Selectively inhibits MAO-B, which preferentially metabolizes dopamine over norepinephrine and 5-HT, thereby ↑ the availability of dopamine. |
| CLINICAL USE | Adjunctive agent to L-dopa in treatment of Parkinson disease. |
| TOXICITY | May enhance adverse effects of L-dopa. |




**Green** = Kaplan, Deja. First Aid, or Tulane

# Treatment Algorithm for Parkinson's Disease




**Green** = Kaplan, Deja. First Aid, or Tulane

**Parkinson's Disease:** *"Cogwheel" rigidity, resting tremor, stooped posture, dyskinesia, 'masked faces', drooling, dementia,*

- **Primary lesion of nigrostriatal DA neurons → ↑cholinergic activity in striatum**
- **TREATMENT:** ↑DA or ↓cholinergic tone to balance ACh & DA

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **DOPAMINE AGONISTS** | | | |
| **LEVODOPA (L-DOPA)** | **INDIRECT** Dopamine Agonist – *stimulates **D2*** Crosses BBB via neutral AA transporter & then converted to DA in remaining nigrostriatal DA cells<br><br>**Most will be converted to DA (+ NE & EPI) in the periphery, so it's given with **Carbidopa (Sinemet)**, a peripheral dopa decarboxylase (DDC) inhibitor*<br><br>Large dose required due to **First Pass Effect** | Alleviates akinesia & rigidity<br>Improves posture, gait, facial expressions, speech, depression, & mental function<br>*(Not very effective against tremor!)* | **Cardiovascular**: arrhythmias, tachy<br>Orthostatic HTN, NV + anorexia<br>**L-DOPA DYSKINESIAS**: *tongue movements, bobbing head, myoclonic contractions, jerking movements of hand/arm/leg*<br>**MOTOR FLUCTUATIONS with *long-term treatment***<br>– Freezing episodes<br>– "Wearing off" effect: Tx w/ COMT inhibitor Entacapone<br>– Peak-dose dyskinesias 1-2 hours after dose<br>– On-off Syndrome: Tx with Rpinirole (DA agonist)<br>**Vivid dreams** (subside with time), psychotic reactions<br>***Contraindications: psychosis, patients with endocrine, renal, hepatic, CV, or pulmonary disease, MI***<br>**DRUG INTERACTIONS: given w/ MAOIs → HTN crisis** |
| **PRAMIPEXOLE** | DA agonist – D2 | Given in combo w/ L-DOPA for *advanced* disease | NV<br>**DYSKINESIA**<br>Hallucinations, confusion<br>**PERIPHERAL VASOPASM (Raynaud's)** |
| **ROPINIROLE**<br>APOMORPHINE | Direct DA agonist | Given in combo w/ L-DOPA for *advanced* disease<br>**On/Off Syndrome** | |
| **GIVEN IN COMBINATION WITH LEVODOPA** | | | |
| **CARBIDOPA*** | ***Peripheral* DDC Inhibitor**<br>Does not cross BBB, allows L-DOPA to cross CNS before it converts to DA | ***Sinemet: Carbidopa + L-DOPAA***<br>**↓L-DOPA dose by 75%!**<br>**↓*Most* adverse effects of L-DOPA**<br>**↑Therapeutic efficacy** | **Adverse effects that are unresolved with Carbidopa:**<br>*Orthostatic HTN, dyskinesia, adverse mental effects* |
| **AMANTADINE** | ↑Release of DA stored in synaptic vesicles<br>↓Re-uptake of released DA by presynaptic neuron | Normally used for the flu, but used in PD as ***conjunctive tx for L-DOPA induced dyskinesia*** | *Ankle edema, postural hypotension, insomnia* |
| **SELEGILINE**<br>Rasagiline | **Irreversible MAO-B Inhibitor** | Prolongs effects of L-DOPA<br>Slow disease progression | ***Insomnia, confusion, hallucinations*** |
| **TOLCAPONE**<br>**ENTACAPONE*** | **COMT Inhibitors**<br>**Inhibits breakdown of DA in CNS**<br>Extensive **First Pass Metabolism;** short half-life | ↑Peak levels of L-DOPA → ↑duration of effect<br>↓L-DOPA dose by 20-30%<br>**Wearing-off Response** | **Black Box: HEPATOTOXIC**<br>***Not hepatotoxic: PREFERRED***<br>**Dyskinesias**<br>Hallucinations |
| **ANTI-CHOLINERGIC** | | | |
| **BENZTROPINE**<br>Trihexyphenidyl | **Block DA re-uptake** | ***Correct imbalance of DA-ACh in striatum***<br>**Benefit: against TREMOR!**<br>*Not as effective as L-DOPA* | ***Atropine-like side effects***<br>Periphery: Dry mouth, mydriasis, cycloplegia, tachy, urinary retention<br>Central: Disruption of memory, delirium, paranoia, hallucinations |

# TREATMENT OF HUNTINGTON'S CHOREA

**Huntington disease drugs**

Neurotransmitter changes in Huntington disease: ↓ GABA, ↓ ACh, ↑ dopamine.
Treatments:
- Tetrabenazine and reserpine—inhibit vesicular monoamine transporter (VMAT); limit dopamine vesicle packaging and release.
- Haloperidol—$D_2$ receptor antagonist.

**Huntington's Chorea:** *Chorea, dementia, Family Hx: teeth grinding, facial grimacing, difficulty swallowing, depression*

– Loss of striatal GABAergic inhibitor neurons → Atrophy of caudate → **Overactivity of nigrostriatal DA system**

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| TETRABENAZINE<br>Reserpine | Blocks **VMAT** in neurons → NTs are then metabolized by MAO & COMT & not released into the synapse<br>**Deletes DA from nerve terminals** | *Reduces chorea severity* | *Hypotension*<br>*Parkinsonism symptoms*<br>*Depression:* Tx w/ Fluoxetine, TCAs, carbamazepine |
| **NEUROLEPTICS (Antipsychotics)** | Fluoxetine, TCAs, carbamazepine: treatment of depression associated with HD<br>Atypical Antipsychotics (*Clozapine, Quetiapine, Risperidone*): control psychosis associated with HD & have less side effects than Typical Antipsychotics (i.e. Haloperidol) | | |

# TREATMENT OF ALZHEIMER'S DISEASE

**Alzheimer drugs**

| | |
|---|---|
| **Memantine** | |
| MECHANISM | NMDA receptor antagonist; helps prevent excitotoxicity (mediated by $Ca^{2+}$). |
| TOXICITY | Dizziness, confusion, hallucinations. |
| **Donepezil, galantamine, rivastigmine, tacrine** | |
| MECHANISM | AChE inhibitors. |
| TOXICITY | Nausea, dizziness, insomnia. |

**Alzheimer's Disease:** *Age-related dementia; can't remember facts/events, can't recognize familiar faces (late-stage), 'Sundowner Syndrome'*

– **Amyloid plaques, neurofibrillary tangles,** loss of cholinergic neurons early in disease
– ↓ ACh, 5-HT, NE; ↑ **glutamate**

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **DONEPEZIL** | **REVERSIBLE, Selective AChE Inhibitor**<br>***Metabolized by CYP450*** | **Mild, Moderate, & SEVERE AD**<br>*Given at bed time* | **At initiations or dose increases:**<br>**GI symptoms**: ND, anorexia, weight loss, dyspepsia |
| **RIVASTIGMINE** | **Pseudoreversible AChE & BuChE Inhibitor** | Mild & Moderate AD<br>*Mild-moderate dementia due to PD* | |
| **GALANTAMINE** | **REVERSIBLE, Competitive BuChE** > AChE **Inhibitor** | Mild & Moderate: *Delays worsening for 6-12 months* | |
| TACRINE | Cholinesterase Inhibitor | NO LONGER USED! | HEPATOTOXICITY |
| **MEMANTIME** | **NMDA glutamate receptor antagonists** | **Mild, Moderate AD** if contraindication of AChE inhibitor<br>**SEVERE AD:** *↓rate of decline in thinking, ↑ability to perform daily tasks* | *Dizziness, HA, confusion, constipation*<br>***Adjust dose in renal impairment*** |
| **ADJUNCTS:** | Citalopram: ↓depression & anxiety<br>Sodium Valproate: treat severe aggression | | |

**Green** = Kaplan, Deja. First Aid, or Tulane

# SEDATIVE-HYPNOTICS + ANXIOLYTICS: Ethanol

| | |
|---|---|
| **Alcoholism** | Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, DTs) when intake is interrupted.<br>Complications: alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy.<br>Treatment: disulfiram (to condition the patient to abstain from alcohol use), acamprosate, naltrexone, supportive care. Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family. |
| **Wernicke-Korsakoff syndrome** | Caused by vitamin $B_1$ deficiency. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff psychosis). Associated with periventricular hemorrhage/necrosis of mammillary bodies. Treatment: IV vitamin $B_1$. |
| **Mallory-Weiss syndrome** | Partial thickness tear at gastroesophageal junction caused by excessive/forceful vomiting. Often presents with hematemesis and misdiagnosed as ruptured esophageal varices. |

**Delirium tremens (DTs)** Life-threatening alcohol withdrawal syndrome that peaks 2–4 days after last drink.
Characterized by autonomic hyperactivity (e.g., tachycardia, tremors, anxiety, seizures). Classically occurs in hospital setting (e.g., 2–4 days postsurgery) in alcoholics not able to drink as inpatients. Treatment: benzodiazepines.
Alcoholic hallucinosis is a distinct condition characterized by visual hallucinations 12–48 hours after last drink. Treatment: long-acting benzodiazepines (e.g., chlordiazepoxide, lorazepam, diazepam).

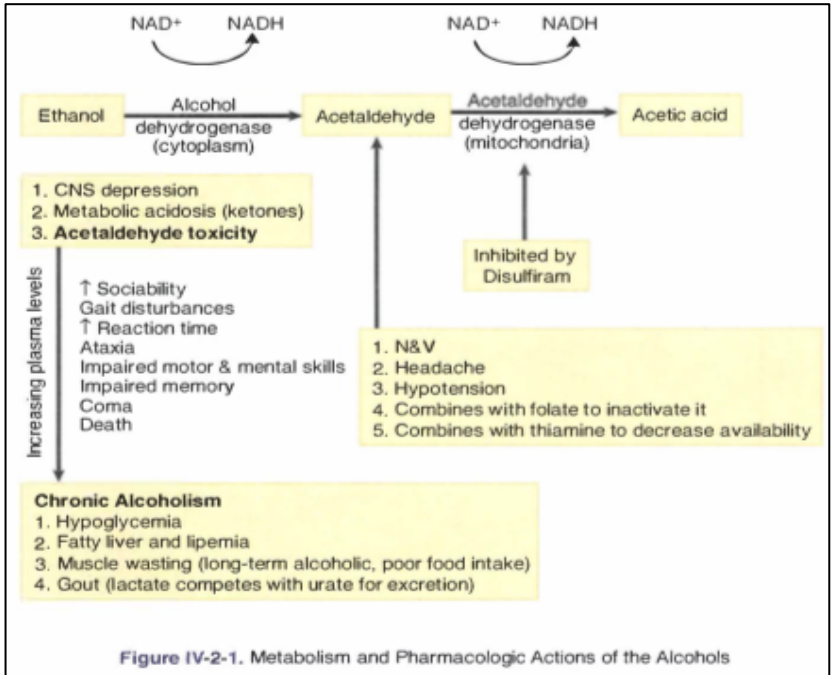


Figure IV-2-1. Metabolism and Pharmacologic Actions of the Alcohols

**Green** = Kaplan, Deja. First Aid, or Tulane

## ETHANOL:

- Potentiates **GABA-A** R → ↑$Cl^-$ conduction + inhibition of adenosine reuptake
- Rapidly absorbed from intestine; food in stomach slows rate
- **ZERO ORDER KINETICS**
- 90-98% metabolized to **$CO_2$** in the **LIVER**
- Excreted by **KIDNEY** > LUNG

***INDICATIONS:** solvent, topical use in poison ivy, fever, & disinfectant; trigeminal neuralgia, & methanol & ethylene glycol poisoning

**ACUTE Effects of Alcohol:**

- ***Paradoxical excitation***: inhibits GABA neuron & *disinhibits* motor neuron activity
- *Sedation*, *slurred speech, ataxia*
- High doses: *respiratory & cardiovascular depression, hypothermia, coma, & death*
- *Diuresis* from ADH inhibition
- Treat acute intoxication with GI lavage, hemodialysis, & sedative if needed

**CHRONIC Effects of Alcohol:**

- Korsakoff Syndrome & Thiamine Deficient
- Fetal Alcohol Syndrome in pregnancy
- Irritation & inflammation of gut
- Fatty liver → hepatitis & cirrhosis
- HTN, cardiomyopathy
- Gynecomastia, testicular atrophy
- Tolerance to alcohol & cross-tolerance to other sedative-hypnotics & narcotics from downregulation of GABA

| DRUG | ACTION | ADVERSE EFFECTS |
|---|---|---|
| **Treatment of Acute Alcohol Withdrawal** | | |
| **Long-Acting Benzo:** **CHLORDIAZEPOXIDE** **DIAZEPAM** | Provides a "tapering off" effect | *Metabolites will accumulation so do not give a patient with hepatic dysfunction long acting!* |
| **Short-Acting Benzo:** **OXAZEPAM** | Treatment of acute alcohol withdrawal in patients with **HEPATIC DYSFUNCTION** | |
| **Treatment of Chronic Alcoholism** | | |
| **Alcohol Withdrawal Syndrome:** irritability, sleep disturbance → seizures, toxic psychosis, delirium tremens (DTs – severe agitation, confusion, hallucinations, fever, tachycardia) | | |
| **DILSULFIRAM/ANTABUSE** Tetraethylthiuram disulfide | Inhibition of acetaldehyde DH<br>**If patients drink alcohol on this drug they will have flushing, palpitations, dyspnea, NV, Has, hypotension | *The adverse effects of drinking alcohol with this drug is the main mechanism of action* |
| **CLONIDINE** | Reduces sympathetic effects of ethanol withdrawal | |
| **Benzodiazepine:** **CHLORDIAZEPOXIDE** | Reduce behavioral agitation association with ethanol withdrawal | |
| **NALTREXONE** | Opiate antagonism reduces some of the reinforcing effects of ethanol abuse & reduces relapse | **Don't give w/ disulfiram: potential hepatotoxicity |

# SEDATIVE-HYPNOTICS + ANXIOLYTICS: Benzos & Barbs

| | | |
|---|---|---|
| **Barbiturates** | Phenobarbital, pentobarbital, thiopental, secobarbital. | |
| MECHANISM | Facilitate $GABA_A$ action by ↑ **duration** of $Cl^-$ channel opening, thus ↓ neuron firing (barbi**durates** ↑ **durat**ion). Contraindicated in porphyria. | |
| CLINICAL USE | Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental). | |
| TOXICITY | Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by EtOH use); dependence; drug interactions (induces cytochrome P-450).<br>Overdose treatment is supportive (assist respiration and maintain BP). | |
| **Benzodiazepines** | Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam. | |
| MECHANISM | Facilitate $GABA_A$ action by ↑ **frequency** of $Cl^-$ channel opening. ↓ REM sleep. Most have long half-lives and active metabolites (exceptions: **A**lprazolam, **T**riazolam, **O**xazepam, and **M**idazolam are short acting → higher addictive potential). | "**Fre**nzodiazepines" ↑ **fre**quency.<br>Benzos, barbs, and EtOH all bind the $GABA_A$ receptor, which is a ligand-gated $Cl^-$ channel.<br>**ATOM**. |
| CLINICAL USE | Anxiety, spasticity, status epilepticus (lorazepam and diazepam), detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia). | |
| TOXICITY | Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates.<br>Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). | |
| **Nonbenzodiazepine hypnotics** | **Z**olpidem, **Z**aleplon, es**Z**opiclone. "All **ZZZ**s put you to sleep." | |
| MECHANISM | Act via the BZ1 subtype of the GABA receptor. Effects reversed by flumazenil. | |
| CLINICAL USE | Insomnia. | |
| TOXICITY | Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. ↓ dependence risk than benzodiazepines. | |
| **Buspirone** | | |
| MECHANISM | Stimulates $5\text{-}HT_{1A}$ receptors. | I'm always anxious if the **bus** will be **on** time, so I take **buspir**one. |
| CLINICAL USE | Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Takes 1–2 weeks to take effect. Does not interact with alcohol (vs. barbiturates, benzodiazepines). | |

**Green** = Kaplan, Deja. First Aid, or Tulane

## BENZODIAZEPINES:

- Potentiates **GABA** inhibitory neurotransmission
- Metabolized in the **LIVER** forming glucuronides that are excreted by **KIDNEY**
  **Consider half-life when choosing drug for hepatic or renal patients*
- **EFFECTS & CLINICAL USE:** *calming & anxiety reduction, muscle relaxation, & sleep induction*

Specific Application in Anxiety:
- Situation anxiety (occurs within 3 months & resolves within 6)
- Panic disorder (given initially before antidepressants start to work)
- Social anxiety disorder (for anticipatory anxiety, but SSRI for LT)

| DRUG | HALF-LIFE | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **MIDAZOLAM (Versed)** | Short (*rapid acting*) | **Pre-op sedation + Anesthesia** | **Psychomotor depression**<br>*****Delayed rxn time while driving & ↓balance & coordination***<br>Impaired judgment & loss of self-control<br>Anterograde amnesia<br>**Respiratory depression (life-threatening if taken w/ ETOH or barbs)**<br>Tolerance & cross-tolerance to ETOH & barbs<br>Dependence – ***contraindicated if there's history of drug abuse***<br>****TREAT BENZO OVERDOSE WITH FLUMAZENIL****<br><br>***Contraindicated in pregnancy (fetal deformation)***<br><br>**Sudden discontinuation** → withdrawal symptoms of anxiety, irritability, & tremors; rarely seizures can also occur |
| **TRIAZOLAM** | Short (*rapid acting*) | Insomnia – *falling asleep* | |
| **TEMAZEPAM** | Intermediate (3-18h) | Insomnia – *staying asleep* | |
| **ALPRAZOLAM (Xanax)** | Intermediate (4-20h) | **Anxiety Disorder, Panic Disorder** | |
| **DIAZAPAM** | Long (*slow acting*) | **Anxiety Disorder**<br>**Acute Alcohol Withdrawal**<br>**Skeletal muscle spasm**<br>**Status Epilepticus (anti-convulsant)** | |
| **CHLORDIAZEPOXIDE** | Long (*slow acting*) | **Anxiety Disorder, Alcohol Withdrawal Syndrome** | |
| **CLONAZEPAM** | Long (*slow acting*) | **Panic Disorder**<br>***Alternative Broad Spectrum Seizure Tx due to undesirable sedation & tolerance*** | |

## BARBITUATES:

- Prolongation of GABA-induced $Cl^-$ channel opening → enhancement of synaptic inhibition
- Reduction of GLU-induced depolarization at AMPA-R + depression of VG $Na^+$ & $Ca^{2+}$ channels
- **EFFECTS:** dose-dependent depression, anxiolytic & euphoric effects, ↑total sleep but ↓REM sleep
- **Potentiation by ETOH, antihistamines, & MAO-I**

**TOXICITY**
- Respiratory acidosis + cerebral hypoxia → coma
- Depression of cardiac contractility, hypotension
- Renal failure
- Severe allergic reactions in **asthmatics**

**Tx:** ABC, gastric lavage & activated charcoal

| DRUG | ACTION/INDICATION |
|---|---|
| **PHENOBARBITAL** | **Emergency anti-convulsant & Neonatal hyperbilirubinemia** |
| **AMOBARBITAL** | Narcoanalysis by carotid infusion to determine dominant hemisphere for speech pre-neurosurgery |
| **THIOPENTAL** | Ultrashort acting IV anesthetic |

## NON-BENZO HYPNOTICS

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **BUSPIRONE (BuSpar)** | Partial 5-HT1A agonist → Down regulates presynaptic 5HT1A-R<br>***Pure anxiolytic without sedative actions or abuse potential*** | **GAD** (ESP. if hx of substance abuse) | *Takes weeks to see the anxiolytic effect* |
| **MELATONIN** | Pineal hormone w/ high affinity for receptors in suprachiasmatic nucleus | Mild sedative | |
| RAMELTEON | Melatonin-R agonist | Sedative | |
| DIPHENHYDRAMINE | 1st generation H1 antagonist | | Little toxicity |

**Green** = Kaplan, Deja. First Aid, or Tulane

# SEDATIVE-HYPNOTICS + ANXIOLYTICS (+ ANTIDEPRESSANTS): SSRI/SNRI

| **SSRIs** | Fluoxetine, paroxetine, sertraline, citalopram. | Flashbacks paralyze senior citizens. |
|---|---|---|
| MECHANISM | 5-HT–specific reuptake inhibitors. | It normally takes 4–8 weeks for antidepressants to have an effect. |
| CLINICAL USE | Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social phobias, PTSD. | |
| TOXICITY | Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).<br>Serotonin syndrome with any drug that ↑ 5-HT (e.g., MAO inhibitors, SNRIs, TCAs)—hyperthermia, confusion, myoclonus, cardiovascular instability, flushing, diarrhea, seizures. Treatment: cyproheptadine (5-$HT_2$ receptor antagonist). | |

| **SNRIs** | Venlafaxine, duloxetine. |
|---|---|
| MECHANISM | Inhibit 5-HT and norepinephrine reuptake. |
| CLINICAL USE | Depression. Venlafaxine is also used in generalized anxiety disorder, panic disorder, PTSD. Duloxetine is also indicated for diabetic peripheral neuropathy. |
| TOXICITY | ↑ BP most common; also stimulant effects, sedation, nausea. |

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Selective inhibition of **5-HT reuptake** → ↑**5HT** in the synaptic cleft → ***antidepressant + anxiolytic effects***
- Biotransformation in the liver; **Inhibit CYP450**
- **INDICATIONS: Anxiety disorders** (GAD, Panic disorder, SAD, OCD, bulimia nervosa, gambling – *Takes 4-6 weeks to see effect so often benzos are given initially*
- **DOC for DEPRESSION**

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **FLUOXETINE (PROZAC)** | SSRI<br>↑*Anxiety or agitation during early tx*<br>***Long half life!*** | *Safer than TCA & MAOIs for depression –* ***withdrawal effects are "relatively mild" due to long lasting effects!*** | GIT: weight gain, NVD; HA<br>**SEXUAL DYSFUNCTION** – ***Treat with BUPROPION***<br>*****Bupropion can ↑risk of seizures***<br>Restlessness (akathisia), insomnia, fatigue<br>**SEROTONIN SYNDROME** w/ OD or drug interactions<br><br>***May precipitate mania in bipolar patients ("Unmask mania")*** |
| **CITALOPRAM** | SSRI | | |
| **ESCITALOPRAM (LEXAPRO)** | SSRI | | |
| SERTRALINE (ZOLOFT) | SSRI | Social Anxiety Disorder (SAD), PTSD | |
| **PAROXETINE** | SSRI<br>Short half-life | **Social Anxiety Disorder (SAD), PTSD** | |

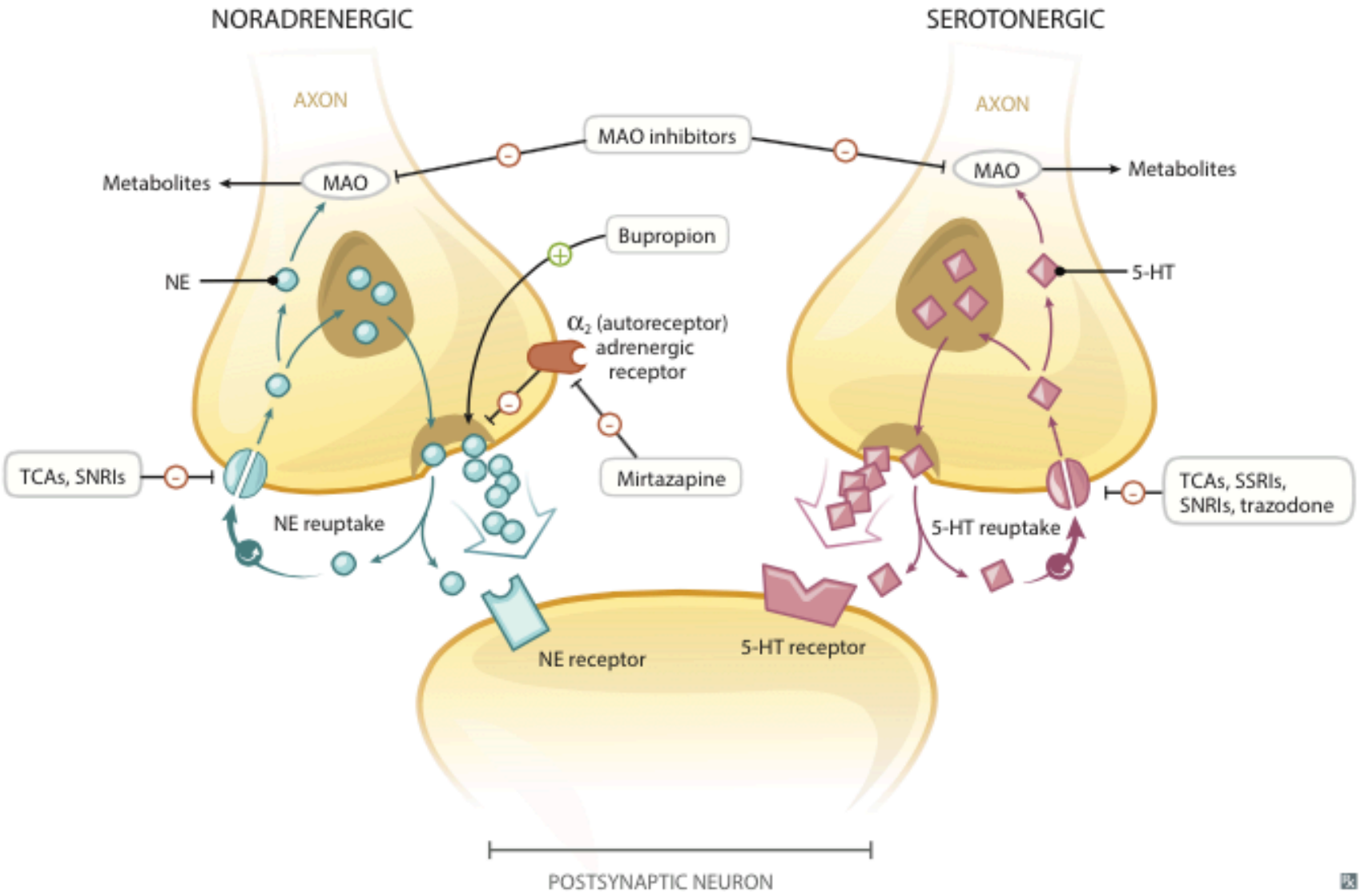
## SELECTIVE SEROTONIN & NEREPINEPHRINE REUPTAKE INHIBITORS (SNRI)

- Selective blockade of **NET & SERT** → ↑**NE & 5-HT**
- **INDICATIONS:** Major depression, chronic pain disorders, fibromyalgia, perimenopausal symptoms

| | | |
|---|---|---|
| **VENLAFAXINE (Effexor)** | **Social Anxiety Disorder (SAD)**<br>**Generalized Anxiety Disorder (GAD)**<br>**Obsessive Compulsive Disorder (OCD)**<br>**Depression** | Anticholinergic, sedation, HTN<br>*Do not combine with MAOIs* |
| DESVENLAFAXINE | | |
| **DULOXETINE (CYMBALTA)** | **Depression**<br>**Fibromyalgia**<br>**Diabetic neuropathy** | |

# TREATMENT OF DEPRESSION: MAOIs, TCAs, (SSRI/SNRIs), Atypical

## Antidepressants




**Green** = Kaplan, Deja. First Aid, or Tulane

| | |
|---|---|
| **Tricyclic antidepressants** | Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine. |
| MECHANISM | Block reuptake of norepinephrine and 5-HT. |
| CLINICAL USE | Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis. |
| TOXICITY | Sedation, $\alpha_1$-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval.<br>**Tri-C's**: **C**onvulsions, **C**oma, **C**ardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline). Treatment: $NaHCO_3$ to prevent arrhythmia. |
| **Monoamine oxidase (MAO) inhibitors** | **T**ranylcypromine, **P**henelzine, **I**socarboxazid, **S**elegiline (selective MAO-B inhibitor).<br>(**MAO** **T**akes **P**ride **I**n **S**hanghai). |
| MECHANISM | Nonselective MAO inhibition ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine). |
| CLINICAL USE | Atypical depression, anxiety. |
| TOXICITY | Hypertensive crisis (most notably with ingestion of tyramine, which is found in many foods such as wine and cheese); CNS stimulation. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan (to prevent serotonin syndrome). |

**Atypical antidepressants**

| | |
|---|---|
| **Bupropion** | Also used for smoking cessation. ↑ norepinephrine and dopamine via unknown mechanism. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. No sexual side effects. |
| **Mirtazapine** | $\alpha_2$-antagonist (↑ release of norepinephrine and 5-HT) and potent 5-$HT_2$ and 5-$HT_3$ receptor antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in elderly or anorexic patients), dry mouth. |
| **Trazodone** | Primarily blocks 5-$HT_2$ and $\alpha_1$-adrenergic receptors. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Called trazo**bone** due to male-specific side effects. |

## MONOAMINE OXIDASE INHIBITORS (MAOI)

- Inhibit intracellular MAO in CNS neurons → **↓degradation of catecholamines & serotonin**
- **Antidepressant action is attributed to inhibition of the MAO-A isoform → ↑NE & 5-HT**
- **INDICATIONS:** Depression that is UNRESPONSIVE to other treatment; **DOC: *Atypical Depression (patient with ↑eat & ↑sleeping)***

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **PHENELZINE & TRANYLCYCPROMINE** | **IRREVERSIBLE MAO-A inhibitor** | **NOT** 1st line for regular depression | **HYPERTENSIVE CRISIS** with **Tyramine**: *Wine & Cheese Phenomenon*<br>**SEROTONIN SYNDROME** from combining MAOIs: *confusion, agitation, tremor, high fever, sweating, nausea, diarrhea, seizures*<br>**POSTURAL HTN**<br>Rare, but severe ***hepatotoxicity*** |
| MOCLOBEMIDE | Reversible MAO-A inhibitor | | |
| **SELEGILINE** | **IRREVERSIBLE MAO-B inhibitor**<br>**↑Dopamine** | **Major Depression (2nd DOC)**<br>Adjunctive therapy in Parkinson's | |

## TRICYCLIC ANTIDEPRESSANTS (TCA)

- Non-selective **COMPETITIVE** blockade of **NET & SERT reuptake transporters; ↑5-HT, NE, DA**
- Rapid absorption & extensive 1st pass metabolism → low & inconsistent bioavailability
- Highly plasma protein bound; highly bound in tissues (**↑lipophilicity**)
- Biotransformation: hepatic metabolism; **CYP450** → active metabolites
- **DRUG INTERACTIONS:**
  *SSRIs inhibit CYP450 enzyme & cause **↑TCA levels!**
  Do not combine with MAOIs!

| | | | |
|---|---|---|---|
| **IMIPRAMINE** | | **Major Depression** not responsive to other drugs<br>**Chronic pain, Enuresis** | **Block**: α1, M, H1 receptors<br>Anti-muscarinic → ***tachycardia***<br>Block $Na^+$ channels → **ARRYTHMIAS*** |
| Desipramine | Active metabolite of imipramine | Cocaine craving + withdrawal | |
| **AMITRIPTYLINE** | | **Neuropathic pain, Migraines** | |
| Nortriptyline | Active metabolite of amitriptyline | | ***May precipitate mania in bipolar patients ("Unmask mania")*** |
| **CLOMIPRAMINE** | | **Phobias & Anxieties, OCD** | |

## ATYPICAL ANTIDEPRESSANTS

| | | | |
|---|---|---|---|
| MAPROTILINE + REBOXITINE | Specific NE reuptake inhibitor | **Low NE Depression** | |
| MIRTAZAPINE | ↑NE & 5-HT via blockade of α2 & postsynaptic 5-HT receptors | | *Few adverse effects* |
| TRAZADONE<br>NEFAZODONE | 5-HT antagonists/Reuptake inhibitors | | Trazadone has pronounced sedative effects |

# TREATMENT OF BIPOLAR DISORDER: Lithium

**Lithium**

| | |
|---|---|
| MECHANISM | Not established; possibly related to inhibition of phosphoinositol cascade. |
| CLINICAL USE | Mood stabilizer for bipolar disorder; blocks relapse and acute manic events. Also SIADH. |
| TOXICITY | Tremor, hypothyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis. Causes Ebstein anomaly in newborn if taken by pregnant mother. Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT with $Na^+$. Thiazide use is implicated in lithium toxicity in bipolar patients. |

LMNOP—Lithium side effects:
- Movement (tremor)
- Nephrogenic diabetes insipidus
- HypOthyroidism
- Pregnancy problems

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| LITHIUM | Alters $Na^+$ transport in nerve & muscle cells<br>**Inhibits recycling of neuronal membrane phophoinositides: ↓IP levels** | **1st Line for Maintenance Tx of Bipolar Disorder**<br>**Mania stage of Bipolar**<br>**"MOOD STABILIZER"** | Very narrow **Therapeutic Index** – *monitoring required*<br><br>**SEE MNEMONIC ABOVE**<br>**POLYURIA/POLYDIPSIA** (competes with ADH in kidney)<br>**Ataxia + tremor**<br>**Goiter + Hypothyroidism**<br>**Weight gain**, skin rash<br><br>**DRUG INTERACTIONS:**<br>Serum Lithium levels are increased by: Diuretics, NSADs, ACE-inhibitors |

***Atypical antipsychotics are also used in treatment of acute mania or long-term maintenance of bipolar disorder** (Tulane Q is a guy on lithium who is tired of constantly having to go to the bathroom, weight gain, etc. & the next DOC would be atypical anti-psychotics)*

# ANTI-PSYCHOTICS (Treatment of Schizophrenia)

| | | |
|---|---|---|
| **Antipsychotics (neuroleptics)** | Haloperidol, trifluoperazine, fluphenazine, thioridazine, chlorpromazine (haloperidol + "-azines"). | |
| MECHANISM | All typical antipsychotics block dopamine $D_2$ receptors (↑ [cAMP]). | **High** potency: **Tri**fluoperazine, **F**luphenazine, **H**aloperidol (**Try** to **Fly High**)—neurologic side effects (e.g., Huntington disease, delirium, EPS symptoms). |
| CLINICAL USE | Schizophrenia (primarily positive symptoms), psychosis, acute mania, Tourette syndrome. | **Low** potency: **C**hlorpromazine, **T**hioridazine (**C**heating **T**hieves are **low**)—non-neurologic side effects (anticholinergic, antihistamine, and $\alpha_1$-blockade effects). |
| TOXICITY | Highly lipid soluble and stored in body fat; thus, very slow to be removed from body.<br>Extrapyramidal system side effects (e.g., dyskinesias). Treatment: benztropine or diphenhydramine.<br>Endocrine side effects (e.g., dopamine receptor antagonism → hyperprolactinemia → galactorrhea).<br>Side effects arising from blocking muscarinic (dry mouth, constipation), $\alpha_1$ (hypotension), and histamine (sedation) receptors.<br>Can cause QT prolongation. | **C**hlorpromazine—**C**orneal deposits; **T**hioridazine—re**T**inal deposits; haloperidol—NMS, tardive dyskinesia.<br>Evolution of EPS side effects:<br>▪ 4 hr acute dystonia (muscle spasm, stiffness, oculogyric crisis)<br>▪ 4 day akathisia (restlessness)<br>▪ 4 wk bradykinesia (parkinsonism)<br>▪ 4 mo tardive dyskinesia |
| OTHER TOXICITIES | **Neuroleptic malignant syndrome (NMS)**—rigidity, myoglobinuria, autonomic instability, hyperpyrexia. Treatment: dantrolene, $D_2$ agonists (e.g., bromocriptine).<br>**Tardive dyskinesia**—stereotypic oral-facial movements as a result of long-term antipsychotic use. | For NMS, think **FEVER**:<br>**F**ever<br>**E**ncephalopathy<br>**V**itals unstable<br>**E**nzymes ↑<br>**R**igidity of muscles |
| **Atypical antipsychotics** | **Ol**anzapine, **cloz**apine, **quet**iapine, **risper**idone, **a**ripiprazole, **z**iprasidone. | It's **atypical** for **old** **clos**ets to **quiet**ly **risper** from **A** to **Z**. |
| MECHANISM | Not completely understood. Varied effects on 5-$HT_2$, dopamine, and α- and $H_1$-receptors. | |
| CLINICAL USE | Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome. | |
| TOXICITY | Fewer extrapyramidal and anticholinergic side effects than traditional antipsychotics. Olanzapine/clozapine may cause significant weight gain. Clozapine may cause agranulocytosis (requires weekly WBC monitoring) and seizure. Risperidone may increase prolactin (causing lactation and gynecomastia) → ↓ GnRH, LH, and FSH (causing irregular menstruation and fertility issues). All may prolong QT interval. | Must watch **cloz**apine **cloz**ely! |

| ***Receptor Type*** | ***Side Effects*** |
|---|---|
| $D_2$ | EPS, prolactin elevation |
| $M_1$ | Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision |
| $H_1$ | Sedation, weight gain, dizziness |
| $\alpha_1$ | Hypotension |
| 5-$HT_{2A}$ | Anti-EPS (?) |
| 5-$HT_{2C}$ | Satiety blockade |

D=dopamine; EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

Robinson DS. *Primary Psychiatry.* Vol 14, No 10. 2007.

**Green** = Kaplan, Deja. First Aid, or Tulane

## Schizophrenia

- Cognitive deficiencies + depression/anxiety, aggression/hostility, suicidal tendencies + Positive & Negative symptoms = Inability to function in work/school & interpersonal relationships
  **POSITIVE SYMPTOMS:** delusions, hallucinations, thought disorders
  **NEGATIVE SYMPTOMS:** social withdrawal, reduced motivation, substantial changes in sleep habits (insomnia)
- *The same symptomatology can be seen with amphetamine abuse. Amphetamines stimulate release of & block reuptake of dopamine. Schizophrenia is hypothesized to be a hyperdopaminergic pathology. Thus,* ***DA receptor antagonists*** *are therapeutic.*

## TYPICAL ANTIPSYCHOTICS: *Acute use, not maintenance*

- Block D2 receptors: ↓ positive symptoms & worsen negative symptoms
- Low bioavailability; lipophilic, cross BBB easily, ↑Therapeutic Index
- High protein binding: placenta + breast milk

**Dopamine Receptors:**
D-1 & D-5: postsynaptic, ↑cAMP via $G_s$
D-2, 3, 4: postsynaptic or presynaptic; ↓cAMP via $G_i$
***Antipsychotics have high affinity for D-2 receptors ($G_i$)*

| DRUG | CHARACTERISTICS | ADVERSE EFFECTS |
|---|---|---|
| **CHLORPROMAZINE & THIORIDAZINE** | **LOW POTENCY (HIGH DOSE)**<br>*Lower risk for extrapyramidal side effects (EPS)* | **ANTICHOLINERGIC:** *dry mouth, blurred vision, urinary retention,* ***coma, convulsion, cardiotoxicity***<br>**α1 ANTAGONIST**: orthostatic hypotension, ejaculatory dysfunction<br>**ENDOCRINE EFFECTS:** amenorrhea, **Hyperprolactinemia**, gynecomastia, lactation<br>**H1 ANTAGONIST:** sedation, weight gain<br><br>****TYPICAL ANTIPSYCHOTICS HAVE INCREASED RISK OF SIDE EFFECTS****<br>**EXTRA-PYRAMIDAL SYMPTOMS:** mimics Basal Ganglia disorders; Parkinsonian symptoms, akathisia, & stiffness; "mask-like" facial appearance, abnormal posturing, tongue protrusions<br>**TARDIVE DYSKINESIA: CHRONIC, LONG-TERM EFFECT**; facial grimacing, lip smacking, toe tapping, pill rolling movements; (**TX**: BENZODIAZEPINE or β-blockers)<br>**Neuroleptic Malignant Syndrome:** ***rigidity, mental confusion, & fever*** (Discontinue drug + IV fluids + **Bromocriptine/Dantrolene**)<br>**Acute Dystonia**: arching of the back (Tx with IM/IV **diphenhydramine or benztropine**) |
| **FLUPHENAZINE** | **HIGH POTENCY (LOW DOSE)**<br>*Higher risk for extrapyramidal side effects (EPS)* | |
| **HALOPERIDOL** | **MOST POTENT!!!** | |

## ATYPICAL ANTIPSYCHOTICS: *Maintenance DOCs*

- **Block 5-HT2 & D2 receptors: IMPROVE NEGATIVE SYMPTOMS!!**
- Significant first pass metabolism
- **ALSO INDICATED IN ACUTE MANIA+LONG TERM BIPOLAR DISORDER & HUNTINGTON'S!**

**COMMON ADVERSE EFFECTS: DECREASED EPS!!**

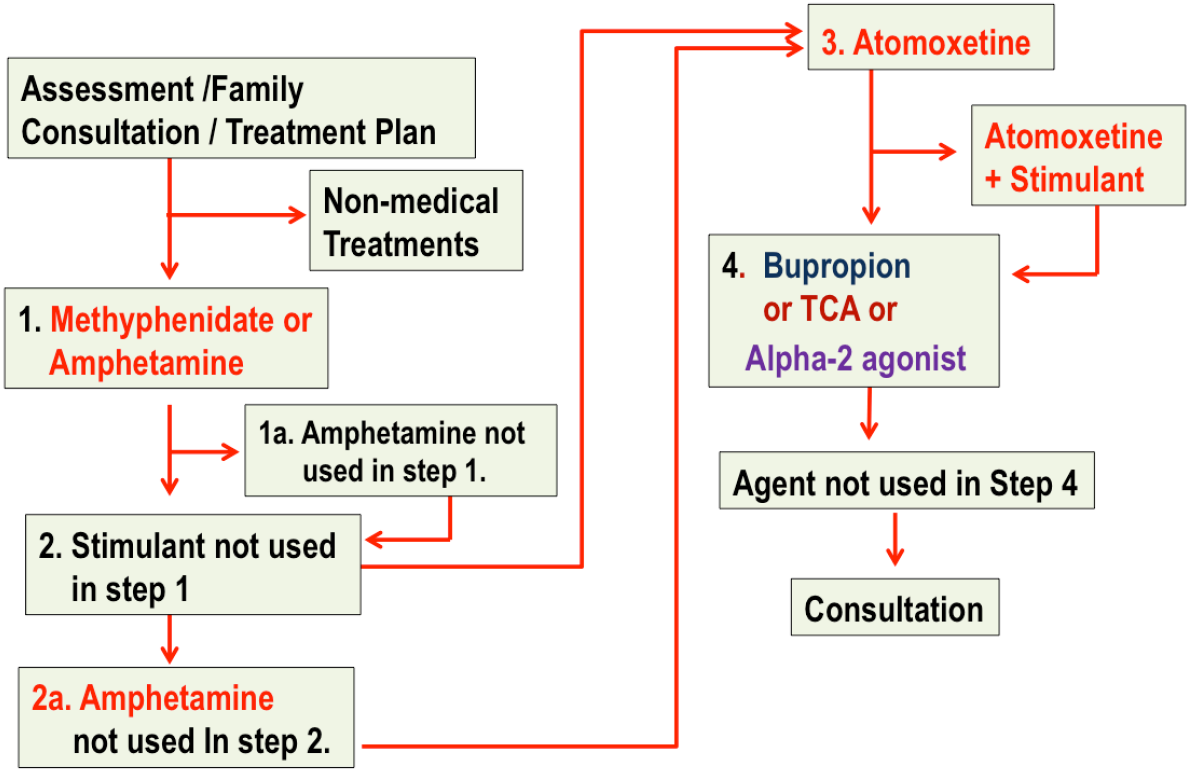
- **WEIGHT GAIN + Insulin Resistance seen more in ATYPICAL than typical!**
- ***Atypicals have ↓side effects, but in some cases will still show similar symptoms to typical antipsychotics (EPS, neuroleptic malignant syndrome, etc.)***

| | | |
|---|---|---|
| **CLOZAPINE** | High selectivity & high affinity to **D4** | **AGRANULOCYTOSIS**<br>**Sialorrhea (drooling)** |
| **RISPERIDONE** | Metabolized by CYP450 12D6<br>Levels ↑ by: Fluoxetine, Sertraline, Paroxetine | *Associated with* ***STROKE*** *when used in dementia* |
| **OLANZAPINE** | Metabolized by CYP450 1A2<br>Levels ↑ by: Fluvoxamine<br>Levels ↓ by: Cigarette smoking | *Associated with* ***STROKE*** *when used in dementia* |
| QUETIAPINE | Metabolized by **CYP450 3A4**<br>Levels ↑ by many drugs | |

## TREATMENT OF ADHD

| | |
|---|---|
| **CNS stimulants** | Methylphenidate, dextroamphetamine, methamphetamine. |
| MECHANISM | ↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine. |
| CLINICAL USE | ADHD, narcolepsy, appetite control. |

# ADHD ALGORITHM

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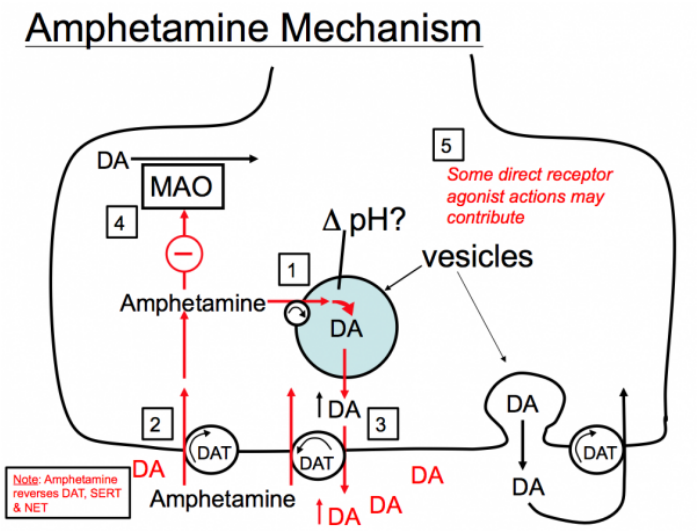
## ADHD: *Poor attention & concentration*

| DRUG | MOA | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **AMPHETAMINES (CNS Stimulants)**<br>– ↑**Brain DA levels**: *stimulate release of DA, **block DA & NE re-uptake**, inhibit MAO*<br>– Improve core symptoms of ADHD: inattention, impulsivity, hyperactivity, impulsive aggression, social interactions | | | |
| **METHYLPHENIDATE (Ritalin)** | Structurally related to amphetamine<br>**DA & NE Re-uptake Inhibitor:** Prolongs effects | **ADHD & Narcolepsy** | **Loss of appetite** & abdominal pain<br>**Insomnia, HA, nervousness**<br>Psychiatric effects, irritability, dysphoria<br>**Seizures**<br>**Abuse potential**<br>***Contraindications: psychosis, mania, Tourette's, narrow-angle glaucoma*** |
| **AMPHETAMINE & D-AMPHETAMINE** | | | |
| LISDEXAMPHETAMINE | Prodrug of D-amphetamine | | |
| **OTHER** | | | |
| **ATOMOXETINE (Strattera)** | **NON-stimulant**<br>**Selective inhibitor of NE Re-uptake**<br>**Metabolized by CYP2D6 & glucuronidation**<br>Highly plasma protein bound | **ADHD: Children & Adults** | **BLACK BOX WARNING:↑risk of suicidal ideation** (kids & adolescents) |
| CLONIDINE + GAUNFACINE | **Selective α2-adrenergic receptor agonists**<br>α2 downregulation | **ADHD: Children (6-17 y/o)** | Dry mouth, constipation, hypotension, bradycardia, syncope<br>**Sedation** |
| **Not approved for, but used for ADHD:** Bupropion & TCAs | | | |




**Amphetamine Mechanism of Action:**

1. Increases the release of monoamines (NE, 5-HT and DA) from their vesicular storage sites within presynaptic nerve terminals
2. Competes with monoamines for reuptake via DAT, NET or SERT
3. Facilitates the release of cytoplasmic presynaptic monoamines by inducing "reverse" transporter exchange (i.e. exchange of intracellular monoamines for extracellular amphetamine - a symport mechanism)
4. Weakly inhibits MAO, causing ↑presynaptic monoamine levels
5. Amphetamines may have some direct receptor agonist actions (i.e. 5-HT) in some areas of the CNS

## Medications for selected psychiatric conditions

| PSYCHIATRIC CONDITION | PREFERRED DRUGS |
|---|---|
| ADHD | Stimulants (e.g., methylphenidate) |
| Alcohol withdrawal | Long-acting benzodiazepines (e.g., chlordiazepoxide, lorazepam, diazepam) |
| Bipolar disorder | Lithium, valproic acid, atypical antipsychotics |
| Bulimia | SSRIs |
| Depression | SSRIs |
| Generalized anxiety disorder | SSRIs, SNRIs |
| Obsessive-compulsive disorder | SSRIs, clomipramine |
| Panic disorder | SSRIs, venlafaxine, benzodiazepines |
| PTSD | SSRIs, venlafaxine |
| Schizophrenia | Atypical antipsychotics |
| Social phobias | SSRIs, β-blockers |
| Tourette syndrome | Antipsychotics (e.g., fluphenazine, pimozide), tetrabenazine, clonidine |