

## Introduction

### Classes of Neurotransmitters

<b>Amino Acids</b>		GABA ( $\gamma$ -aminobutyric acid)	
		Glutamate	
		Aspartate (NMDA)	
		Glycine	
<b>Acetylcholine</b>		Acetylcholine	
<b>Amines</b>		Dopamine	
		NE, E	
		5-hydroxytryptamine (serotonin)	
		Histamine	
<b>Peptides</b>	<b>Endorphin family</b>	proenkephalin derivatives	
		proopiomelanocortin derivatives	
		prodynorphin derivatives	
	<b>Vasotocin family</b>	vasopressin	
		oxytocin	
	<b>Glucagon family</b>	glucagon	
		vasoactive intestinal polypeptide (VIP)	
		secretin	
		growth hormone-releasing factor	
		<b>Neurokinins</b>	
		<b>Cholecystokinins</b>	
		<b>Neuropeptides Y</b>	
	<b>Others</b>	<b>Purines</b>	
<b>NO</b>			
<b>Arachidonic Acid derived</b>		prostaglandins	
		thromboxanes	
	leukotrienes		

### Ligand-gated ion channels

Includes receptors for:

- ▶ Nicotinic AchR
- ▶ Most amino-acid receptors
  - ▶ GABA<sub>A</sub> R
  - ▶ *most* glutamate R
  - ▶ aspartate R
  - ▶ glycine R
  - ▶ (NOT GABA<sub>B</sub> and *some* glutamate R)
- ▶ one subtype of serotonin R: 5-HT<sub>3</sub>

Ion channel is a tetramer or pentamer of 4TM subunits

### G-protein coupled receptors (GPCR)

**Includes receptors for all others!**

- ▶ Muscarinic cholinergic receptors
- ▶ GABA<sub>B</sub>
- ▶ some glutamate receptors
- ▶ all other receptors for amine and peptide neurotransmitters

7TM receptor. Agonist binds to extracellular side; G protein binds to intracellular side.

G protein couples receptor to effector:

G protein composed of 3 subunits

$\alpha$ : specific for receptor, binds GTP  
GTP hydrolysis activates effector

$\alpha$  or  $\beta$ - $\gamma$  dimer **regulate effector:**

- ▶ adenylyl cyclase
- ▶ phospholipase C
- ▶ inward-rectifying K<sup>+</sup> channel
- ▶ Ca<sup>2+</sup> channel
- ▶ PIP-3-kinase

<b>Mechanisms of termination of NT action</b>	<ul style="list-style-type: none"> <li>▶ Ach is metabolized by AchE</li> <li>▶ Amine and aa NT's taken up by specific transport systems on presynaptic membrane</li> <li>▶ Other NTs metabolized by enzymes, which may or may not be near the synapse</li> </ul>		
<b>Mechanisms by which a medication can affect neurotransmission</b>	<ol style="list-style-type: none"> <li>1. agonist or antagonize receptor</li> <li>2. bind to site distinct from NT binding site and alter affinity of receptor for NT</li> <li>3. inhibit presynaptic reuptake of NT</li> <li>4. inhibit synthesis or metabolism of NT</li> <li>5. inhibit or potentiate release of NT</li> </ol>		
<b>Acetylcholine</b>	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>Cholinergic antagonists:</p> <ul style="list-style-type: none"> <li>▶ relative excess of Ach in parkinson's, can use muscarinic antagonists to treat</li> <li>▶ relative excess cause EPS; can use cholinergic antagonists to treat EPS caused by antipsychotic drugs (dopaminergic antagonists)</li> <li>▶ anticholinergic blockade causes: antiemetic, sedation, amnesia</li> </ul> </td> <td style="width: 50%; vertical-align: top;"> <p>Cholinergic agonists:</p> <ul style="list-style-type: none"> <li>▶ Alzheimers treated with AchE inhibitors</li> <li>▶ Excessive AchE doses produce central cholinergic syndrome → convulsions, coma, death</li> <li>▶ Centrally-acting nicotinic agonists may have analgesic properties</li> </ul> </td> </tr> </table>	<p>Cholinergic antagonists:</p> <ul style="list-style-type: none"> <li>▶ relative excess of Ach in parkinson's, can use muscarinic antagonists to treat</li> <li>▶ relative excess cause EPS; can use cholinergic antagonists to treat EPS caused by antipsychotic drugs (dopaminergic antagonists)</li> <li>▶ anticholinergic blockade causes: antiemetic, sedation, amnesia</li> </ul>	<p>Cholinergic agonists:</p> <ul style="list-style-type: none"> <li>▶ Alzheimers treated with AchE inhibitors</li> <li>▶ Excessive AchE doses produce central cholinergic syndrome → convulsions, coma, death</li> <li>▶ Centrally-acting nicotinic agonists may have analgesic properties</li> </ul>
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<b>Epibatidine</b>	Centrally-acting nicotinic agonist. Has analgesic activity. Isolated from skin of poisonous tricolor frog.		
<b>GABA</b>	<p>Inhibitory.</p> <p>GABA<sub>A</sub>: ligand-gated Cl<sup>-</sup> ion channel, hyperpolarizes membrane more common in CNS</p> <p>significant heterogeneity: diverse effects of meds → many, many GABA<sub>A</sub> subtypes.</p> <p><b>benzodiazepines: ↑ (= "potentiate") effect of GABA at GABA<sub>A</sub> receptor.</b></p> <p>Newer anticonvulsants: ↓ GABA reuptake</p> <p>endogenous ligand at receptor for Δ<sup>9</sup>-THC: ↓ GABA release</p> <p>GABA<sub>B</sub>: GPCR. Baclofen acts as an agonist</p>		
<b>Gabapentin</b>	<p>↑ GABA release from nerve terminals.</p> <p>Used as an anticonvulsant and in the treatment of chronic pain</p>		
<b>Baclofen</b>	<p>Centrally-acting muscle relaxant.</p> <p>Used to treat muscle spasms associated with SC injuries and neurodegenerative diseases.</p>		
<b>Glycine</b>	Inhibitory. Receptors located primarily in brain stem and SC.		
<b>NMDA (Glutamate and aspartate)</b>	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>Excitatory neurotransmitter.</p> <p>Many, many glutamate/aspartate subtypes.</p> <p>Some are ligand-gated ion channels and some are GPCR's.</p> </td> <td style="width: 50%; vertical-align: top;"> <p>NMDA (N-methyl-D-aspartate) receptors: excessive activity associated with neuronal injury and death.</p> <p>NMDA antagonists produce analgesia, dissociative anesthesia</p> </td> </tr> </table>	<p>Excitatory neurotransmitter.</p> <p>Many, many glutamate/aspartate subtypes.</p> <p>Some are ligand-gated ion channels and some are GPCR's.</p>	<p>NMDA (N-methyl-D-aspartate) receptors: excessive activity associated with neuronal injury and death.</p> <p>NMDA antagonists produce analgesia, dissociative anesthesia</p>
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<b>Ketamine Phencyclidine (PCP) Amantadine Memantine</b>	<p>Antagonists at NMDA receptors.</p> <p>Ketamine and PCP cause dissociative anesthesia</p> <p>Amantadine used to treat Parkinson disease</p> <p>Memantine used to treat advanced Alzheimer disease</p>		

<b>Dopamine</b>	<p>D<sub>1</sub>, D<sub>5</sub>: ↑ adeny cyclase  D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>: ↓ adeny cyclase  Dopaminergic neurons involved in pathways that affect behavior and movement.  Prevalent in basal ganglia, nucleus accumbens, amygdala.</p>	<p>Loss of dopaminergic neurons in basal ganglia → Parkinson's  Dopamine antagonists:  ▶ effective in treating psychoses such as acute mania and schizophrenia  ▶ may cause dysphoria, catatonia in "normals"  ▶ DA antagonists are antiemetic  Dopamine agonists/potential:  ▶ Cocaine inhibits reuptake of dopamine → reinforcing effect of cocaine  ▶ Dopamine agonists often cause nausea  ▶ Newer anticonvulsants ↑ DA release</p>
<b>NE</b>	<p>Both α and β adrenoreceptors in CNS.  α<sub>1</sub>: causes depolarization due to ↓ in K<sup>+</sup> conductance, activation of adeny cyclase, and/or stimulation of phospholipase C  α<sub>2</sub>: causes hyperpolarization due to ↑ inward rectifying K<sup>+</sup> conductance.  β: ↑ adeny cyclase</p>	<p>Along with serotonin, NE-neurons regulate mood.  Depression associated with ↓ central noradrenergic activity: earlier antidepressants (tricyclics and MAO inhibitors) potentiate effects at these neurons.</p>
<b>Clonidine Dexmedetomidine</b>	<p>α<sub>2</sub> agonists. Have useful antihypertensive activity. Unlike many antihypertensives, rarely cause hypotension.  Profoundly sedating without affecting ventilatory drive.</p>	
<b>Serotonin (5 HT)</b>	<p>5-HT<sub>1</sub> receptor has at least 5 subtypes (5-HT<sub>1A</sub> → 5-HT<sub>1E</sub>): all are GPCR's linked to adeny cyclase inhibition or to K<sup>+</sup> or Ca<sup>++</sup> channels.  ↳ Associated with regulation of mood as well as pathogenesis of migraine  5-HT<sub>2</sub> receptor has at least 3 subtypes (5-HT<sub>2A</sub> → 5-HT<sub>2C</sub>): GPCR's linked to activation of phospholipase C.  5-HT<sub>3</sub> receptor is ligand-gated ion channel  5-HT<sub>4</sub> – 5-HT<sub>7</sub> are all GPCR's  Many subtypes of receptors, but only a few have specific agonists or antagonists.  5-HT receptors important in regulation of mood. Newer antidepressants are inhibitors of serotonin (&lt; NE) reuptake.</p>	<p>5-HT<sub>1</sub>:  agonists:  ▶ used to treat headaches  ▶ anxiolytic agents  5-HT<sub>2</sub>:  agonists:  ▶ cause hallucinations (LSD)  antagonists:  ▶ antipsychotic  ▶ antimigraine  5-HT<sub>3</sub>:  antagonists:  ▶ antiemetics in chemotherapy pts or pts recovering from general anesthesia</p>
<b>Opioid peptides</b>	<p>Three families of opioid peptides:  ▶ enkephalins  ▶ dynorphins  ▶ endorphins  Each family begins as large polypeptide that is cleaved.</p>	<p>Three (or four) classes of opioid receptors:  μ, κ, δ, (σ)</p>

<b>Enkephalins</b>	<p>Pentapeptides with four amino acids in common (named on basis of fifth aa).  Primarily act as NT's released from sort interneurons <b>within the spinal cord</b>  Also found in adrenal medulla and in catecholamine-containing nerve terminals.  <b>Endogenous <math>\delta</math>-opioid agonists:</b> Enkephalins (and exogenous opioids) bind to <math>\delta</math> receptors on nerve terminals containing NT's like substance P: Inhibition of substance P released may be a mechanism of opioid analgesia.  Enkephalins metabolized extremely rapidly in vivo: IV admin not useful.  Stable analogues have been synthesized, may find future use as analgesics.</p>		
<b>Dynorphins</b>	<p>Endogenous ligands at the <math>\kappa</math> receptor. Similar distribution to enkephalins.  <math>\kappa</math>-opioid receptor most prevalent opioid receptor in CNS.</p>		
<b>Endorphins</b>	<p>Endogenous <math>\mu</math>-opioid agonists.</p>		
<b>Proopiomelanocortin (POMC)</b>	<table border="0"> <tr> <td data-bbox="418 646 959 896"> <p>Contains many opioid and nonopioid peptides. Found in anterior pituitary and hypothalamus.  The final 31 aa's form <math>\beta</math>-endorphin (the most important of the humoral endogenous opioids). <math>\beta</math>-endorphin is an important endogenous ligand at the <math>\mu</math>-receptor</p> </td> <td data-bbox="992 646 1471 896"> <p>Selective cleavage of POMC yields many nonopioid hormones:  ▶ ACTH  ▶ MSH  ▶ lipotropins</p> </td> </tr> </table>	<p>Contains many opioid and nonopioid peptides. Found in anterior pituitary and hypothalamus.  The final 31 aa's form <math>\beta</math>-endorphin (the most important of the humoral endogenous opioids). <math>\beta</math>-endorphin is an important endogenous ligand at the <math>\mu</math>-receptor</p>	<p>Selective cleavage of POMC yields many nonopioid hormones:  ▶ ACTH  ▶ MSH  ▶ lipotropins</p>
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## Neurodegenerative Diseases

### Experimental or theoretical etiology of neuronal death

Toxic: 6-hydroxydopamine of MPTP

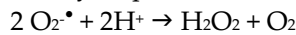
**Excitotoxicity:** Excess glutamate involving the NMDA receptor (mediates influx of calcium ions which causes neuronal death in excess)

#### ROS:

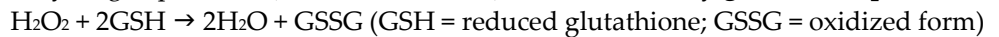
ROS can sometimes be generated when oxygen binds to heme



Normally, superoxide anion is metabolized by **superoxide dismutase (SOD)**:



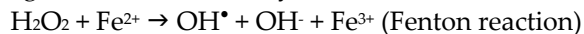
And hydrogen peroxide (which is also toxic) is metabolized by **glutathione peroxidase**



Hydrogen peroxide is also produced by MAO in neurons:

oxidation of a monoamine produces ammonia and hydrogen peroxide

If ↓ glutathione to detoxify  $\text{H}_2\text{O}_2$ , the VERY reactive hydroxyl radical is produced:



Parkinson's: may reflect loss of ability of cell to protect itself from oxygen radicals

ALS: May involve defect in SOD

### Management of Parkinson Disease

#### Parkinson disease

Four characteristics:

- 1) Bradykinesia (slowness of movement)
- 2) Rigidity
- 3) Tremor
- 4) Balance impairment

Typically begins in late middle age with resting tremor (tremor disappears with voluntary movement). About 1/3 develop dementia if they live long enough.

Parkinsonism: similar symptoms to Parkinson disease, but usually reversible. More often than not, symptoms are caused by medications. i.e. toxic effects of dopamine antagonists used to treat psychoses.

Disease due to loss of dopaminergic neurons in substantia nigra which project to caudate and putamen. Characteristics of Parkinson's are seen when loss exceeds 80%. Leads to relative excess in cholinergic neuronal activity → *therapy involves either potentiating dopaminergic activity or inhibiting cholinergic activity in the striatum.*

Drugs effective in treatment include:

- ▶ Levodopa (DA precursor)
- ▶ Dopamine agonists
- ▶ Cholinergic antagonists
- ▶ Selective MAO-inhibitors
- ▶ COMT-inhibitors
- ▶ NMDA antagonists

#### Levodopa (given w/Carbidopa)

Primary medication used to treat Parkinson disease. DA cannot be used directly because it has ↓ oral bioavailability, does not cross BBB, and is associated with significant nausea.

Levodopa is rapidly decarboxylated to dopamine by **aromatic amino acid decarboxylase**, therefore it is *almost always given in combination with an inhibitor of this enzyme such as carbidopa.*

Major problem: Patients become refractory in a few years.

AE's: N & V, hallucinations, orthostatic hypo

If abruptly stopped → **neuroleptic malignant syndrome** may result.

- PK:
- ▶ rapid-onset, short duration
  - ▶ Transported across gut epithelium and BBB by active transport system for aromatic aa's. Dietary aa's compete for both of these processes.
  - ▶ In the brain, levodopa actively taken up by presynaptic terminals of DA neurons, decarboxylated to DA, and incorporated into vesicles
  - ▶ Peak effects: 30 min – 1 hr
  - ▶ Duration of action: 4-6 hrs (several doses needed per day)
  - ▶ Wide fluctuations in effect

Just the right amount is needed:

- ▶ too little → rigidity, bradykinesia
- ▶ too much → dyskinesias

<b>Effects of dopamine excess</b>	<p><b>Dyskinesia:</b> commonly presents as <b>choreiform</b> movements (rapidly flowing, nonstereotyped, involuntary movements of body unbeknownst to patient) or <b>dystonia</b> (involuntary sustained posture, may actually occur in dopaminergic excess or deficiency)</p> <p>Nausea, hallucinations, confusion</p> <ul style="list-style-type: none"> <li>↳ antipsychotic and antiemetic medications are dopaminergic antagonists; they should NOT be used to treat toxic effects of levodopa in Parkinson pts!</li> </ul> <p>Peripheral effects of ↑ DA: orthostatic hypotension, cardiac arrhythmias. Nonselective MAO inhibitors should be stopped 2 weeks prior to starting levodopa therapy to prevent ↑↑ DA concentrations that can cause hypertensive crisis or malignant cardiac arrhythmia.</p>	
<b>Advantages of Dopaminergic agonists over Levodopa in Parkinson's</b>	<ul style="list-style-type: none"> <li>▶ No requirement for enzymatic conversion by intact neuron</li> <li>▶ Selective for certain subtypes of DA receptors</li> <li>▶ Longer duration of action</li> <li>▶ No conversion to ROS</li> </ul>	
<b>Bromocriptine</b>	<p>Dopaminergic agonist with long history of use in PD.</p> <p>D<sub>2</sub> and D<sub>3</sub> agonist and D<sub>1</sub> antagonist.</p> <p>Taken 3x/daily.</p>	<p>Shares beneficial and toxic effects of levodopa.</p> <p>Ergot derivative → can cause retroperitoneal and pulmonary fibrosis and vasospasm (avoid on Raynaud dz and other disorders of small arteries)</p>
<b>Pergolide</b>	<p>Dopaminergic agonist, very similar to bromocriptine except is an agonist at D<sub>1</sub>.</p>	
<b>Pramipexole Ropinirole</b>	<p>Dopaminergic agonists. Greater activity at D<sub>3</sub> compared to D<sub>2</sub>.</p> <p>May not have cross-refractivity.</p>	
<b>Selegiline</b>	<p>Selective inhibitor of MAO-B (the form of the enzyme present in striatum).</p> <p>↓ DA metabolism and ↓ neuronal production of hydrogen peroxide.</p> <p>No need to avoid tyramine because MAO-A (in the periphery and gut) is not inhibited.</p>	<p>Produces few AE's in early Parkinson pts.</p> <p>As dz progresses, selegiline may potentiate the adverse motor effects of levodopa.</p>
<b>Trihexyphenidyl Benztropine Diphenhydramine</b>	<p>Centrally acting muscarinic antagonists useful in parkinson dz.</p> <p>Diphenhydramine: antihistamine with antimuscarinic effects</p> <p>Primarily useful early in disease.</p>	<p>Typical anticholinergic AE's (sedation, dry mouth, urinary retention)</p>
<b>Amantadine</b>	<p>Weak antagonist at NMDA receptor, may be used in early PD.</p> <p>Used to prevent influenza A</p>	
<b>Tolcapone Entacapone</b>	<p>Inhibitors of carboxy-O-methyl transferase (COMT).</p> <p>Act by peripherally increasing half-life of levodopa (similar to carbidopa).</p>	<p>COMT inhibitors less toxic than DA agonists or muscarinic antagonists.</p> <p>Tolcapone may very rarely cause hepatic necrosis: monitor LFT's.</p> <p>Entacapone is not hepatotoxic.</p>
<b>Management of disease progression</b>	<p>No clear consensus on when to start therapy, or how to use therapy.</p> <p>As the disease progresses, it becomes far more difficult to manage.</p>	

## Management of Alzheimer Disease

**Alzheimer disease** Loss of cholinergic neurons in hippocampus and cortex (note that amnesia can be produced by centrally-acting anticholinergic such as scopolamine).

**Tacrine**  
**Donepezil**  
**Rivastigmine**  
**Galantamine** Centrally-acting AchE inhibitors. Cholinergic excess: Nausea, vomiting, diarrhea  
Small but statistically significant improvements in neuropsychiatric test scores. Improvements lasted less than a year.

**Memantine** NMDA antagonists. Approved for advanced AD.  
Note that some other NMDA antagonists produce dissociate anesthesia and hallucinations, but not this one.

**Coxibs** May ↓ risk of developing AD.  
May cause regression of plaques.  
Not known: difference in ASA vs. ibuprofen vs. naproxen, or if new COX-2 inhibitors are also effective.

## Management of ALS Disease

**Riluzole** Prevents release of neurotransmitter glutamate.  
Barely significant prolongation of survival (19 months vs. 17 months)

## Management of Huntington Disease

**Out of Luck** Can treat paranoia/depression symptoms only

## Management of Headache

**Tension headaches** usually bilateral and bifrontal/occipitonal  
"Vise clamping head"  
Most common form of headache

**Cluster headaches** A few short-lived attacks of periorbital pain per day for a few months  
Often followed by symptom-free period of many months before next episode  
80% male  
Pain begins without warning and reaches a peak within a few minutes, lasts for an hour or two  
Pain is almost always unilateral and has autonomic features (lacrimation, eye reddening, stuffiness, nausea, ptosis).  
Can be precipitated by ingestion of EtOH.

**Migraine headaches** "Classic migraine": migraine with aura  
"Common migraine": migraine w/o aura, is far more common  
Frontotemporal pay (uni- or bilateral), lasts from a few hours to days.  
F > M  
Many sufferers "grow out" of their affliction after middle age.  
Former theory: intracranial vasodilation.  
Based on observation that vasoconstrictors can alleviate pain.  
Theory is discredited but these medications are still used.  
Current theory: hereditary dysfunction of seritonerpic neural transmission. Current medications are agonsts or antagonists at specific subtypes of serotonin (5-HT) receptors.

<b>Ergot poisoning</b>	<p><math>\alpha</math>-adrenergic agonism → gangrene</p> <p>uterine stimulation → abortion</p> <p>psychosis → 5-HT agonism</p>	
<b>Ergotamine</b> <b>Dihydroergotamine</b>	<p>Relatively nonselective agonist at 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, and <math>\alpha</math>-adrenergic R's</p> <p>Usually given with Caffeine</p> <p>PO, suppository</p> <p>Dihydroergotamine may be given IV or IM for more rapid onset.</p>	<p>Nausea (can be problematic as nausea almost always accompanies migraine attack.)</p> <p>Vasoconstriction can cause:</p> <ul style="list-style-type: none"> <li>▶ Paresthesias in fingers and toes</li> <li>▶ Angina pectoris</li> </ul> <p>⚠ Should NOT be given to pregnant women, because uterine contractions may lead to miscarriage!</p>
<b>Methysergide</b>	<p>5-HT<sub>2</sub> antagonist</p> <p>In contrast to other Ergot constituents, has little vasoconstrictive or oxytocic activity.</p> <p>Ineffective in treating migraine attack; only used prophylactically.</p>	<p>Retroperitoneal, pleuropulmonary, pericardia, or endocardial fibrosis (to minimize risk, give for no more than a few months at a time with a several-week long break in between)</p>
<b>Sumatriptan</b> <b>Zolmitriptan</b> <b>Naratriptan</b> <b>Rizatriptan</b> <b>Eletriptan</b>	<p>Selective 5-HT<sub>1D</sub> agonist. Has less activity at other 5-HT<sub>1</sub> receptors and essentially no activity at other 5-HT or adrenergic receptors.</p> <p><i>Probably acts by preventing 5-HT release.</i></p> <p>The 5-HT<sub>1D</sub> receptor blocks the release of serotonin from serotonergic nerves via a presynaptic mechanism. Unknown why agonist here relates to migraine pain.</p> <p>May be given SubQ: onset in 10 min.</p> <p>Orally: onset in 30 min.</p> <p>Naratriptan: slower onset and longer duration, fewer recurrences</p> <p>Zolmitriptan/Rizatriptan: faster onset after oral admin than Sumatriptan, available in orally disintegrating tablets</p> <p>Other developments: Nasal spray</p>	<p>Should NOT be given IV! Can cause MI and death.</p> <p>Contraindicated in pts with vasospastic disease (Prinzmetal angina, Raynaud)</p> <p>Use cautiously with CAD.</p> <p>May experience general warmth or tingling</p> <p>None of the “triptan” agents should be given within a day of an ergot drug or within 2 weeks of a MAO inhibitor.</p>
<b>Management of headache</b>	<p>Tension headaches: Nonopioid analgesics such as ASA, APAP, ibuprofen. Treat anxiety or depression as appropriate.</p> <p>Cluster headaches: triptans, ergotamine, methysergide. Often respond to meds ineffective in treating migraines, such as lithium, prednisone, verapamil.</p> <p>Episodic migraine: Most effective: parenteral sumatriptan. If unresponsive to triptans, may try ergotamine.</p> <p>Prophylaxis of migraine: <math>\beta</math>-blockers, valproic acid (anticonvulsant), verapamil, tricyclics, methysergide (in progression from least → most toxic).</p>	

## Psychopharmacology: Antipsychotic, Antianxiety, Antidepressants & Mood-Stabilizing Agents

<b>Psychosis</b>	<p>Impairment of behavior and inability to think coherently, comprehend reality, or have insight into the presence of these abnormalities.</p> <p>Schizophrenia is the most common psychosis:</p> <ul style="list-style-type: none"> <li>▶ chronically disordered thinking</li> <li>▶ emotional withdrawal</li> <li>▶ delusions, ▶ auditory hallucinations</li> </ul>	<p>Common symptoms:</p> <ul style="list-style-type: none"> <li>Delusions (false beliefs)</li> <li>Hallucinations (abnormal sensations)</li> </ul>
<b>Major depression Bipolar disorder</b>	<p>Major Depression</p> <p>Approximately 10% of the population will at some point be affected by major depression. Sadness and despair, mental slowing, loss of concentration, insomnia or hypersomnia, Anorexia or overeating; ~15% of affected patients will attempt suicide</p> <p>Bipolar is much less common. Alternating mania and depression.</p>	
<b>Anxiety disorders</b>	<p>Severe and disabling symptoms, but can still comprehend reality.</p> <p>Can have large benefit with combination of psychotherapy and drug therapy</p>	
<b>Cognitive Disorders</b>	<p>Usually associated with specific neuropathological, metabolic, or toxic changes.</p> <p>Usually not amenable to successful pharmacological intervention.</p>	
<b>Personality disorders</b>	<p>Lifelong conditions characterized by certain personality styles: Drugs usually not effective (avoidant, withdrawn, paranoid, dependent).</p> <p>Can also have behavioral patterns (substance abuse, abnormal eating, hypochondriasis)</p>	
<b>Antipsychotics</b>		
<b>Overview of Antipsychotics</b>	<p>Phenothiazines: chlorpromazine</p> <p>Butyrophenones: haloperidol</p> <p>Atypical: olanzapine</p>	<p>Neuroleptic (good synonym)</p> <p>Major tranquilizer (bad synonym)</p>
<b>Chlorpromazine</b>	<p>Prototypical antipsychotic. Phenothiazine.</p> <p>Very dirty drug: competitive antagonist at:</p> <ul style="list-style-type: none"> <li>▶ D<sub>2</sub> (primary antipsychotic effect)</li> <li>▶ Muscarinic</li> <li>▶ H<sub>1</sub></li> <li>▶ α-adrenergic</li> <li>▶ 5-HT<sub>2</sub></li> </ul> <p>When given to psychotic pt: → improvement in thought disorder, fewer hallucinations &amp; delusions, reality perception improves</p> <p>When given to normal pt: → diminished behavior, can induce catatonic state w/preserved memory and consciousness.</p> <p>Antiemetic effect by blocking DA receptors in chemoreceptor trigger zone.</p> <p>May be given IM, but should rarely be given IV due to profound vasodilation.</p>	<p>anti-cholinergic AE's</p> <ul style="list-style-type: none"> <li>▶ dry mouth, blurry vision, sedation, urinary retention</li> </ul> <p>α-blockade:</p> <ul style="list-style-type: none"> <li>▶ orthostatic hypotension</li> <li>▶ nasal stuffiness</li> </ul> <p>DA blockade in basal ganglia → EPS</p> <ul style="list-style-type: none"> <li>▶ Akathisia (can't sit still)</li> <li>▶ Dystonia (contractions of face/neck)</li> <li>▶ Rigidity (parkinsonism)</li> <li>▶ Tardive dyskinesia (permanent stereotyped movements, may be paradoxically suppressed w/↑ chlorpromazine)</li> </ul> <p>Neuroleptic malignant syndrome:</p> <ul style="list-style-type: none"> <li>▶ hyperthermia (↑ muscle contractures) resembles malignant hyperthermia</li> <li>▶ stupor</li> <li>▶ ↑ CK, myoglobinemia</li> </ul> <p>↓ seizure threshold</p> <p>↑ PRL secretion (DA is released by hypothal to inhibit prolactin secretion by pituitary)</p> <ul style="list-style-type: none"> <li>▶ Cholestatic jaundice</li> </ul>

<b>Thioridazine</b> <b>Trifluoperazine</b> <b>Fluphenazine</b>	Phenothiazines. Thioridazine: ↑ anticholinergic, ↑ $\alpha$ -blockade Trifluoperazine, Fluphenazine: ↓ anticholinergic, ↑ DA blockade Fluphenazine: Available as fatty acid esters dissolved in oil (for noncompliant patient IM injection every few weeks).	Thioridazine: greater sedating and hypotensive effects vs. chlorpromazine, causes less EPS. Trifluoperazine and fluphenazine less sedating, cause fewer hypotensive effects, more EPS. ☠ Trifluoperazine may prolong QT.
<b>Haloperidol</b>	Prototype Butyrophenone. May be given IV or IM Available as fatty acid esters dissolved in oil (for noncompliant patient IM injection every few weeks).	Causes little sedation or hypotension Common EPS
<b>Clozapine</b> <b>Olanzapine</b> <b>Quetiapine</b> <b>Risperidone</b> <b>Aripiprazole</b> <b>Ziprasidone</b>	Atypical antipsychotics. Atypical because they have $\downarrow\downarrow$ DA or cholinergic antagonism. Antipsychotic activity due to 5-HT <sub>2</sub> blockade. Aripiprazole: partial agonist at both D <sub>2</sub> and 5-HT <sub>1A</sub> receptors Good $\alpha$ -antagonists: orthostatic hypotension common Some may cause significant weight gain Effectiveness: ▶ clozapine > risperidone/olanzapine ▶ clozapine is most toxic ▶ risp/ola are better than phenothiazines & butyrophenones All are orally effective. Ziprasidone and olanzapine may be given IM Risperidone: Available as fatty acid esters dissolved in oil (for noncompliant patient IM injection every few weeks).	Potent $\alpha$ -blockers → orthostatic hypotension Rare EPS Clozapine: may cause ▶ weight gain ▶ diabetes ▶ <b>seizures</b> ▶ <b>agranulocytosis (monitor WBCs)</b> Olanzapine (closely related to Clozapine): ▶ NO seizures ▶ NO agranulocytosis ▶ weight gain ▶ diabetes Risperidone: ▶ EPS @ ↑ doses ▶ weight gain Ziprasidone: ▶ rarely EPS ▶ ↑ QT Quetiapine, ziprasidone, aripiprazole: ▶ No weight gain
<b>Choice of antipsychotic</b>	Emergency use ▶ haloperidol, chlorpromazine, ziprasidone Depot formulations ▶ haloperidol, fluphenazine, risperidone Chronic use ▶ choice based on adverse effects, efficacy	
<b>Prochlorperazine</b> <b>Droperidol</b>	Classical antipsychotics marketed as antiemetics. Prochlorperazine is very similar to chlorpromazine. Available in tablets, liquid, suppository, and IM, NOT IV. Droperidol is very similar to haloperidol. Excellent antiemetic at doses below those that cause sedation. Available IM or IV injection.	Droperidol: ▶ much less likely than prochlorperazine to cause orthostatic hypotension. ▶ Rare EPS at nonsedating doses.

## Antianxiety agents

<b>Diazepam (Valium®)</b> <b>Chlordiazepoxide</b> (diazepam pro-drug) <b>Lorazepam</b> <b>Oxazepam</b> (diazepam active metabolite) <b>Alprazolam</b> <b>Clonazepam</b>	<p>Prototypical antianxiety agent. Benzodiazepine.</p> <p>Potentiates the effects of GABA (inhibitory neurotransmitter).</p> <p>Note that barbiturates and general anesthetics do NOT have an antianxiety effect despite also being able to potentiate the effects of GABA.</p> <p>Diazepam binds to benzodiazepine R that this located close to the GABA receptor and increases the affinity of the GABA R for GABA: → GABA binding ↑ Cl<sup>-</sup> conductance → hyperpolarization</p> <p>Causes pleasant sedation (in contrast to unpleasant sedation produced by antipsychotic medications).</p> <p>Excellent anticonvulsant</p> <p>Pharmacokinetics:</p> <ul style="list-style-type: none"><li>▶ rapidly absorbed</li><li>▶ 90% protein bound</li><li>▶ large V<sub>d</sub>, small clearance</li><li>▶ long half-life (20 hr)</li><li>▶ nordazepam (active metabolite): 100 hr half-life</li><li>▶ not water-soluble (IV preparation contains propylene glycol)</li><li>▶ not reliably absorbed from IM</li></ul>	<p>Anterograde amnesic effect that occurs even when patient does not appear very sleepy.</p> <p><i>Anterograde amnesia: amnesic for events occurring after drug administration.</i></p> <p><i>Retrograde administration: No drug can reliably cause this.</i></p> <p>Causes ventilatory depression but rarely apnea (but can be potentiated by other ventilatory depressants such as opioids or EtOH).</p> <p>Don't withdraw too quickly, or you may get seizures. It may take a few days to see withdrawal symptoms because active metabolite has long half-life.</p> <p>Can cause disinhibition.</p> <p>Continued therapy: ↓ sedative effect, but anxiolytic effect is preserved.</p> <p>Does NOT ↓ REM sleep (in contrast to barbiturates and EtOH), but it does ↓ stage 4 sleep and ↑ overall sleep time.</p> <p>AE's: mostly extension of effects, rarely fatal</p> <ul style="list-style-type: none"><li>▶ sedation</li><li>▶ ataxia</li><li>▶ ventilatory depression</li></ul>
<b>Alprazolam (Xanax®)</b>	<p>Has four rings in contrast to typical benzodiazepine's three rings.</p> <p>Useful in panic disorder and agoraphobia</p>	
<b>Clonazepam (Klonopin®)</b>	<p>Primarily used as anticonvulsant Also useful in panic disorder</p> <p>Least likely to result in breakthrough anxiety between doses, only needs to be taken 2x/day</p> <p>Less of addictive rush associated with diazepam.</p>	
<b>Buspirone (Buspar®)</b>	<p>5-HT<sub>1A</sub> partial agonist, little activity at DA or GABA receptors. Not a benzodiazepine.</p> <p>Does not cause sedation or have anticonvulsant effect.</p> <p>No tolerance: no cross-tolerance with benzodiazepines or other CNS depressants</p> <p>Less anxiolytic effect than diazepam, not effective in panic attacks</p> <p>Useful in people who have abused benzodiazepines → little abuse potential</p>	
<b>Flumazenil (Romazicon®)</b>	<p>Competitive antagonist of benzodiazepines, used to treat overdoses.</p> <p>Not without its own problems, only use in UNSAFE benzodiazepine overdose.</p> <p>Shorter-acting than benzodiazepines, may need repeated dosing to reverse benzos.</p>	<p>May produce a state of extreme agitation.</p>

## Mood-Disorders

<b>Tricyclic Antidepressants</b>	<p>inhibit NE reuptake</p> <p>Tertiary: <b>amitriptyline</b> is prototype; very sedating, significant anticholinergic effects</p> <p>Secondary: <b>desipramine</b> is prototype; less sedating; fewer anticholinergic effects</p>	
<b>Amitriptyline (Elavil®)</b> <b>Imipramine (Tofranil®)</b> <b>Clomipramine (Anafranil®)</b> <b>Doxepin (Sinequan®)</b>	<p>Prototypical <b>tertiary</b> tricyclic antidepressant.</p> <p>Inhibits the reuptake of NE and Serotonin</p> <p>Has both central and peripheral anticholinergic effects.</p> <p>When given to “normal” people, no ↑ in mood.</p> <p>When given to person with depression, ↑ mood <b>after a few weeks</b> (lag time)</p> <p>Tolerance develops to sedating effects, but not to antidepressant effects.</p> <p>Facilitates both falling and staying asleep (insomnia and early awaking are symptoms of depression).</p> <p>Sleep is less physiological: ↑ stage-4 sleep, ↓ REM sleep</p> <p>Fatal dose is 1-2 week’s supply (many depressed people have killed themselves this way: 4<sup>th</sup> leading cause of drug-induced death)</p>	<p>Sedation, difficulty concentrating (unpleasant).</p> <p>Prominent anticholinergic effects: dry mouth &amp; blurred vision.</p> <p>Orthostatic hypotension (<math>\alpha</math> blockade)</p> <p>↓ seizure threshold, may ↑ freq of seizures in epileptics, but little danger in non-epileptics</p> <p>Some depressed patients will go “beyond” normal and become manic (more likely w/bipolar)</p> <p>Weight gain</p> <p>ECG Δ’s:</p> <ul style="list-style-type: none"> <li>↑ HR (atropine-like effect)</li> <li>↑ conduction time; ↓ contractility</li> <li>flattening or inversion of T waves</li> <li>⚠ beware in pts on Class I antiarrhythmics!</li> <li>⚠ overdosing is often fatal! → ventricular arrhythmias!</li> <li>larger dose → slower absorption</li> <li>⚡ Lidocaine is antiarrhythmic of choice</li> </ul>
<b>Desipramine (Norpramin®)</b> <b>Nortriptyline (Pamelor®)</b>	<p>Desipramine: prototypical <b>secondary</b> tricyclic</p> <p>Similar effects on cardiac conduction and may be lethal in overdose</p>	<p>Causes much less sedation than amitriptyline as well as fewer anticholinergic AE’s and less weight gain</p>
<b>Trazodone (Desyrel®)</b> <b>Nefazodone (Serzone®)</b>	<p>Atypical antidepressants.</p> <p>Do not have typical tricyclic structure.</p>	<p>Very sedating but have little anticholinergic activity and minimal effects on cardiac conduction</p>
<b>Bupropion (Wellbutrin®)</b> <b>Zyban® (controlled release)</b>	<p>Atypical antidepressant.</p> <p>Useful in diminishing symptoms of nicotine withdrawal.</p>	<p>Lack of sedative, anticholinergic, orthostatic, and cardiac conduction effects</p> <p>↓↓ seizure threshold more than any other antidepressant.</p>
<b>Fluoxetine (Prozac®)</b> <b>Citalopram (Celexa®)</b> <b>Escitalopram (Lexapro®)</b> <b>Paroxetine (Paxil®)</b> <b>Venlafaxine (Effexor®)</b> <b>Sertraline (Zoloft®)</b> <b>Fluvoxamine (Luvox®)</b>	<p>Selective serotonin reuptake inhibitors (SSRI)</p> <p>Very safe, lack of typical antidepressant adverse effects, very safe even in OD.</p> <p>Sometimes prescribed to “normals”</p> <p>Escitalopram is active isomer of citalopram.</p> <p>Fluoxetine, paroxetine, sertraline also used to treat panic attacks and OCD</p> <p>Fluvoxamine is used primarily for OCD</p> <p>Fluoxetine only SSRI approved for use in children (depression &amp; OCD)</p>	<p><i>Cause no sedation, anticholinergic, orthostatic, or cardiac conduction effects</i></p> <p><i>Do not promote weight gain</i></p> <p><i>Do not affect seizure threshold</i></p> <p>Mild AE’s: headache, nausea, nervousness, insomnia, fatigue, impotence. EPS may occur (TD very rare). Most inhibit P450.</p> <p>Questions about suicide risk. May show 2x increase in risk of attempt. Controversial.</p> <p>May cause mania (probably underlying bipolar)</p>

<b>Isocarboxazid (Marplan®)</b> <b>Phenelzine (Nardil®)</b> <b>Tranylcypromine (Parnate®)</b>	<p>Monoamine oxidase inhibitors (MAOI).  Nonspecific: inhibit both MAO-A (gut) &amp; MAO-B (brain)  First class of medications used to treat depression  Today not used as first-line therapy (reserved for pts who do not respond to other meds).  Note that the selective MAO-B inhibitor Selegiline far less likely to be involved in significant drug interactions.</p>	<p>Potentially dangerous because of large number of drug interactions and potential for many of these interactions to be fatal.  ⚠ Must avoid tyramine → hypertensive crisis!  ⚠ Must avoid the opioid <b>Meperidine</b> (Libby Zion): If MAO is inhibited, meperidine metabolite may cause hyperpyrexia &amp; seizures.</p>
<b>Lithium</b> <b>Lithium carbonate (Eskalith CR®)</b> <b>Lihobid®)</b> Lithium citrate syrup	<p>Primary medication used in bipolar disorder.  Alkali metal, similar chemistry to Na<sup>+</sup> and K<sup>+</sup>.  No known physiological function.  At therapeutic concentrations, Li<sup>+</sup> ↑ release of NE and DA (but not Serotonin) from nerve terminals in response to AP.  Note that persons with bipolar disorder usually managed differently than those persons whose illness is manifested by depressive symptoms.  PK:  ▶ Well absorbed from GI tract  ▶ not bound to plasma proteins  ▶ distributed throughout total body water  ▶ completely excreted in urine  ▶ terminal half-life about 1 day  ▶ hyponatremia markedly ↓ Li<sup>+</sup> excretion (prolonged effect w/renal impairment)</p>	<p>Significant toxicity @ 2x therapeutic concentration: must closely monitor plasma Li ion concentration.  Therapeutic doses cause thirst, weight gain, drowsiness, T-wave flattening  Mild toxicity: nausea, vomiting, abdominal pain and diarrhea sedation, tremor.  Severe toxicity: hyperreflexic w/ CN and other focal neurological signs., <b>Nephrogenic DI</b>, can cause permanent renal damage.  Deadly intoxication: seizures, coma, death. If pt survives, may be followed by permanent neurological impairment.  Lithium intoxication treated with dialysis.  Watch for drug interactions: Anything that changes urine flow or ion concentrations can interact with lithium!</p>
<b>Management of acute mania and bipolar disorder</b>	<p>Acute mania:  ▶ neuroleptic and/or sedative  ▶ Several days are required for achieving a stable plasma lithium concentration  Chronic bipolar disorder  ▶ Anticonvulsant in combination with lithium → lower doses of Li<sup>+</sup> required.  ▶ carbamazepine OR valproic acid  ▶ Lithium  Some patients, whose bipolar disorder is PRIMARILY depressive, may respond best to antidepressant (even though label says not to use in bipolar disorder).  More recently, some psychiatrists have used carbamazepine or valproic acid as first-line therapy in bipolar disorder: Li<sup>+</sup> rarely used these days as sole med in bipolar.  After a first manic episode, drug therapy usually continued for 6-12 mo after normalization of mood.</p>	

## Sedatives and Hypnotics

### Sedative

A medication to produce sleepiness. Most have other features.

Benzodiazepines commonly used as preoperative sedatives because they ↓ anxiety and produce amnesia

Opioids commonly used as sedatives during noxious procedures because they produce analgesia + sedation.

Characteristics of an ideal medication used to facilitate sleep:

- ▶ rapid onset of action
- ▶ duration long enough to permit a normal night's rest
- ▶ not too long a duration to cause hangover
- ▶ cause minimal Δ's in pattern of various stages of sleep
- ▶ produce no tolerance nor physical dependence
- ▶ be safe in large overdose
- ▶ produce no adverse psychological effects (like amnesia)

### Hypnotic

Medication to produce unconsciousness (or a state resembling sleep from which the patient cannot be aroused).

Often a single med is both sedative and hypnotic depending on the dose (↓ dose for sedative).

Many sedative/hypnotics have other functionality.

- ▶ benzodiazepines: antianxiety, anticonvulsant
- ▶ barbiturates: anticonvulsants, general anesthetic agents
- ▶ H<sub>1</sub> antagonists used to treat allergic disorders

### Triazolam (Halcion<sup>®</sup>) Oxazepam (Serax<sup>®</sup>) Estazolam (ProSom<sup>®</sup>)

Benzodiazepines. Relatively safe sedatives.

These benzodiazepines have rapid onset, short duration, and no active mets → suitable for use as sleep aids.

Characteristics of benzodiazepine sleep:

- ▶ ↓ stage 0 sleep (time required to fall asleep = latency)
  - ▶ ↓ time spent in stages 3 and 4
  - ▶ ↑ time spent in stage 2
  - ▶ ↓ time in REM, but ↑ # REM cycles
- overall, these alterations in pattern of sleep are not disruptive. Persons usually awaken refreshed. Pretty physiologic.

Tolerance and dependence develop

Amnesia is prominent side effect

Agent chosen on basis of kinetics

Note that some benzodiazepines that are FDA-approved for nighttime sedation are too slow in onset and too long in duration to be useful:

- ▶ Flurazepam (Dalmane<sup>®</sup>)
- ▶ Quazepam (Doral<sup>®</sup>)

### Midazolam (Versed<sup>®</sup>)

Midazolam is the only water-soluble benzodiazepine → available as IM. Very short duration of action, no metabolites.

- ▶ used for noxious procedures & preoperative sedation

Midazolam: significant ventilatory depression in combination with opioids!

### Zolpidem (Ambien<sup>®</sup>) Zaleplon (Sonata<sup>®</sup>) Eszopiclone (Lunesta<sup>®</sup>)

Benzodiazepine agonists that are used for nighttime sedation. EXPENSIVE!

Not structurally in benzodiazepine class. Bind near benzodiazepine receptor.

Similar pharmacological effects to triazolam, but produce less tolerance, less amnesia.

Triazolam and oxazepam available as generics (much less expensive than zolpidem, zaleplon, eszopiclone).

Eszopiclone is approved for long-term treatment of insomnia.

### Dose-dependent kinetics of benzodiazepines and benzodiazepine agonists

With ↑ dose → ↑ (more rapid) onset, ↑ (longer) duration

If dose is too low, pt may awaken early and have daytime anxiety the following day & rebound insomnia the following night

If dose is too high, pt may have daytime sedation & motor impairment.

<b>Thiopental (Pentothal<sup>®</sup>)</b> <b>Methohexital (Brevital<sup>®</sup>)</b>	Short-acting barbiturates. Used primarily as general anesthetics	
<b>Phenobarbital (Luminal<sup>®</sup>)</b>	Long-acting barbiturate, used primarily as anticonvulsant.	
<b>Pentobarbital (Nembutal<sup>®</sup>)</b> <b>Secobarbital (Seconal<sup>®</sup>)</b>	Intermediate-acting barbiturates. Before the introduction of the benzodiazepines, were used as nighttime sedatives.	Rarely used these days for that reason due to excessive duration of action, ↓↓ REM, and danger of overdose. ⚠ But may be used in pregnant women: 50 year safety record
<b>Diphenhydramine</b> <b>(Benadryl<sup>®</sup>)</b> <b>(Sominex<sup>®</sup>)</b>	Antihistamines (H <sub>1</sub> agonists) are very safe sedatives, available without a prescription. ↓ REM sleep Does NOT produce ventilatory depression Do not produce physiologic sleep.	
<b>Ethanol</b>	Lousy sedative. Rapid onset of CNS depression followed by CNS excitation	Rapid onset of sleep → very early awakening ↓ REM

## Anticonvulsants

### Partial seizures

Begins in discrete site in cortex. Three types.

- 1) **Simple partial:** preservation of consciousness, rhythmic contraction of muscle(s)
- 2) **Complex partial:** impairment of consciousness, rhythmic contraction of muscle(s) or complex behavior. Also called psychomotor or temporal lobe epilepsy.
- 3) **Partial with generalized tonic-clonic:** begin as simple or complex partial and evolve into generalized tonic-clonic

### Generalized seizures

Begins in both cerebral hemispheres from the outset. Three types.

- 1) **Absence**
- 2) **Myoclonic:** brief, jolt-like contraction of muscle or many muscles. *Consciousness preserved.*
- 3) **Tonic-clonic (grand mal):** *loss of consciousness*; alternating period of sustained muscle contractions ( $\uparrow$  muscle tone) and clonus (alternating contraction and relaxation of muscles). Post ictal phase lasts minutes  $\rightarrow$  hours.

### Phenobarbital (Luminal<sup>®</sup>)

Barbiturate. Highest ratio of anticonvulsant efficacy to sedation. Tolerance develops to sedating effect but not to anticonvulsant effect. Often used less in children (irritability & hyperactivity in younger patients).

First medication to be used in seizures, still in use today

PK: Slow onset after oral administration and long half-life of several days.

Effective in generalized tonic-clonic seizures and partial seizures.

Induces synthesis of microsomal enzymes (P450 and glucuronyl transferase)  
 $\rightarrow$   $\uparrow$  metabolism of many drugs

Induces synthesis of heme biosynthesis  $\rightarrow$  contraindicated in porphyria

### Phenytoin (Dilantin<sup>®</sup>)

Does not produce generalized depression of CNS (as does phenobarbital); is not sedating.

Given for seizure prophylaxis, not for acute seizures.

Causes a slowing in the rate of recovery of Na<sup>+</sup> channels.

PK:  $\blacktriangleright$  Oral administration.

$\blacktriangleright$  Slow and variable absorption.

$\blacktriangleright$  Differences in bioavailability in preparations from different manufacturers.

$\blacktriangleright$  Should not be given IM or SubQ  
 $\rightarrow$  precipitates in interstitial fluid.

$\blacktriangleright$  Half life of one to a few days

$\blacktriangleright$  *extensively metabolized* to inactive products

$\blacktriangleright$  Extensively bound to plasma proteins  
 $\rightarrow$  drug interactions if displaced from albumin

Effective in generalized tonic-clonic seizures and partial seizures.

Also useful in chronic pain syndromes and as antiarrhythmic (Class Ib)

$\otimes$  If given IV, must be given slowly because high blood concentrations cause cardiac arrhythmias  $\rightarrow$  CV collapse.

Acute overdose: arrhythmias, hypotension, CNS depression

Chronic therapy:

$\blacktriangleright$  ataxia

$\blacktriangleright$  gingival hyperplasia

$\blacktriangleright$  hirsutism in females

$\blacktriangleright$  BM suppression

Small therapeutic index

MANY DRUG INTERACTIONS

Can interfere with folate absorption  
 $\rightarrow$  macrocytic anemia

<b>Primidone (Mysoline®)</b>	Prodrug metabolized to phenobarbital, but more rapidly and completely absorbed after oral administration.	
<b>Carbamezepine (Tegretol®)</b>	<p>Chemically similar to tricyclic antidepressants, but has an effect on Na<sup>+</sup> channels like phenytoin. Metabolized by P450 epoxidation of central ring and this epoxide metabolite is both stable and as active as the parent drug.</p> <p>PK: ▶ Oral administration. ▶ Slow and variable absorption ▶ in chronic therapy, half-life 16 hrs ▶ induces its own metabolism</p> <p>Useful in generalized tonic-clonic seizures and simple and complex partial seizures.</p> <p>Also used in neuropathic pain (trigeminal neuralgia and pain of tabes dorsales)</p> <p>Useful in bipolar disorder, especially in persons unresponsive to Li<sup>+</sup>.</p>	<p>Sedation, ataxia, vertigo, blurred vision (tolerance develops to these effects)</p> <p>Occasionally:</p> <ul style="list-style-type: none"> <li>▶ ↓ in release of ADH</li> <li>▶ BM suppression</li> <li>▶ Stevens-Johnson syndrome immune-mediated skin exfoliation; must be managed as 3<sup>rd</sup> degree burn</li> <li>▶ Hepatic failure</li> </ul> <p>Acute overdose: coma and ventilatory depression.</p>
<b>Oxcarbazepine (Trileptal®)</b>	<p>Similar to carbamazepin, but fewer adverse effects.</p> <p>Approved as single-agent therapy and in addition to other meds for partial seizures. But can probably replace Carbamezepine.</p>	No cases of Stevens-Johnson syndrome, BM suppression, nor hepatic failure have been reported
<b>Ethosuximide (Zarontin®)</b>	<p>Narrow spectrum: Selective for absence seizures (drug of choice)</p> <p>Commonly used in children.</p> <p>Anticonvulsant action due to antagonism of low-threshold Ca<sup>2+</sup> currents in thalamus.</p> <p>PK: ▶ well absorbed after oral administration ▶ half life about 3-5 days</p>	<p>CNS (sedation, dizziness, headache) → tolerance develops to these AE's</p> <p>GI (nausea, vomiting, anorexia)</p> <p>Hypersensitivity (urticaria, *Stevens-Johnson, SLE, *BM suppression)</p> <p>* very rare</p>
<b>Valproic acid (Depakene®)</b>	<p>Simple molecule accidentally discovered to have anticonvulsant properties. Originally used as solubilizing vehicle for other anticonvulsants</p> <p>Effects on Na<sup>+</sup> channels similar to phenytoin</p> <p>Effects on Ca<sup>2+</sup> channels similar to ethosuximide.</p> <p>PK: ▶ oral administration ▶ rapid and complete absorption ▶ metabolized by glucuronidation and FA hydroxylases in mitochondria</p> <p>Effective against all types of seizures: Broadest spectrum</p> <p>Very effective in bipolar disorder. Many psychiatrists prefer it to Li<sup>+</sup> as first-line drug.</p> <p>Also approved for prophylaxis of migraine</p>	<p>Hepatotoxicity! (up to 50% will have asymptomatic ↑ LFT's)</p> <p>1/10,000 fulminant hepatic necrosis: babies and young children taking multiple meds are at greatest risk</p> <p>Nausea, anorexia, occasionally sedation and ataxia.</p>

<b>Clonazepam (Klonopin®)</b>	Benzodiazepine. Effective against many types of seizures except generalized tonic-clonic seizures: simple partial, complex partial, absence, myoclonic. In contrast to other anti-convulsants, as tolerance develops to sedating and ataxic effects of clonazepam, anticonvulsant efficacy also decreases (over 6 months). One of the most effective treatments for panic disorder.	
<b>Diazepam</b>	one of the drugs of choice for status epilepticus	
<b>Gabapentin (Neurontin®)</b>	Derivative of GABA, designed as GABA agonist; does not bind to GABA receptors. ↑ release of GABA from nerve terminals PK: ▶ Rapidly absorbed after oral admin ▶ excreted unchanged ▶ short half life of 7 hours Partial seizures (only approved w/ others) Also useful in neuropathic pain syndromes.	Minimal toxicity, no important interactions. Sedation or ataxia, but tolerance to these effects develops over a few weeks
<b>Other Anticonvulsants</b>	Just know that they are used for partial seizures w/other meds. Maybe know what's in bold. Primarily second line therapy.	
<b>Lamotrigine (Lamictal®)</b>	<b>Inhibits Na<sup>+</sup> channels like phenytoin.</b> Well absorbed after oral admin, half life about a day	sedation, dizziness, ataxia
<b>Topiramate (Topamax®)</b>	<b>Inhibits Na<sup>+</sup> channels and potentiates GABA at its receptor</b> Also approved for prophylaxis of migraine & chronic pain	Cognitive impairment
<b>Tiagabine (Gabitril®)</b>	<b>Inhibits GABA reuptake</b>	sedation, ataxia, cognitive impairment
<b>Levetiracetam (Keppra®)</b>	Unique/obscure MOA	Sedation, ataxia Agitation, depression, psychosis
<b>Zonisamide (Zonegran®)</b>	<b>Blocks Na<sup>+</sup> channels and Ca<sup>++</sup> channels and ↑ release of DA and Serotonin</b> Inhibits carbonic anhydrase → ↑ risk of stones	Sedation, ataxia, nausea, anorexia, cognitive impairment, psychosis Renal stones

### Management of Epilepsy

Initially, begin therapy with a single drug and search for structural lesion. Slowly increase dose. If drug doesn't work, switch to different drug.

Plasma concentration doesn't necessarily correlate with effectiveness, but it does relate to toxicity.

Drugs should be tapered to avoid status epilepticus

Most common cause of drug failure: noncompliance

Risk factors for recurrence of seizures:

- ▶ positive FHx
- ▶ requirement for more than one med
- ▶ post-childhood onset of epilepsy
- ▶ EEG abnormalities during therapy

Most anticonvulsants are teratogenic in animals. Recurrent seizures are also harmful to both mother and fetus.

The therapeutic goal of status epilepticus is to end abnormal electrical activity as quickly as possible: medical emergency, can have permanent injury

- ▶ diazepam or thiopental IV → often causes apnea, hypotension

## Opioids

<b>Definition of Opioid</b>	Natural or synthetic compound that has agonist or antagonist activity at the receptors to which morphine binds	
<b>μ Opioid Receptor</b>	give enough full μ agonist and you can make anyone apneic	μ1: supraspinal analgesia, sedation μ2: spinal analgesia, ventilatory depression
<b>κ Opioid Receptor</b>	κ agonists tend to produce analgesia not as high in efficacy as μ agonists, and even a large OD won't cause apnea	κ1: spinal analgesia κ3: supraspinal analgesia, ventilatory depression, sedation
<b>δ Opioid Receptor</b>	no drugs yet	δ: spinal analgesia
<b>σ Opioid Receptor</b>	Agonists: dysphoric & hallucinogenic: pentazocine, ketamine, PCP	Better to call it "phencyclidine receptor" phencyclidine = PCP
<b>Opioid Effects</b>	<ul style="list-style-type: none"> <li>▶ Analgesia <ul style="list-style-type: none"> <li>▶ ↓ SC transmission of pain</li> <li>▶ ↓ cortex response to pain</li> <li>▶ full agonists VERY effective (but at cost of severe ventilatory depression)</li> <li>▶ constant, prolonged pain better relieved than sharp, intermittent pain</li> <li>▶ neuropathic pain doesn't respond well</li> </ul> </li> <li>▶ Sedation <ul style="list-style-type: none"> <li>▶ pleasant drowsiness, ↓ concentration, little amnesia</li> <li>▶ anxiolysis only if etiology of anxiety is pain or fear of pain</li> <li>▶ occasional dysphoria</li> </ul> </li> <li>▶ Ventilatory Depression PRODUCED BY ALL AGONISTS <ul style="list-style-type: none"> <li>▶ ↓ response to CO<sub>2</sub> in medulla <ul style="list-style-type: none"> <li>▶ setpoint to CO<sub>2</sub> increased</li> <li>▶ don't measure ventilatory RATE to check for ventilatory depression → measure PO<sub>2</sub></li> </ul> </li> <li>▶ Dose-response: <ul style="list-style-type: none"> <li>▶ low dose: ↓ RR +/- TV; high dose: ↓ TV; highest dose: apnea</li> </ul> </li> <li>▶ effect potentiated by other CNS depressants</li> <li>▶ depth of sedation poor indicator of ventilatory drive</li> <li>▶ equianalgesic doses of agonists produce equivalent degrees of ventilatory depression</li> </ul> </li> <li>▶ Tolerance <ul style="list-style-type: none"> <li>▶ ↓ in apparent duration and intensity of effect, can be overcome by ↑ dose</li> <li>▶ cross-tolerance to other opioids</li> <li>▶ develops primary to depressant effects (analgesia, vent depression, euphoria)</li> <li>▶ little/no tolerance to stimulant effects (miosis, ↓ GI motility, ↑ GI sphincter)</li> <li>▶ physical dependence, withdrawal syndrome <ul style="list-style-type: none"> <li>▶ uncomfortable, NOT life threatening; withdrawal does NOT involve seizures</li> </ul> </li> </ul> </li> <li>▶ Other opioid effects <ul style="list-style-type: none"> <li>▶ cough suppression: dextromethorphan is the D isomer of morphine; NOT analgesic</li> <li>▶ miosis: effect @ Edinger-Westphal nucleus. Doesn't take very much to get pinpoint.</li> <li>▶ nausea, vomiting, bradycardia, vasodilation</li> <li>▶ GI smooth muscle spasm (CONSTIPATION), histamine release (NOT allergic!)</li> </ul> </li> </ul>	
<b>Morphine</b>	<ul style="list-style-type: none"> <li>▶ slow onset, long duration. It's actually pumped out of CNS (nearly) as fast as it comes in.</li> <li>▶ ↓ oral bioavailability, ↑ first pass effect</li> <li>▶ metabolized to 3- and 6-glucuronides <ul style="list-style-type: none"> <li>▶ Morphine-6-glucuronide is active and more potent than parent compound</li> </ul> </li> <li>▶ Significant histamine release</li> </ul>	

<b>Codeine</b>	<ul style="list-style-type: none"> <li>▶ Inactive pro-drug of morphine</li> <li>▶ requires 3-O-demethylation by 2D6 2D6 has the greatest degree of polymorphism of any CYP enzymes: about 10% of caucasians 2D6 deficient</li> <li>▶ usually given orally in combination with acetaminophen</li> </ul>	
<b>Meperidine</b>	<ul style="list-style-type: none"> <li>▶ Don't use it, there are almost always better alternatives (but useful for shivering)</li> <li>▶ much faster onset than morphine after injection</li> <li>▶ shorter duration than morphine</li> <li>▶ metabolized to normeperidine, a CNS stimulant</li> </ul>	<ul style="list-style-type: none"> <li>▶ NORmeperidine toxicity likely (normeperidine has a slower half-life, so even though meperidine levels could be OK, normeperidine levels would keep rising)</li> <li>▶ MAOI therapy</li> <li>▶ renal failure</li> <li>▶ chronic, high-dose therapy</li> </ul>
<b>Methadone</b>	<ul style="list-style-type: none"> <li>▶ ↑↑ oral bioavailability</li> <li>▶ first dose: kinetics similar to morphine. But repeated doses result in longer half-life</li> <li>▶ steady state: long duration, possibly once daily dosing</li> <li>▶ minimal euphoria, "rush"</li> <li>▶ often used for withdrawal prophylaxis</li> </ul>	
<b>Hydromorphone</b>	<ul style="list-style-type: none"> <li>▶ 2 advantages over morphine: <ul style="list-style-type: none"> <li>▶ faster onset than morphine</li> <li>▶ no histamine release</li> </ul> </li> <li>▶ Commonly used as morphine substitute</li> </ul>	Beware: 8x more potent than morphine: FAR too easy to OD a patient
<b>Oxycodone</b>	<ul style="list-style-type: none"> <li>▶ high oral bioavailability</li> <li>▶ often given in combination with acetaminophen</li> <li>▶ long-acting oral preparation for chronic pain</li> </ul>	
<b>Fentanyl</b>	<ul style="list-style-type: none"> <li>▶ <b>very rapid onset after injection</b></li> <li>▶ short duration due to redistribution</li> <li>▶ used for acute pain or noxious procedures</li> <li>▶ patch available for chronic pain: but DO NOT USE patch for acute pain, since it takes 4 or 5 days to reach stable half life → by then the acute pain may be gone and you get an imbalance in the pain:ventilatory depression ratio.</li> </ul>	
<b>Nalbuphine Butorphanol</b>	<ul style="list-style-type: none"> <li>▶ μ antagonists, κ partial agonists</li> <li>▶ very sedating</li> <li>▶ ceiling effect for analgesia &amp; ventilatory depression: even large doses don't cause apnea or significant pain relief</li> <li>▶ can be used for analgesia in labor</li> </ul>	<ul style="list-style-type: none"> <li>▶ May cause withdrawal in tolerant persons</li> <li>▶ little abuse potential</li> </ul>
<b>Buprenorphine</b>	<ul style="list-style-type: none"> <li>▶ Used in chronic management of previous abusers.</li> <li>▶ μ-opioid partial agonist</li> <li>▶ tight binding, slow dissociation → therefore no rush if heroin is injected</li> </ul>	<ul style="list-style-type: none"> <li>▶ May cause withdrawal in tolerant persons only (but not in nontolerant people)</li> <li>▶ little abuse potential</li> </ul>
<b>Naloxone</b>	<ul style="list-style-type: none"> <li>▶ ANTAGONIST at μ, κ, δ receptors</li> <li>▶ Competitive antagonist (surmountable)</li> <li>▶ Rapid onset, short duration</li> </ul>	<ul style="list-style-type: none"> <li>▶ Almost no effect in people with no pain and no opiates in blood</li> <li>▶ Can result in severe pain and ↑↑ HR in a person with pain</li> </ul>

## Local Anesthetics (starred drugs (\*) = one of the "big three")

<b>Old axon research</b>	charged ( $R_3N^+H$ ) form active	uncharged ( $R_3N$ ) form crosses membrane
<b>Local Anesthetic Blockade</b>	<p><math>Na^+</math> channel is a tetramer (4 subunits). Local anesthetics bind to <math>Na^+</math> channel in open state (all 4 subunits rotated to "open" position). Blockage <math>\uparrow</math> by more positive resting potential or higher stimulation frequency (active nerve blocked more readily – in practice this is just theoretical since patients keep their limb/whatever still).</p> <p>In general, smaller fibers easier to block than larger ones. Myelinated are easier to block than unmyelinated (only node of Ranvier needs to be blocked) Small unmyelinated fibers (C) overall are easier to block than large myelinated fibers (A<math>\delta</math>).</p> <p>Order of onset of blockade:</p> <ul style="list-style-type: none"><li>▶ first: sympathetics <math>\rightarrow</math> vasodilation (can block with just low concentration of anesthetic)</li><li>▶ second: pain, temperature (can block with intermediate concentration of anesthetic)</li><li>▶ last: motor, proprioception (need high concentration of anesthetic to block)</li></ul> <p>Offset in reverse order</p>	
<b>Procaine</b>	▶ Ester class of local anesthetics	▶ Metabolized to PABA (can be allergenic)
<b>* Lidocaine</b>	<ul style="list-style-type: none"><li>▶ Essentially no one is allergic (2 documented cases in history of mankind)</li><li>▶ most commonly used local anesthetic</li><li>▶ fast onset, short duration</li><li>▶ low toxicity: relatively safe even with accidental IV admin</li><li>▶ versatile</li></ul>	
<b>* Bupivacaine</b>	<ul style="list-style-type: none"><li>▶ amide local anesthetic</li><li>▶ relatively lipid soluble<ul style="list-style-type: none"><li>▶ <math>\uparrow</math> toxicity</li><li>▶ long duration, slow onset</li><li><math>\rightarrow</math> no one has yet separated <math>\uparrow</math> toxicity from long duration</li></ul></li><li>▶ very slow dissociation from sodium channel</li><li>▶ versatile<ul style="list-style-type: none"><li>▶ local infiltration</li><li>▶ nerve, plexus block</li><li>▶ spinal, epidural block</li></ul></li></ul>	▶ Toxic!
<b>* Mepivacaine</b>	<ul style="list-style-type: none"><li>▶ fast onset (as fast as lidocaine)</li><li>▶ intermediate duration</li><li>▶ low toxicity (like lidocaine)</li><li>▶ uses<ul style="list-style-type: none"><li>▶ local infiltration</li><li>▶ nerve, plexus block</li><li>▶ epidural block (not spinal)</li></ul></li></ul>	
<b>Tetracaine</b>	<ul style="list-style-type: none"><li>▶ slow onset, very long duration</li><li>▶ only used in spinal anesthesia</li><li>▶ systemic toxicity rare since spinal doses are small</li></ul>	▶ MOST TOXIC

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**Comparison of Duration & Toxicity of lidocaine, mepivacaine, bupivacaine, tetracaine**

Duration:  
lidocaine (quickest) < mepivacaine < bupivacaine < tetracaine (longest)  
Toxicity:  
lidocaine ≈ mepivacaine (least toxic) << bupivacaine < tetracaine (most toxic)

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**Proparacaine**

- ▶ Only used for topical anesthesia of the cornea
  - ▶ causes less corneal pitting and erosion than other agents (cocaine and lidocaine cause pitting and erosion of corneal epithelium)
  - ▶ high risk for abuse in ocular pain syndromes → eye pain physiologically important! NEVER appropriate to write prescription
  - ▶ Uses:
    - ▶ measurement of IOP
    - ▶ foreign body removal
    - ▶ ocular surgery
- 

**Benzocaine**

- ▶ lacks aminoester moiety
  - ▶ topical application only
  - ▶ useful for bronchoscopy or esophageal endoscopy
- 

**Local Anesthetic Toxicity**

- CNS:
- ▶ initial effect is excitation: restlessness, tremor, visual changes (auras), seizures
    - ▶ similar to cocaine (word on the street is that most blow is lidocaine)
  - ▶ later effect is inhibition (apnea, hypotension)
- CV:
- ▶ ↓ excitability, conduction velocity, contractile force
  - ▶ ventricular fibrillation → asystole, especially bupivacaine → does not respond to antiarrhythmics or cardioversion. Treat with CPR for a very long time
  - ▶ Hypersensitivity
    - ▶ common with esters, rare with amides, basically unknown with lidocaine
    - ▶ esters metabolized to PABA
    - ▶ amide solutions may contain:
      - ▶ preservatives (similar to PABA)
      - ▶ epinephrine (may cause symptoms)
- 

**Technique: Local Infiltration**

- ▶ Most common technique
  - ▶ local anesthetic solution injected into the skin in area to be numbed
  - ▶ dilute solution used (motor block not needed)
  - ▶ solution usually contains EPI to prolong duration & prevent toxicity through venous infiltration
    - ▶ EXCEPTIONS: fingers, toes, ears, nose, penis → endarteries w/o collaterals!!
- Advantages:
- ▶ No anatomical knowledge required
- Disadvantages:
- ▶ Difficult to anesthetize large areas
  - ▶ Difficult to anesthetize infected areas
    - ▶ infected tissue has ↓ pH
    - ▶ bugs can metabolize anesthetic
  - ▶ Difficult to anesthetize certain tissues (i.e. can't anesthetize peritoneum with local injection into stomach)
- 

**Technique: Peripheral nerve block**

- ▶ local anesthetic solution injected near peripheral nerve
- ▶ can use several techniques to localize:
  - ▶ near another landmark (i.e. near artery if pt has good pulse)
  - ▶ deliberate paresthesia: try to touch nerve with needle (but don't inject into nerve!)
  - ▶ nerve stimulator: only works for mixed nerves with both sensory & motor
- ▶ differential block possible by adjusting concentration of anesthetic

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**Technique: Plexus block**

- ▶ Similar to peripheral nerve block
- ▶ brachial or lumbar plexus blocked proximal to separation of peripheral nerves
- ▶ Duration is longer than block of peripheral nerve

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**Technique: Spinal anesthetic**

- ▶ injection of local anesthetic solution into CSF after performing lumbar puncture
- ▶ physiologically transects spinal cord: temporary paraplegia: NUMB & PARALYZED
- ▶ sympathetic, sensory, and motor blockade: differential block NOT possible
- ▶ Even though always injected into L3/L4, can control spread of block by modifying specific gravity (add sugar) and patient position → can therefore be used for abdominal surgery

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**Technique: Epidural anesthetic**

- ▶ injection of local anesthetic solution into epidural space, usually via catheter
- ▶ segmental block
- ▶ density of block readily adjusted (analgesia vs. anesthesia)

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**Technique: Bier block (intravenous regional)**

- ▶ IV catheter inserted distally in extremity
- ▶ extremity wrapped in bandage to exsanguinate the limb (squish out all the blood)
- ▶ pneumatic tourniquet (BP cuff) on proximal limb, inflated to ~2x systolic BP so no blood can get into arm
- ▶ dilute solution of lidocaine injected
- ▶ for anesthesia of arm (rarely leg)
- ▶ duration limited by tolerance of tourniquet (1.5-2 hr)
- ▶ simple to perform, anesthesia reliable

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**Technique: Topical anesthesia**

- ▶ Mucous membranes easy to anesthetize: pharynx, nares, trachea, esophagus, urethra
- ▶ most commonly used for endoscopy
- ▶ systemic absorption very efficient
- ▶ skin much harder to anesthetize topically; very slow onset

## General Anesthesia

### General Anesthesia

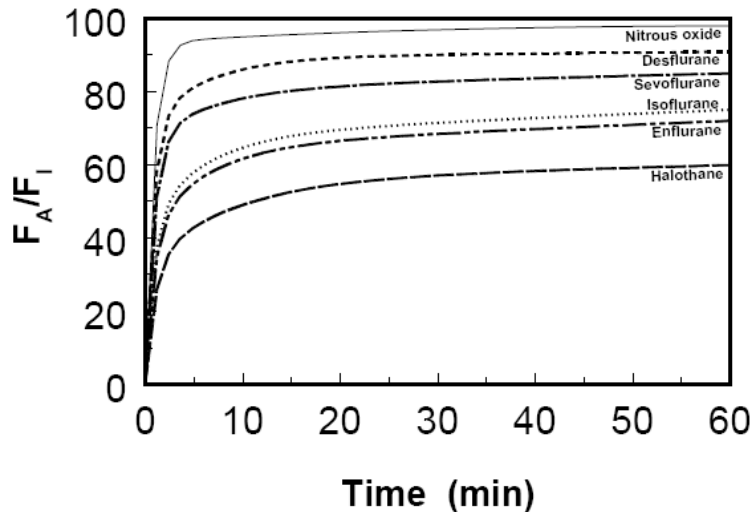
- ▶ Unconsciousness
- ▶ Analgesia = no sympathetic response to noxious stimulus. Note that unconsciousness doesn't necessary mean analgesia.
- ▶ Muscle relaxation (sometimes required, sometimes not)
- ▶ Reflex ablation (i.e. cough reflex)

### Stages of General Anesthesia

- ▶ I: Analgesia
- ▶ II: Delirium
- ▶ III: Surgical anesthesia  
(four planes of only historic significance)
- ▶ IV: Cardiorespiratory collapse

More historical, applies to diethyl ether. With modern IV anesthetics, transition from awake to asleep is too quick to notice stages.

### Factors affecting onset of inhalational anesthetic



$F_A$  = fraction of gas in alveoli  
 $F_I$  = fraction of gas inhaled  
 Drugs with a higher max  $F_A/F_I$  (i.e. nitrous oxide) have:  
 ↓ tissue solubility  
 ↑ (faster) onset

These factors ↑ speed of onset and ↑ speed of offset:

- ▶ ↑ inspired concentration (obvious)
- ▶ ↑ alveolar ventilation (obvious)
- ▶ ↑ flow of gas = "fresh gas flow" (obvious)
- ▶ ↓ FRC (can't exhale the gas quickly)
  - ▶ important in pregnancy  
(↓ FRC → very rapid onset/offset in @ term)
  - ▶ important in ascites (↓ FRC)

These factors ↓ speed of onset and ↓ speed of offset:

- ▶ ↑ solubility (see graph above – Halothane is most soluble and therefore the slowest)
- ▶ ↑ cardiac output (counterintuitive: with ↑ CO, more gas is pumped AWAY from lungs)

### Minimum alveolar concentration (MAC)

- Alveolar concentration of gas at which 50% of individuals do not move in response to a skin incision.
- ▶ ↑ tissue solubility → ↓ MAC (if a gas is very tissue-soluble, you only need a little bit of it for a strong effect)
  - ▶ Can linearly add MACs if you're mixing gas anesthetics
  - ▶ MAC is ↓ by CNS depressants (you need less of gas)
  - ▶ Advanced age ↓ MAC about 7% per decade (need less gas)

Used as a surrogate for brain concentration (which can't be measured)  
 A gas with a very low MAC (high potency) will be slower in kinetics (slower in onset and slower in offset).

### Nitrous Oxide

- ▶ Least soluble inhalational anesthetic (highest MAC = 110%!!)
- ▶ colorless, odorless, tasteless
- ▶ minimal cardiovascular effects

Only gas anesthetic that NEVER triggers malignant hyperthermia!

<b>Halothane</b>	<ul style="list-style-type: none"> <li>▶ Lowest MAC = 0.75%</li> <li>▶ Older halogenated, nonflammable volatile alkane anesthetic</li> <li>▶ Doesn't smell too bad</li> <li>▶ Bronchodilator</li> <li>▶ Not much of a vasodilator</li> </ul>	<p>↓ CO (↓ contractility → ↓ BP)</p> <p>Rare, often fatal hepatic failure (not used much anymore because of this)</p>
<b>Isoflurane</b> <b>Enflurane</b>	<ul style="list-style-type: none"> <li>▶ Most commonly used volatile anesthetic. Ether.</li> <li>▶ MAC 1.15%</li> <li>▶ Doesn't smell too good → not a good choice for inhalational induction</li> <li>▶ Bronchodilator</li> <li>▶ ↓ SVR (in contrast to Halothane) like all ethers</li> <li>▶ little effect on CO (in contrast to Halothane)</li> <li>▶ Enflurane: isomer of isoflurane, less frequently used. ↓ CO and ↓ SVR. Skeletal muscle relaxation.</li> </ul>	
<b>Desflurane</b>	<ul style="list-style-type: none"> <li>▶ Least soluble volatile (comes in a liquid) agent</li> <li>▶ MAC 6.0% → very rapid onset/offset Major advantage: allows rapid waking up</li> <li>▶ ↓ SVR like all ethers</li> </ul>	<p>▶ Bronchoconstrictor, pretty irritating</p>
<b>Sevoflurane</b>	<ul style="list-style-type: none"> <li>▶ Doesn't smell too bad</li> <li>▶ Bronchodilator</li> <li>▶ MAC 2.0%: more rapid than isoflurane, slower than desflurane</li> <li>▶ Significantly metabolized, but not to anything toxic</li> <li>▶ ↓ SVR like all ethers</li> <li>▶ Useful for inhalational induction, especially for children (since they don't like to get IV's)</li> </ul>	
<b>IV Induction Agents</b>		
<b>Thiopental</b>	<ul style="list-style-type: none"> <li>▶ Shortest acting barbiturate. Rarely used today (hangover)</li> <li>▶ Rapid onset of hypnosis after IV injection: fall asleep in 1 min!</li> <li>▶ ↓↓ brain metabolic and electrical activity</li> <li>▶ ↓↓ SVR and CO</li> <li>▶ ↓↓ ventilatory drive</li> <li>▶ contraindicated in porphyria (like all barbiturates)</li> <li>▶ Rapid offset of effect due to <b>redistribution</b>: metabolism/elimination not as important</li> </ul>	
<b>Propofol</b>	<ul style="list-style-type: none"> <li>▶ Most commonly used induction agent</li> <li>▶ More rapid recovery than w/ thiopental</li> <li>▶ less hangover, nausea, vomiting</li> <li>▶ ↓↓ BP compared to thiopental (little Δ in HR)</li> <li>▶ Antiemetic</li> <li>▶ Euphoric effect → abused by anesthesiologists</li> </ul>	<p>▶ Pain on injection frequent: major downside Related to kallikrein.</p>
<b>Etomidate</b>	<ul style="list-style-type: none"> <li>▶ Major advantage: least effects on SVR, CO: only really used in people where ↓ SVR and ↓ CO not acceptable</li> </ul>	<ul style="list-style-type: none"> <li>▶ Most emetogenic: lots of barfing</li> <li>▶ Inhibits cortisol synthesis for ~8 hrs. Imidazole (slightly antifungal). Binds to P450 (but no drug interactions). Inhibits 11β-OH P450 → stops cortisol synthesis → possible Addisonian crisis</li> </ul>

- Ketamine**
- ▶ Dissociative anesthetic: eyes open, but don't respond to pain
  - ▶ ↑ SNS → ↑ HR, ↑ CO, ↑ BP
  - ▶ ↑ ICP → don't use w/intracranial mass!
  - ▶ longer duration than other IV agents
  - ▶ emergence delirium and hallucinations (coadminister with benzodiazepine to prevent)
  - ▶ May be given IM (only induction agent with this property)

*Opioids commonly used during general anesthesia*

- General Characteristics of Opioids**
- ▶ Analgesia
  - ▶ ↓ MAC
  - ▶ Ventilatory depression (all anesthetics except nitrous oxide cause VD)
  - ▶ ↓ GI motility → postoperative ileus

**Opioids usually given by Bolus**

- Morphine**
- ▶ histamine release → ↓ BP and reflex tachycardia
  - ▶ slow onset of effect (~90 min peak)
- Meperidine**
- ▶ should NOT be used anymore
  - ▶ histamine release
  - ▶ onset more rapid than morphine
  - ▶ severe interaction w/ MAO inhibitors
- Fentanyl, Sufentanil**
- ▶ very high potency
  - ▶ rapid onset
  - ▶ effect terminated by redistribution (like thiopental)

**Opioids usually given by Infusion**

(to rapidly titrate opioid effect)

- ▶ **Alfentanil, Sufentanil**
  - ▶ rapid onset
  - ▶ effect terminated by redistribution
  - ▶ sufentanil is shorter-acting
- ▶ **Remifentanil**: Dr. Dershwitz's favorite opioid
  - ▶ rapid onset
  - ▶ effect terminated by rapid nonspecific esterase metabolism → unique!
  - ▶ shortest acting drug in anesthesia: very close to an on/off switch
  - ▶ ideal for a surgery with extreme operative pain that has little residual post-operative pain (i.e. bronchoscopy)

**Naloxone**

- ▶ Opioid **antagonist** ▶ Morphine + naloxone ≠ water
- ▶ Reverses opioid-induced ventilatory depression **AND** analgesia → use carefully or it can cause extreme pain
- ▶ Shorter acting than the opioids it is used to reverse (except remifentanil)

*Adjunct agents (anxiolysis & anti-emetics)*

**Midazolam**

Water soluble injectable benzodiazepine for anxiolysis & sedation

**Droperidol**

Antiemetic.  
DA blocker, doesn't cause dysphoria

**Ondansetron**

5HT<sub>3</sub> blocker. Antiemetic.

**Other antiemetics**

**Antihistamines, transdermal scopolamine, dexamethasone** It's a mystery: dexamethasone is antiemetic.

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**Receptors in chemoreceptor trigger zone**

DA, 5HT, cholinergic

If you block these receptors  
→ antiemetic

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*A "typical" general anesthetic*

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>▶ Interview patient, insert IV</li><li>▶ Midazolam for sedation &amp; anxiolysis</li><li>▶ propofol for induction</li><li>▶ analgesia</li><li>▶ muscle relaxant for tracheal intubation</li><li>▶ nitrous oxide + volatile agent</li></ul> | <ul style="list-style-type: none"><li>▶ mechanical ventilation</li><li>▶ muscle relaxant, opioid as needed</li><li>▶ stop volatile agent well in advance of case end<br/>duration of anesthesia dependent on duration of dose:<br/>long dose → long fade time</li><li>▶ reverse neuromuscular blockade (cholinesterase inhibitor)</li><li>▶ Stop N<sub>2</sub>O, give 100% O<sub>2</sub></li><li>▶ Extubate when awake and breathing</li></ul> |
|--|--|

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**Malignant Hyperthermia**

"The scariest thing that can happen in the OR"

These days, the only people who die of MH are those in a setting with no dantrolene.

- ▶ A pharmacogenetic disorder
- ▶ triggered by **volatile anesthetics** or **succinylcholine**
- ▶ sustained contracture of skeletal muscles without relaxation  
→ hypermetabolic state
- ▶ hypercarbia, metabolic acidosis
- ▶ treat with **dantrolene** → acts intracellularly to inhibit excitation:contraction coupling

## Toxicology

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### Minimizing ingested poison absorption

- ▶ Induction of vomiting. Contraindicated if:
    - ▶ pt is unconscious
    - ▶ substance is caustic (can burn esophagus)
    - ▶ substance is volatile (↑ absorption through lungs)
    - ▶ very rapid (wastes time)
  - ▶ Gastric lavage. Risks of:
    - ▶ esophageal perforation
    - ▶ aspiration
  - ▶ Activated charcoal: adsorbs organic lipid-soluble compounds, but NOT ions ( $\text{Li}^+$ ,  $\text{Fl}^-$ ,  $\text{CN}^-$ )
  - ▶ Bowel cleansing: produce profuse watery diarrhea
- 

### ↑ clearance rate of poison

- ▶ Alkalinize urine to ↑ excretion of acidic compounds (uncharged compounds are reabsorbed)
    - ▶  $\text{NaHCO}_3$ , acetazolamide
    - ▶ can be used for barbiturates, salicylates (acidic compounds)
  - ▶ Acidify urine to ↑ excretion of basic compounds (amphetamines)
    - ▶  $\text{NH}_4\text{Cl}$
  - ▶ Dialysis to excrete water-soluble, low MW, not protein-bound substances (i.e. ASA)
- 

### Carbon Monoxide Poisoning

- ▶ Characteristics
    - ▶ 200 x affinity for  $\text{Hb}^{2+}$  compared to  $\text{O}_2$
    - ▶ Displaces  $\text{O}_2$  → can measure carboxyhemoglobin
    - ▶ Shifts  $\text{O}_2$  curve to L
    - ▶ Binds cytochrome oxidase
    - ▶ Variable half-life depending on inspired  $\text{O}_2$ 
      - 4-6 hrs in room air; ~60 min w/100%  $\text{O}_2$ ; ~20 min w/ w/100%  $\text{O}_2$  @ 3 ATM
  - ▶ Symptoms depend on % Hb with bound CO. Only a few % of inspired CO can kill you
    - ▶ 10% mild headache, vasodilation. A heavy smoker will have a value of ~8%
    - ▶ 20% throbbing headache
    - ▶ 30% visual  $\Delta$ 's, dizziness, severe headache
    - ▶ 40% unconsciousness, reflex SNS discharge → ↑ HR, RR
    - ▶ 50% intermittent seizures
    - ▶ 60% hypotension, ventilatory depression
    - ▶ 70% *game over, man, game over!*
  - ▶ Treatment
    - ▶ Eliminate source of CO (sometimes you don't have to be a genius...)
    - ▶ Give 100%  $\text{O}_2$  ASAP
    - ▶ consider mechanical ventilation, paralysis (↓  $\text{O}_2$  utilization by skeletal muscle)
    - ▶ consider hyperbaric therapy
    - ▶ consider barbiturate coma (↓  $\text{O}_2$  utilization by brain)
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### ASA Poisoning

- ▶ Uncouples oxidative phosphorylation. Lethal dose ≈ 10-30 g
- ▶ Initially resp alkalosis (compensatory met acidosis); later combined met + resp acidosis
- ▶ Treatment:
  - ▶ Most important: **induce vomiting**
  - ▶ ↓ absorption (vomiting, charcoal)
  - ▶ ↑ elimination: ↑ urinary pH (it's a weak acid)
  - ▶ correct acid-base
  - ▶ consider mechanical ventilation
  - ▶ consider dialysis: ASA dialyzes well because it's entirely charged @ physiological pH

<b>Acetaminophen Poisoning</b>	<ul style="list-style-type: none"> <li>▶ Management: similar to ASA overdose <ul style="list-style-type: none"> <li>▶ ↓ absorption (vomiting, charcoal)</li> <li>▶ N-acetylcysteine (have about a 36 hour therapeutic window)</li> </ul> </li> </ul>	
<b>Cyanide Poisoning</b>	<ul style="list-style-type: none"> <li>▶ Sources: HCN as pesticide, CN<sup>-</sup> in photography, metallurgy, ore extraction, fruit pits (apricots)</li> <li>▶ Chemistry: Binds tightly to Fe<sup>3+</sup> (Methemoglobin) <ul style="list-style-type: none"> <li>▶ Major target: cytochrome oxidase (also inhibited by CO)</li> <li>▶ Creates lactic acidosis (can't do aerobic metabolism)</li> <li>▶ Lethal dose: ≈ 200 mg KCN or 50 mg HCN</li> </ul> </li> <li>▶ Most popular suicide method for chemistry grad students</li> <li>▶ Intrinsic detoxification for millimolar quantities of cyanide in diet: <b>rhodanase</b>  CN<sup>-</sup> (cyanide) + S<sub>2</sub>O<sub>3</sub><sup>2-</sup> (thiosulfate) → (rhodanase enzyme) SCN<sup>-</sup> (thiocyanate) + SO<sub>3</sub><sup>2-</sup> (sulfate)  thiocyanate is much less toxic than cyanide, is excreted in urine</li> <li>▶ Management: only low exposure accidental exposures can be treated since toxic dose is so low <ul style="list-style-type: none"> <li>▶ Intentionally induce methemoglobin: convert Hb<sup>2+</sup> to Hb<sup>3+</sup>  amyl nitrite (inhaled), sodium nitrite (IV)  Hb<sup>3+</sup> becomes "sink" for CN to bind to → forms irreversible complex w/cyanide</li> <li>▶ Sodium thiosulfate (IV) to resupply rhodanase reaction</li> <li>▶ 100% O<sub>2</sub></li> <li>▶ Consider gastric lavage. Not initial step because there is very likely none left in GI tract.</li> <li>▶ Very often fatal</li> </ul> </li> </ul>	
<b>Methanol Poisoning</b>	<ul style="list-style-type: none"> <li>▶ Alcohol Metabolism:  <b>ethanol</b> → (ADH) <b>acetaldehyde</b> → (aldehyde dehydrogenase) <b>acetic acid</b></li> <li>▶ Methanol metabolism:  <b>methanol</b> → (ADH) <b>formaldehyde</b> → (aldehyde dehydrogenase) <b>formic acid</b></li> </ul> <p>Formic acid is extremely toxic to the retina: just a few teaspoons (≈15 mL) required for blindness  Ethanol can prevent methanol conversion to formic acid</p>	
<b>Pesticide Poisoning</b>	<p>Organophosphates: more specific for insect cholinesterases, but high doses essentially look like chemical warfare agent poisoning.</p> <ul style="list-style-type: none"> <li>▶ malathion, ▶ parathion, ▶ diazinon</li> </ul> <p>Carbamates: less toxic, potentially reversible</p> <ul style="list-style-type: none"> <li>▶ carbaryl, ▶ aldicarb, ▶ baygon, ▶ ficam</li> </ul> <p>Management of pesticide toxicity:</p> <ul style="list-style-type: none"> <li>▶ same as chemical warfare agents</li> <li>▶ prevent additional absorption <ul style="list-style-type: none"> <li>▶ skin: bathing</li> <li>▶ GI: gastric lavage, charcoal</li> </ul> </li> <li>▶ atropine to dry secretions</li> <li>▶ Pralidoxime to reactivate cholinesterase</li> </ul>	<p>Pesticide toxicity:</p> <p>↑ Muscarinic effects:</p> <ul style="list-style-type: none"> <li>▶ nausea, vomiting</li> <li>▶ pulmonary secretions</li> <li>▶ sweating, salivation</li> <li>▶ miosis</li> <li>▶ bradycardia</li> </ul> <p>↑ Nicotinic effects:</p> <ul style="list-style-type: none"> <li>▶ HTN</li> <li>▶ muscle weakness, twitching</li> </ul> <p>CNS effects:</p> <ul style="list-style-type: none"> <li>▶ anxiety, restlessness</li> <li>▶ seizures, coma</li> </ul>
<b>Arsenic</b>	<ul style="list-style-type: none"> <li>▶ Arsenic <ul style="list-style-type: none"> <li>▶ Usually ingested in drinking water</li> <li>▶ Natural constituent of groundwater</li> <li>▶ groundwater contamination from agricultural runoff</li> <li>▶ very occasionally used in medicines (e.g. Trypanosomiasis)</li> </ul> </li> <li>▶ Treatment of arsenic poisoning <ul style="list-style-type: none"> <li>▶ initially: dimercaprol</li> <li>▶ chronic therapy: penicillamine, succimer (not approved)</li> </ul> </li> </ul>	

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## Lead Poisoning

### Environmental sources of lead

- ▶ Lead salts used as paint pigments until 1978; *in house dust*
- ▶ Tetraethyllead used as gasoline additive through 1970's; *in dirt*
  - ▶ Absorbed from dirt by acidic fruits (tomatoes)
- ▶ Lead pipes, lead solder to join copper pipes: acidic pH causes Pb to leak out
- ▶ Industry: batteries, radiators

### Lead Kinetics

- ▶ after GI absorption, circulates bound to Hb; half-life in circulation  $\approx$  2 months
- ▶ redistributes to bone; half-life in bone  $\approx$  30 years

### Lead Toxicity in Adults: hard to diagnose with vague symptoms

- ▶ **GI** (vague): anorexia, constipation, metallic taste. Later  $\rightarrow$  painful intestinal spasms
- ▶ **Renal**: proteinuria, hematuria, cell casts
- ▶ **Heme**: microcytic, hypochromic anemia
- ▶ **Neuro**: peripheral neuropathy, HTN

### Lead Toxicity in Children

- ▶ CNS: headache, irritability, ataxia,  $\downarrow$  IQ, behavioral problems
- ▶ Abdominal pain, anemia
- ▶ Routine screening recommended:
  - ▶ [Pb] > 10  $\mu\text{g}/\text{dL}$   $\rightarrow$   $\Delta$  environment
  - ▶ [Pb] > 25  $\mu\text{g}/\text{dL}$   $\rightarrow$  chelation therapy

### Treatment: Chelation therapy:

#### EDTA (ethylenediaminetetraacetic acid)

- ▶  $\text{Na}_2\text{EDTA}$   $\downarrow\downarrow$   $[\text{Ca}^{2+}]$  even though it's not used clinically for this effect
- ▶  $\text{Ca}_2\text{EDTA}$  used in therapy  $\rightarrow$  Pb displaces Ca from  $\text{Ca}_2\text{EDTA}$
- ▶ Must be given IV or IM
- ▶ Causes proximal tubule damage
- ▶ Also chelates essential metals: Cu, Zn, Fe

#### Dimercaprol

- ▶ used in combination with EDTA in Pb poisoning
- ▶ solution in peanut oil
- ▶ must be given IM
- ▶  $\uparrow$  HR, BP
- ▶ Requires alkaline urine

#### Penicillamine: metabolite of penicillin

- ▶ effective orally  $\rightarrow$  useful in long-term outpatient management of Pb poisoning
- ▶ Also used in Wilson disease
- ▶ Toxicity: autoimmune phenomena (can also trigger SLE-like syndrome)

#### Succimer: Newest chelating agent

- ▶ effective orally
- ▶ less toxic than dimercaprol, penicillamine
- ▶ does not chelate essential heavy metals (Cu, Zn, Fe)
- ▶ Only approved in Pb poisoning
- ▶ Toxicity: chemical hepatitis

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## Mercury

- ▶ Elemental Hg: vapor at room temp
- ▶ Hg salts: used in medicine through 1970's
  - ▶ also used in many industries
  - ▶ converted to **methylmercury** by bacteria  $\rightarrow$  poisons sulfhydryl enzymes, rises in food chain
- ▶ Mercury poisoning: primarily CNS symptoms and signs  $\rightarrow$  visual and hearing loss, ataxia
- ▶ Treatment: Chelation therapy  $\rightarrow$  dimercaprol, penicillamine, succimer (not approved)