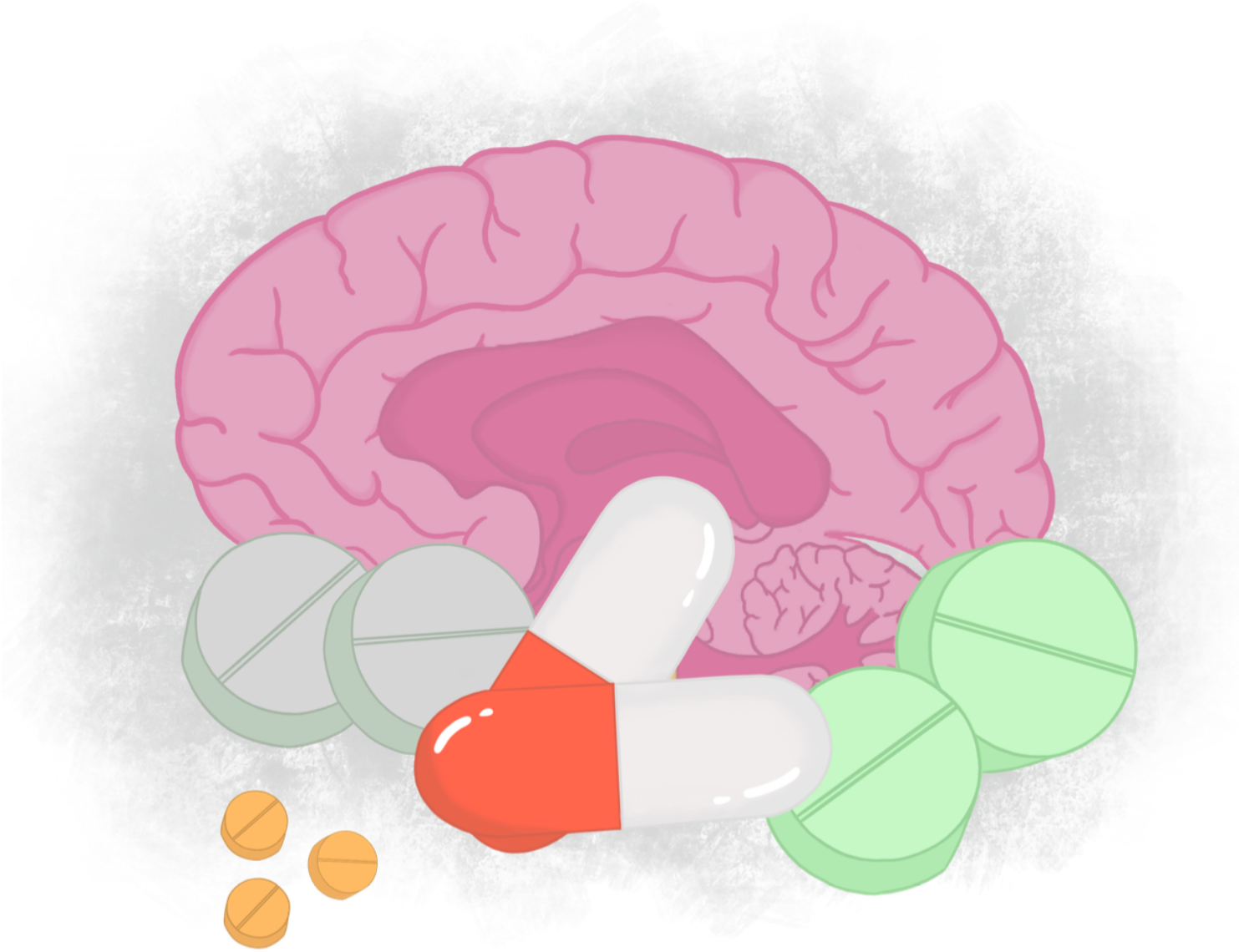

Pharmacology Exam 2

Marie Rishovd • Hanna Bentsen

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Authors
Marie Rishovd
Hanna Bentsen

Editors
Marie Rishovd
Hanna Bentsen
Anna Emilie Høifødt

Illustrators
Anna Edine Lind Jodalen
Marie Rishovd

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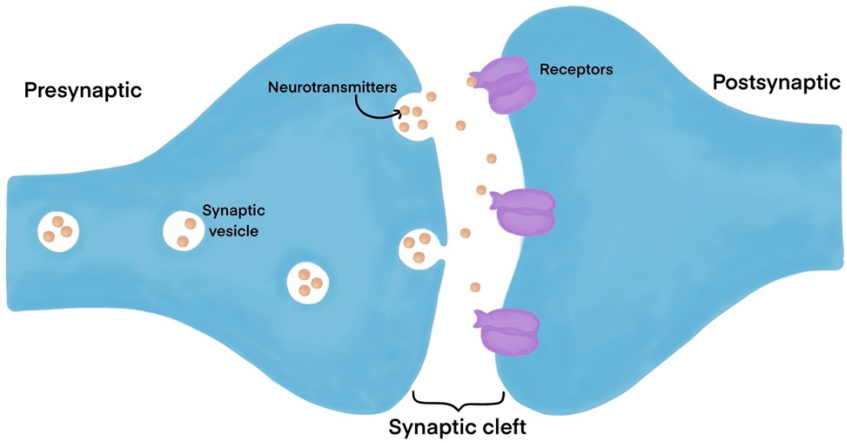
Section 1 – Neurotransmitters of the CNS

1.1 – General

- Neurotransmitters are chemical messengers that transmits a signal from one nerve cell to another
- Criteria to be classified as a neurotransmitter
  1. Synthesis and Release: A neurotransmitter must be synthesized in a neuron and released from a presynaptic terminal
  2. Specific Responses: It should reproduce specific responses at the postsynaptic neurons, either excitatory or inhibitory
  3. Antagonist Blockage: The effect of the neurotransmitter should be dose-dependently blocked by antagonists
  4. Termination: After exerting its effect, a neurotransmitter must be reabsorbed, metabolized or inactivated to terminate the stimulation and prevent prolonged signaling

Neurotransmitters: Chemical messengers that transmits signals between neurons
Neuromodulators: Substances released by neurons that regulate the activity of neurotransmitters

1.1.1 – Types of Amino Acid Transmitters



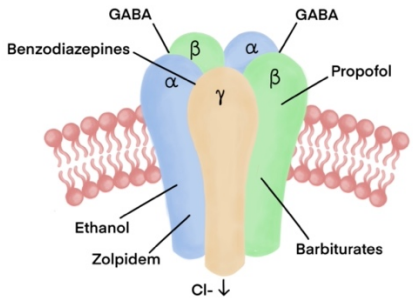
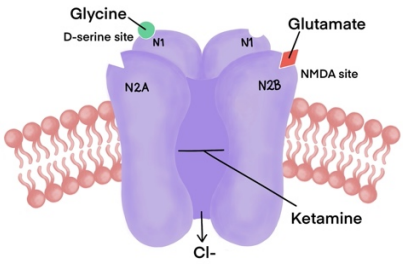
- Most CNS drugs are exerted directly at the synapses.
- A synapse is the junction between two nerve cells, where a neural message is transmitted through the action of a neurotransmitter.
- Presynaptic is before the synapse, while postsynaptic is after the synapse.

- When neurotransmitters attach to their respective receptor, they will either cause an excitatory or inhibitory response;
    1. Excitatory is more likely to fire an action potential
    2. Inhibitory is less likely to fire an action potential
- Drugs act through different mechanisms;
    1. Presynaptically by altering the synthesis, storage, release, reuptake or metabolism of the neurotransmitter
    2. Postsynaptically mainly on receptors
    3. On the second messengers

1.2 – GABA and Glutamate

- GABA and glutamate are both amino acid neurotransmitters, amino acids which can transmit a nerve message across a synapse.
- Glutamate is the primary excitatory neurotransmitter, which allows for firing of action potentials.
- GABA is the primary inhibitory neurotransmitter, which inhibits firing of action potentials.

1.2.2 – Types of Amino Acid Transmitters

	Gamma-aminobutyric acid (GABA)		Glutamate		
Importance	Can reduce neural transmission[1]		Important in learning and memory		
Effect	Inhibitory		Excitatory		
Location	Brain and spinal cord		All levels of CNS		
Receptor	GABA receptor 		NMDA receptor complex[2] 		
Receptor subtypes	$GABA_A$	$GABA_B$	NMDA	AMPA	Kainate
Drugs	**Benzodiazepines Barbiturates Zolpidem Alcohol**	**Baclofen**	**Phencyclidine Ketamine Memantine**	**Piracetam**	
Most common clinical use	Sedation	Treat spacticity	Treat seizures		

[1]The sedative effect of GABA is because of the ability to reduce neural transmission
[2]The NMDA receptor complex has a binding site for both glycine and glutamate

1.2 – Other Neurotransmitters

Neurotransmitter	Type of neurotransmitter	Importance in CNS	Clinical significance in CNS	Location
Glycine	Amino acid	Inhibitory action leading to suppressed neuronal firing	**Strychine** (poison) is an antagonist. No drugs in clinical use	Grey matter of spinal cord
Norepinephrine	Monoamine	Anxiety, learning, memory, mood, sensory, sleep	Target in some antidepressants	Neuronal tracts from locus ceruleus
Dopamine	Monoamine	Drug reinforcement, emesis, mood, motor coordination, olfaction	Target in some recreational use, treatment of parkinsonism	Neuronal tracts from ventral segmental area
Serotonin	Monoamine	Emotions, pain, appetite, sleep, mood, hallucinations	Target of action in most antidepressants	Neuronal tracts from raphe nuclei
Histamine	Monoamine	Modulate arousal, appetite, and memory	Drowsiness and sedation from some antihistamines	Widely distributed in brain
Acetylcholine	Cholinergic	Memory, arousal, and attention	Target in some drugs for Parkinson's and Alzheimer's disease	Spinal cord
Endorphins	Neuropeptide (opioid peptide)	Inhibit pain transmission, lower stress, improve mood	Drugs like **morphine** mimic its effect	Spinal cord and midbrain
Adenosine triphosphate (ATP)	Purine	Believed to augment the effect of other neurotransmitters	No clinical use	Whole CNS
Adenosine	Purine	Not well understood, but can alter the levels of cAMP	**Caffeine** inhibits adenosine receptors causing CNS stimulation	Whole CNS

Section 2 – Drugs Affecting CNS

2.1 – Sedative-Hypnotic and Anxiolytic Drugs

- Sedative-hypnotic drugs are substances that can induce a calming or sleep-inducing effect.
- Anxiolytic drugs are substances that reduce or alleviate anxiety

2.1.1 – Benzodiazepines and Barbiturates

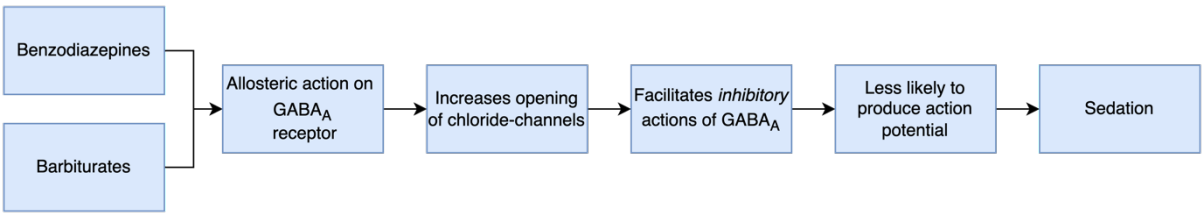
- Both benzodiazepines and barbiturates act on the $GABA_A$ receptor
- Low dose of these drugs results in sedation and anxiety relief, while higher doses can result in hypnosis. However, the depth of the anesthesia is not enough to lose pain stimuli.
- Due to the fact that barbiturates can act on the chloride channel even in the absence of GABA, these drugs exhibit greater toxicity and also has a narrower therapeutic index.

SUFFIX

Benzodiazepines: -pam

SUFFIX

Barbiturates: -tal



	Benzodiazepines	Barbiturates
Mechanism	Binds to the $GABA_A$ receptor to potentiate inhibitory actions by GABA	
$GABA_A$ subunit	Alpha 1 and gamma 2	Beta 2
Effect	Increases the *frequency* of chloride-channel opening	Increases the *duration* of chloride-channel opening
Other effects	Anterograde amnesia[1] Muscle relaxation	Anterograde amnesia[1]
Clinical use	First line acute anxiety states and panic attacks First line for all seizures, including status epilepticus Primary insomnia Anesthesia Bipolar disorders Muscle spasticity Alcohol withdrawal	Anxiety disorders Insomnia Induction of general anesthesia Seizure disorders
Toxicity	CNS depression Mild euphoric effect Hypotension Bradycardia or tachycardia	Hangover and daytime sedation Respiratory depression[2] Coma[2] Death[2]
	Physical dependence Withdrawal syndrome	
Contraindications	Pregnancy	Pregnancy
Drug examples	**Diazepam** **Lorazepam** **Clonazepam** **Flurazepam** **Midazolam**	**Phenobarbital** **Thiopental** **Pentobarbital**
Antidote	**Flumazenil**	No antidote

[1]Will not remember what happens after the drug is administered, because they affect the ability to form new memories

[2]For benzodiazepines these symptoms only occur in combination with other CNS depressants like alcohol. This is because benzodiazepines work only in the presence of GABA, while barbiturates don't depend on its presence.

CLINICAL CORRELATION

Alcohol withdrawal

- Long-acting benzodiazepines like chlordiazepoxide and diazepam is used in the management of alcohol withdrawal
- This is because both alcohol and benzodiazepines act on the GABA receptor
- If the patient has hypokalemia, which is common in alcoholics, the hypokalemia should always be corrected before administering benzodiazepines

CLINICAL CORRELATION

Flumazenil

- An agitated patient with delirium receives Sobril (oxazepam) to calm down
- After a short time, the patient appears to be in a stupurous state
- Flumazenil is a selective competitive antagonist of the GABA receptor, and can therefore be used as an antidote in benzodiazepine toxicity

2.1.2 – Other Sedative-Hypnotic Drugs

- Non-benzodiazepine hypnotic drugs exert the same CNS effects as benzodiazepines, however they are less likely to cause tolerance and withdrawal syndrome
- These drugs can also be antagonized by flumazenil

	Mechanism	Duration	Clinical use	Toxicities
Zolpidem	Interacts with the alpha 1 subunit of $GABA_A$	Medium	To treat sleep onset insomnia	Similar effect as benzodiazepines but smaller
Zaleplon		Short		
Eszopiclone		Long		

CLINICAL CORRELATION

Zopiclone (Imovane)

- Zopiclone is a drug commonly used to treat insomnia
- It is most commonly recommended for short-term treatment of insomnia
- However, it is in some cases used nightly, for example in elderly patients

2.1.3 – Non-Sedating Anxiolytic Drugs

- Buspirone is an atypical sedative-hypnotic drug. It is a very selective anxiolytic drug, with very little CNS depressive effects

	Mechanism	Clinical use	Toxicities
Buspirone	Partial agonist on the serotonin5-HT_{1A} receptor	Due to the very slow onset of action, the drug is used for generalized anxiety disorders rather than panic attacks	Mild headache, dizziness, and nervousness. Low chance of tolerance or withdrawal syndrome with chronic use

2.1.4 – Anxiolytics

- Anxiolytic drugs are drugs used to reduce symptoms of anxiety

	Diphenylmethane derivatives	**Diol derivartives**
Mechanism	Inhibits activity of reticular formation[1]	
Effects	Antihistaminic Spasmolytic Atropinic and antiemetic Weak local anesthesia	Strong hypnotic activity Muscle relaxation
Clinical use	Anxiolytic Antipsychotic Locomotion disease Hallucinations	Anxiolytic Sedation Antiepileptic
Toxicity[2]	Sedation Allergic response Myelosuppression Slight dependency Seizures, ataxia, dizziness	Allergic response Myelosuppression Dependency/tolerance Euphoria or depression
Drugs	**Hydroxizine** **Azacyclonol** **Benxoctamine**	**Meprobamate** **Tybamate** **Phenoglicodol**

[1]Reticular formation is a part of the brainstem that plays a crucial role in regulation of arousal, attention, and consciousness

[2]Toxicities in diphenylmethane derivatives are more common in hydroxyzine than the other drugs

2.1.5 – Other Drugs with Sedative, Hypnotic and/or Anxiolytic Action

- These drug classes are covered completely in pharmacology booklet 1.

Drug class	Mechanism	Effect	Drug example
Antihistamines (1st generation)	Blocks H1 receptor in CNS	Sedative and hypnotic action	**Diphenhydramine[1] Doxepin Hydroxyzine**
Melatonin agonists	Activate melatonin receptors	Sedative and hypnotic action	**Ramelteon**
Beta blocker	Antagonize beta1 and beta2	Anxiolytic No hypnotic action!	**Propranolol[2]**

[1]The active ingredient in many over-the-counter drugs to treat insomnia

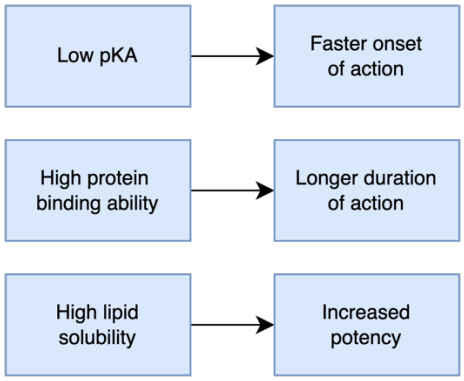
[2]Ability to prevent tachycardia and other signs of sympathetic activation, can therefore be used to treat acute anxiety in for example stage fright

2.2 – Local Anesthetics

- Local anesthetics are drugs that temporarily block nerve signals in a specific area of the body, leading to loss of sensation in that localized region.
- Local anesthetics act on the voltage-dependent sodium channels by blocking them.
- The efficiency of local anesthetics depends on pKA, protein and lipid solubility.

SUFFIX

Local anesthetics: -caine

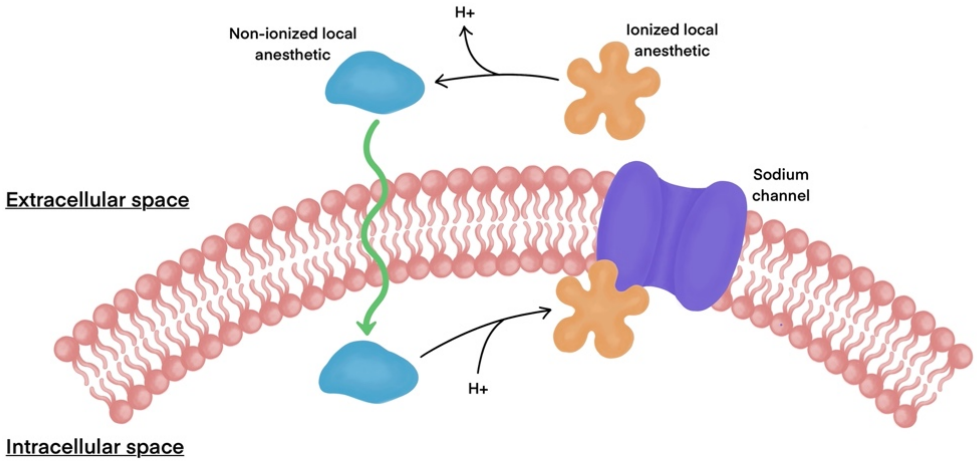


2.2.1 – Classes of Local Anesthetics

- Local anesthetics are divided into ester-bound and amide-bound, nowadays amide-bound is almost only used
- Local anesthetics exist in both ionized and non-ionized forms
  1. Non-ionized form: Penetrate the cell membrane
  2. Ionized form: Bind to and block the sodium channels

RULE

Amide-bound local anesthetics has two "i" in the name



- Epinephrine is a vasoconstrictive agent that can prolong the duration of local anesthetics if administered together. However, it should never be administered to tissues with end arteries as fingers, toes, ears, nose, and penis.

	Amine-bound LA	Ester-bound LA
Mechanism	Irreversible inhibition of the sodium channel	
Inactivation	Liver[1]	Plasma
Stability	Stable[2]	Unstable
Allergic reactions	Rare	Common
Drugs	**Lidocaine** **Bupivacaine** **Ropivacaine** **Prilocaine**	**Cocaine** **Procaine** **Benzocaine** **Proparacaine**

[1]Because amine-bound LA are metabolized in the liver it has a longer half-life and duration
[2]Increased stability make the drugs more resistant to e.g. heat

2.2.2 – Amine-Bound Drugs

	Duration of action	Clinical use	Administration	Toxicity
Lidocaine	Short	EMLA cream Minor surgery Postherpetic neuralgia Ventricular arrhythmia	Topical Infiltration Nerve block Epidural Spinal	Rarely side effects CNS excitation
Prilocaine	Short	EMLA cream	Topical Infiltration	Methemoglobinemia[1]
Mepivacaine	Short		Infiltration Nerve block Epidural Spinal	
Bupivacaine	Medium	Most common LA used for obstetric epidural anesthesia Post-surgical pain	Infiltration Nerve block Epidural Spinal	Myocardial depression
Ropivacaine	Long	Post-surgical pain	Infiltration Nerve block Epidural	Less cardiac toxicity than bupivacaine

[1]Prilocaine is converted to a toxic metabolite than can cause methemoglobinemia if it accumulates, due to this it is only administered topical or by infiltration

CLINICAL CORRELATION

Lidocaine

- Lidocaine is the most commonly used local anesthetic
- Xylocaine is a brand name for lidocaine, which is commonly used for pain relief during insertion of nasogastric tubes or urinary catherization
- The local anesthetics are in these cases administered as a topical gel

2.2.3 – Administration of Local Anesthetics

		Location	Clinical use
Topical		Skin, mucous membranes, cornea	Pruritus Venipuncture or minor surgery[1] Different disorders, e.g. hemorrhoids Ocular surgical procedures
Infiltration		Injection into the subcutaneous tissue[2]	Primarily minor surgical procedures Removal of foreign bodies Dental procedures
Regional anesthesia	**Nerve block**	Injection into a peripheral nerve or nerve plexus to block conductivity to an area of the body	Surgical procedures Ocular surgery
	Spinal[3]	Injection into the subarachnoid space below where the spinal cord terminates (L2/L3)	Surgery
	Epidural	Injection into the lumbar or caudal epidural space	Labor and delivery

[1]Commonly EMLA, which is a liquid combination of lidocaine and prilocaine.
[2]Epinephrine is often used to decrease dose and increase duration of action.
[3]Spinal anesthesia takes a shorter time to perform, has a faster onset and a more efficient block than epidural anesthesia. However, it has a higher chance of hypotension and headache associated with CSF leakage.

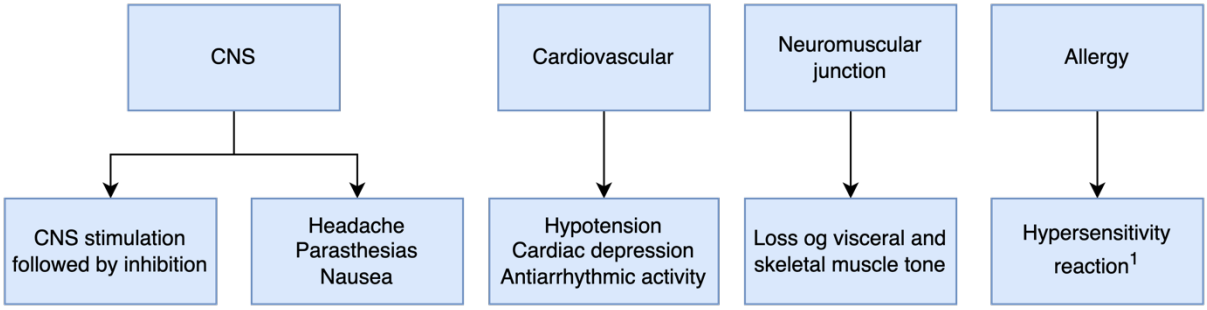
CLINICAL CORRELATION

Epidural anesthesia

- Epidural anesthesia is a commonly used and very popular local anesthetic during physiological labor
- A catheter is put in place, and allows for periodic injections of the anesthesia
- This allows the patient to be relieved of pain but still feel the pressure of the labor
- Provides pain relief to the lower half of the body

2.2.4 – Side Effects of Local Anesthetics

- The most common cause of side effects with the use of local anesthetics is the unintended intravascular injection, which causes systemic toxicity.
- Side effects are listed below;

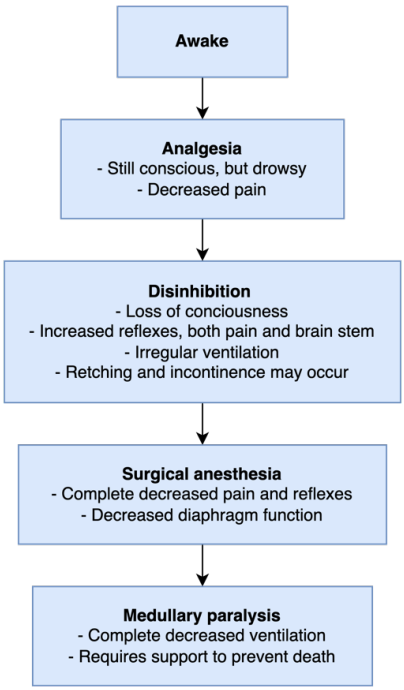


[1]Applies more frequently to ester-type local anesthetics as they are metabolized to paraaminobenzoic acid (PABA), which can cause allergic effects

2.3 – General Anesthetics

- General anesthesia is a state of reversible unconsciousness, loss of sensation, and muscle relaxation induced for medical procedures.
- In general anesthesia all of the below should be present
  1. Unconsciousness
  2. Analgesia
  3. Loss of motor reflexes
  4. Amnesia
  5. Loss of autonomic recovery
- The anesthesia must be readily controllable, with fast induction and recovery. This cannot be achieved by one single drug; therefore, mixed anesthesia is indicated.

Stages of anesthesia

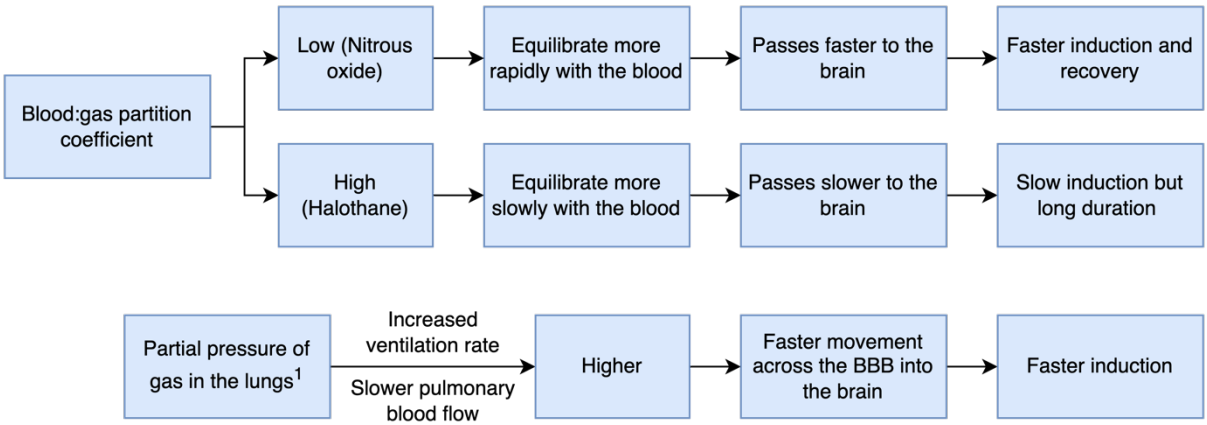


2.3.1 – Inhalational Anesthetics

- General anesthetics that are administered through inhalation rather than parenteral

I. Pharmacokinetics in inhalational anesthetics

- The inhalational anesthetics are both absorbed and eliminated through the lungs, this makes the pharmacokinetics rather different than other drugs
- Different factors determine the induction time and recovery time of the anesthetic
  1. Blood:gas partition coefficient
  2. Partial pressure of the anesthetic
  3. Ventilation rate



[1]Determines the movement of the anesthetic from the lungs to other tissues

II. Potency of inhalational anesthetics

- The potency is best measured by MAC (Minimum Alveolar Concentration). The lower MAC is, the more potent is the anesthetic.
- MAC is the minimum concentration of anesthetic required to prevent movement in response to a noxious stimulus, in 50% of patients
- All anesthetic drugs have a MAC; however, they may vary among patients due to factors such as age and cardiovascular status

III. Drugs

- Inhalational drugs are divided into nonhalogenated and halogenated.
- These drugs act agonistically on the $GABA_A$ receptor chloride channels, and therefore reducing excitability
- Inhalational drugs are the first choice for anesthesia in children, whereas sevoflurane is most common
- Inhalational drugs are rarely used for induction of anesthesia in adults, but can be used for maintenance of anesthesia

		Pharmacokinetics	Clinical use	Toxicity
Non-halogenated	**Nitrous oxide (NO_2)**	Least potent Less reduction in consciousness More analgesia Mild euphoria	Minor surgery Dental procedures Balanced anaesthesia[1]	Quite safe, no cardiovascular or pulmonary depression Megaloblastic anemia
Halogenated	**Halothane**	Rapid induction Rapid recovery Less analgesia Less muscle relaxation	Major surgical procedures Balanced anaesthesia[1]	Halothane hepatitis Malignant hyperthermia[2] Respiratory and cardiovascular depression Cardiac dysrhythmia
	Sevoflurane			
	Isoflurane			
	Desflurane			

[1]Incombination with other anesthetic agents, to provide better analgesia and lower concentration of the other drug. Nitrous oxide and halogenated drugs are commonly used in combination to get the best effect

[2]Malignant hyperthermia is a severe toxicity resulting in muscle fiber break down. Consequences includes rhabdomyolysis and renal failure. Anesthesia should be discontinued, and patient should be treated with dantrolene

CLINICAL CORRELATION

"Laughing gas"

- Nitrous oxide is also called "laughing gas"
- This is due to its mild euphoric effect
- Nitrous oxide can in some cases be administered to pediatric patients to calm them down before stressful situations, like insertion of peripheral venous catheters
- These euphoric effects have also resulted in the occurrence of some recreational use of the drug

2.3.3 – Parenteral Anesthetics

- Parenteral anesthetics are general anesthetics that are administered directly to the vein
- Use of parenteral anesthetics can be followed by an inhalational anesthetic to maintain the anesthesia

	Mechanism	Advantages	Disadvantages	Drugs
Propofol	$GABA_A$ agonist	Rapid onset of action, rapid elimination from the body	Cardiovascular and respiratory depression	**Propofol**
Barbiturates		Rapid onset of action, more slowly eliminated		**Thiopental**
Benzodiazepines		Little cardiovascular or respiratory depression	Slower onset of action than thiopental	**Midazolam**
Etomidate		Rapid onset of action and has the lowest cardiovascular effects		**Etomidate**
Ketamine	Glutamate (NMDA) antagonist	Little effect on respiration Few side effects in children, commonly used in pediatric patients	Increase blood pressure Dissociative anesthesia[1] Delirium and hallucinations during recovery	**Ketamine**
Opiates	Opioid agonists	Potent analgesic effect and no cardiovascular toxicity	Do not produce amnesia or complete loss of conciousness[2]	**Remifentanil** **Fentanyl**

[1]When the patient appears dissociated from the environment without being unconscious, occurs when the drug is administered IV

[2]Because of this, opiates are combined with sedatives such as propofol to produce increase the level of consciousness

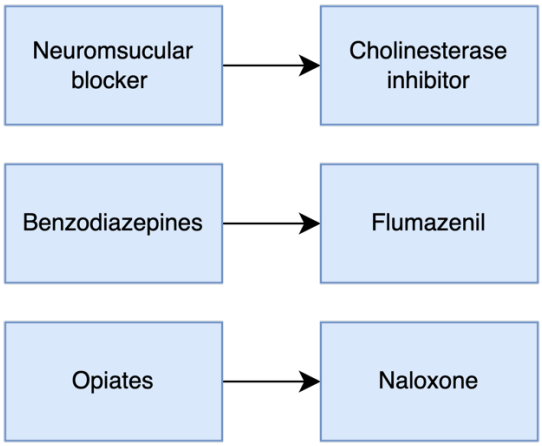
CLINICAL CORRELATION

General anesthesia

- In Norway, continuous infusion of propofol and remifentanil is the most common approach to general anesthesia due to its rapid action and recovery.
- Propofol provides sleep induction while remifentanil provides analgesia.
- You should always be aware of hypotension since it is the most common side effect of both drugs.
- A multimodal approach (the use of more drugs simultaneously) is becoming more common to avoid side effects such as hypotension, to limit the use of opiates, and to provide better post-operative pain management.

2.3.4 – Antagonists of Adjuncts to Anesthesia

- Antagonists to the anesthetic's agent can be given during the recovery from general anesthesia
- When you use a neuromuscular blocker to provide complete muscle paralysis, the antagonist is required to wake up the patient properly. This is to ensure that the respiratory muscles will allow for spontaneous breathing.



2.3.5 – Commonly Used Drugs in General Anesthesia

Induction	IV thiopentone, etomidate, midazolam, or propofol
Muscle paralysis	IV tubocurarine (NMB)
Maintenance of unconsciousness and analgesia	Inhalational anesthetic (NO_2 + halogenated) ± IV analgesic agent (opiate)
Recovery	O_2, cholinesterase inhibitors, naloxone, flumazenil

2.4 – Epilepsy

- Epilepsy is a neurological disorder of unprovoked seizures, whereas seizures are involuntary movements and thoughts caused by episodes of abnormal activity in the brain
- To diagnose epilepsy one of the two must be present
  1. At least 2 epileptic seizures
  2. 1 epileptic seizure if risk factors are present
- Epilepsy can be triggered by underlying disorders such as brain tumor, neurogenerative diseases or head trauma

2.4.1 – Types of Epilepsy

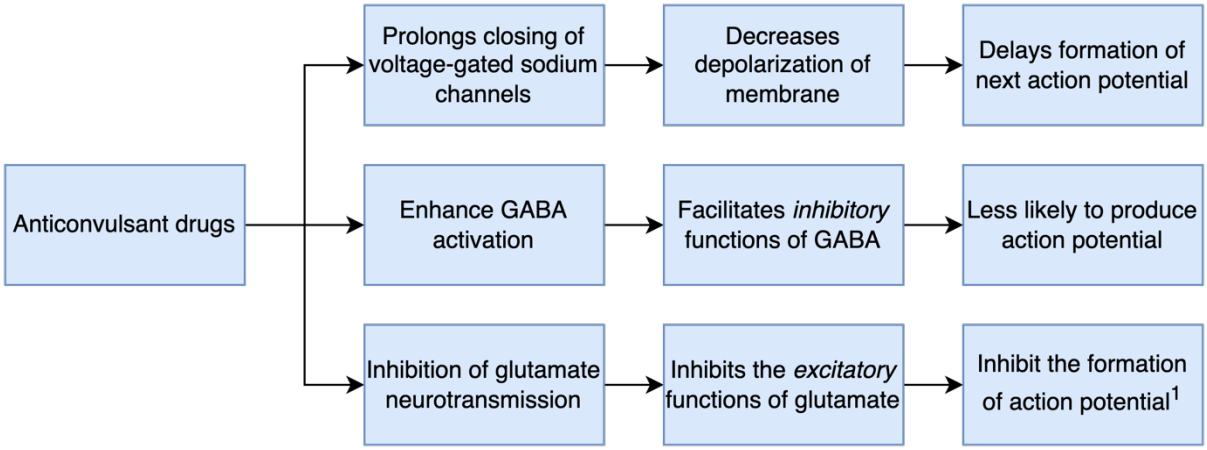
- Generalized seizures: seizures affecting the whole brain and body
- Partial seizures: seizures affecting only a part of the brain and body
- Simple seizures: seizures where the consciousness is not lost
- Complex seizures: seizures where there is a loss of consciousness

Generalized seizures		**Partial seizures**	**Status epilepticus**
Tonic-clonic seizure "grand mal"	**Absence seizure**		
1.Tonic phase with muscle stiffness 2.Clonic phase with rhythmic jerking movements	Seizure with a sudden loss of consciousness and decreased muscle tone	Seizures that originate in only one hemisphere, causing localized symptoms	A medical emergency characterized by prolonged and continuous seizures

2.4.1 – Antiepileptic Drugs (Anticonvulsants)

- Epilepsy is usually treated with a monotherapy, however if there is a lack of effect polytherapy can be considered

I. Mechanism of different anticonvulsants



[1]This mechanism is important as it may terminate the seizure at an early stage by affecting the formation of the seizure foci to begin with.

II. Classification of anticonvulsants

Classic anticonvulsants	Second generation anticonvulsants	Third generation anticonvulsants
Phenytoin Carbamazepine Oxacarbazepine Valproate Ethosuximide Phenobarbital Benzodiazepines	Lamtotrigine Vigabatrine Gabapentine Felbamate Tiagabine Topiramate Levetiracetam Pregabaline Zonisamide	Lacosamide Rufinamide Stripentol Eslicarbazepine Retigabine Perampanel

III. Drugs for partial seizures and generalized tonic-clonic seizures

- The first-line drugs for partial seizures and generalized tonic-clonic seizures are valproate, carbamazepine, and phenytoin
- Second-line drugs are phenobarbital and primidone. Phenobarbital is the oldest anticonvulsant that is used today.

	Valproate	Carbamazepine	Phenytoin
Mechanism	Blocks voltage-gated sodium channels and T-type calcium channels Increase GABA synthesis May decrease glutamate synthesis	Blocks voltage-gated sodium channels	
Other actions		Blocks norepinephrine reuptake	
Cyt P450 enzymes	Inhibits	Induction[1]	Induction
Clinical use	Partial seizures All forms of generalized seizures[2] Manic phase bipolar disorder Prophylaxis migraine	Partial seizures Tonic-clonic seizures First-line trigeminal neuralgia Bipolar disease	Partial seizures Tonic-clonic seizures
Toxicity	Relatively little sedation and drowsiness Nausea, GI complaints, weight gain Mild hepatic toxicity[3] Spina bifida and impaired cognitive development in offsprings	CNS depression GI reactions Aplastic anemia	Ataxia, diplopia, nystagmus, slurred speech Megaloblastic anemia Fetal hydantoin syndrome Osteomalacia Gingival hyperplasia Hirsutism Steven-Johnson syndrome Toxic epidermal necrosis
Related drugs		Oxcarbazepine/Eslicarbazepine	Fosphenytoin

[1]A very potent inducer of cytochrome P450 enzymes, which results in acceleration of metabolism of many different drugs. Due to these drug-drug reactions, carbamazepine is rarely a first-choice drug now
[2]In difference to carbamazepine and phenytoin which can worsen absence seizures
[3]In rare cases, fatal hepatic toxicity has been observed. Therefore, all patients taking valproate should have their liver function monitored

II. Adjunct drugs for partial seizures

- Partial seizures are the most difficult seizures to control, therefore there are some newly developed adjunct drugs to assist the other drugs
- These drugs consist of mainly second-generation antiepileptic drugs

	Mechanism	Clinical use	Toxicity
Clorazepate	Enhances binding of GABA	Adjunct treatment for partial seizures Anxiety disorder	Drowsiness Lethargy Tolerance
Felbamate	Blocks glycine coactivation of NMDA receptors	Partial seizures that are refractory to treatment Children with LGS[1]	Fatal aplastic anemia Acute hepatic failure
Tiagabine	GABA reuptake inhibitor	Adjunct treatment of partial seizures Generalized anxiety disorder Panic attacks	
Gabapentin	Increase release of GABA	All forms of partial seizures Postherpetic neuralgia Restless legs syndrome	Minimal at therapeutic doses
Levetiracepam	Not clear, but delay GABA neurotransmission	Adjunct treatment of partial seizures in children	Dizziness Nervousness
Pregabalin	GABA analog	Adjunct treatment of partial seizures Neuropathic pain Fibromyalgia Generalized anxiety disorders	
Lamotrigine	Blocks sodium and calcium channels, decrease glutamate	Effective adjunct drug to partial seizures All types of seizures LGS[1] Manic phase bipolar disorder	Cerebellar dysfunction Drowsiness Rash Stevens-Johnson syndrome Aseptic meningitis
Vigabatrine	Irreversible inhibitor of GABA-T[3]	Adjunct treatment of partial seizures	Dizziness Drowsiness Psychosis
Zonisamide	Blocks sodium channels and reduces calcium ion flow	Adjunct treatment of partial seizures	Metabolic acidosis[3]
Topiramate	Not clear, blocks voltage-gated sodium channels GABA agonist Glutamate blockage	Adjunct treatment of partial seizures, and all other types of seizures	CNS side effects Steven Johnson syndrome Cleft palate in offspring

[1]Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy, with seizures beginning in early childhood
[2]GABA in the brain is irreversibly broken down by the enzyme GABA transaminase
[3]Serum bicarbonate levels should always be maintained, both before and after treatment

CLINICAL CORRELATION

Stevens-Johnson syndrome

- Stevens-Johnson syndrome is a potentially fatal form of erythema multiforme
- It is characterized by severe mucocutaneous and systemic lesions
- Patients starting to developing rash taking these drugs, should report to their doctor because it can develop into Steven-Johnson
- It is more common for patients taking a combination of lamotrigine and valproate

III. Drugs for generalized absence, myoclonic, or atonic seizures

- Drugs for generalized absence, myoclonic, or atonic seizures are treated with ethosuximide, clonazepam or valproate
- Lamotrigine is sometimes used as an adjunct to the other drugs

	Ethosuximide	**Clonazepam**	**Valproate**
Mechanism	Inhibits T-type calcium channels	A benzodiazepine	Several mechanisms of action[2]
Effect	Long half-life		High efficiancy
Clinical use	Drug of choice in absence seizures in children[1]	Mainly in prolonged epileptic seizures	Absence, myoclonic, and atonic seizures
Toxicity	Little toxicity Dizziness, drowsiness, gastric distress, nausea	Sedation	Relatively little sedation GI effects

[1]Not very effective in adults or in other types of seizures. Valproate is usually used in these cases.
[2]Discussed more in an earlier chapter

IV. Drugs for status epilepticus

- Status epilepticus starts in stage 1, where continuous or multiple seizures are present.
- Seizures are associated with sensory, motor and cognitive impairment

Stage 1	**Early status epilepticus**	5 min	Benzodiazepines, diazepam is first line
Stage 2	**Established status epilepticus**	30-120 min	Intravenous antiepileptic drugs such as phenytoin, phenobarbital or valproate
Stage 3	**“Refractory” status epilepticus**	2-24 hours	Generalized anesthesia
Stage 4	**“Super-refractory” status epilepticus**	>24 hours	Resistant to treatment

2.5 – Psychosis

- A mental health condition in which impairment of the following results in decreased capacity to deal with the reality
  1. The thoughts
  2. Affective response
  3. Ability to distinguish between what is real and not
  4. Ability to relate to others and communicate
- Characteristics include impaired reality testing, hallucinations, and delusions

2.5.1 – Classification of Psychosis

Primary psychosis	Secondary psychosis
When psychosis is the main disorder	When psychosis is caused by another issue
Schizophrenia Schizoaffective disorder Psychotic depression Some cases of bipolar disorder Delusional disorder Brief psychotic disorder Shared psychotic disorder	Medical conditions Substance intoxication or withdrawal Brain lesion

2.5.2 – Symptoms

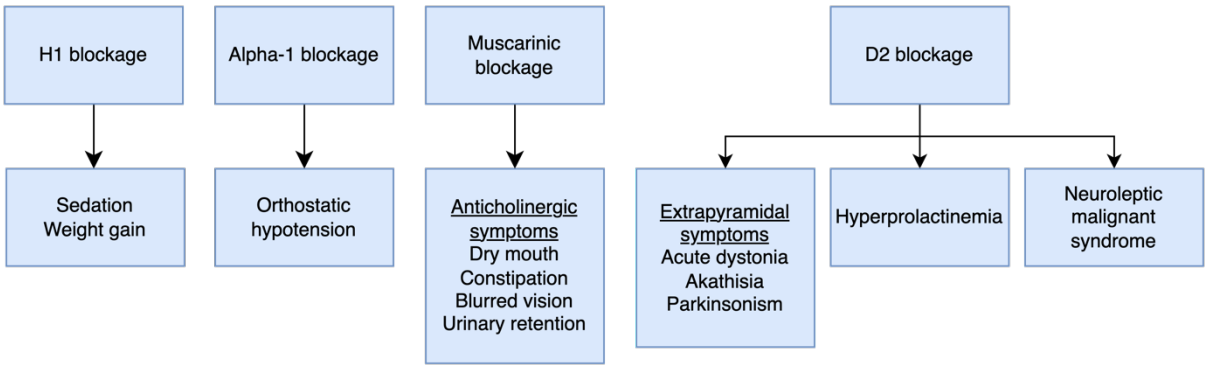
Positive symptoms	Negative symptoms[1]
Symptoms that the patient themselves associate with the disease. Presence of abnormal experiences.	Symptoms that the patient does not acknowledge to be a part of the disease. Absence or reduction of normal functioning.
Delusions Hallucinations Disorganized speech and behaviour	Affective flattening Asociality Anhedonia Avolition Blunted affect

[1]It Is more difficult to treat negative symptoms than positive symptoms

2.5.3 – Antipsychotic Drugs

	Typical antipsychotics (First generation)	Atypical antipsychotics (Second generation)
Main mechanism	D2 antagonism	Block D2 receptors Block serotonin receptors
Other effects[1]	Block alpha-1 Block H1 Block M receptors	
Positive symptoms	Reduction	Reduction
Negative symptoms	Secondary negative symptoms[2]	Some effect on reduction[2]
Clinical use	Positive symptoms of schizophrenia Acute psychosis Tourette's syndrome Small dose for anxiety or insomnia	Schizophrenia Depression
Toxicity	Anticholinergic symptoms Orthostatic hypotension Sedation and weight gain Extrapyramidal symptoms[3] Torsade's de pointes Hyperprolactinemia Neuroleptic malignant syndrome Degenerative retinopathy	
		Agranulocytosis[4] <u>Metabolic side effects</u> Hyperglycemia, diabetes Dyslipidemia, hypercholesterolemia
Drug examples	**Chlorpromazine** **Phenothiazine** **Haloperidol** **Droperidol**	**Clozapine** **Quetiapine** **Risperidone** **Paliperidone**

[1]Due to the drugs being non-selective there are a lot of side effects
[2]Because of underactivity of dopamine. The effect on serotonin in atypical antipsychotics are thought influence the negative symptoms
[3]More common in typical than atypical antipsychotics
[4]Most common with clozapine, and regular monitoring of blood cell counts are indicated



CLINICAL CORRELATION

Neuroleptic malignant syndrome (NMS)

- A patient with psychosis is treated with phenothiazines, after some time he experiences altered mental status, fever and autonomic instability
- For the doctor to diagnose the patient with NMS, at least two of the following must be present: diaphoresis, dysphagia, tremor, incontinence, altered consciousness, mutism, tachycardia, BP change, leukocytosis, muscle enzyme elevations
- Severe rigidity and hyperthermia are common
- The patient should immediately stop the neuroleptic drugs
- Treatment include treating hyperthermia, starting intensive hydration and forced diuresis, and prescribing dantrolene to reduce rigidity

MNEUMONIC

Symptoms in NMS: **FALTER**

Fever
Arms
Leukocytosis
Tremors
Elevated CPK
Rigidity

2.6 Affective Disorders

- Group of disorders affecting the mood
- Include depression and hypomania or mania

2.6.1 – Classification of Affective Disorders

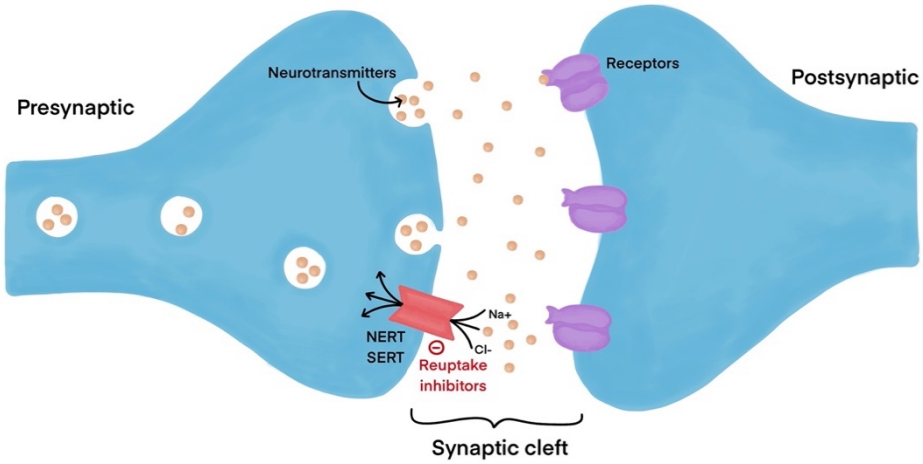
Bipolar and related disorders	Depressive disorders
Bipolar I disorder Bipolar II disorder Cyclothymic disorder	Disruptive mood dysregulation disorder Major depressive disorder (MDD) Persistent depressive disorder (PDD) Premenstrual dysphoric disorder
Substance/medication-induced Caused by another medical condition	

2.6.1 – Depression vs Hypomania

	Depression	Hypomania
Mood	Lowering	Persistent elevation
Self-perception	Reduced self-esteem and self-confidence, ideas of guilt and worthlessness	Marked feels of well-being, grandiose ideas, and overconfidence
Social	Reduced capacity of enjoyment (anhedonia), interest, energy and concentration	Increased sociability, talkativeness, over-familiarity
Activity	Psychomotor retardation	Increased energy and activity
Sleep	Disturbed	Decreased need
Libido	Loss of libido	Increased sexual energy
Appetite	Diminished	Diminished

2.6.2 – Antidepressants

- Treatment of depression is complex at aims at different aspects
    1. Antidepressants
    2. Lifestyle
    3. Psychotherapy
    4. Social
- Remember that all drugs increasing levels of serotonin are at risk of developing serotonin syndrome
- Many antidepressive drugs act on the reuptake transporters. Inhibition of these transporters allows for increased levels of neurotransmitters in the synapse, and thereby increased neurotransmission



I. Tricyclic antidepressants (TCA)

- Block reuptake of norepinephrine (NET) and serotonin (SERT)
- Other actions of TCA include antagonistic activity on H1, M, Alpha 1, and sodium channel
- Since TCA interact with other receptor types it is associated with severe toxicities like seizures and cardiac dysrhythmia
- Toxicity can be lethal, and should be treated with sodium bicarbonate

	Secondary amines	**Tertiary amines**
Mechanism	NET > SERT	More SERT
Clinical	Depression OCD Diabetic neuropathy Anxiety disorders Neuropathic pain Migraine prophylaxis	
Toxicities	Less side effects	More sedation[1] and side effects
Drugs	**Nortriptyline** **Desipramine**	**Amitriptyline** **Clomipramine**

[1]Often administered at bedtime

CLINICAL CORRELATION

Tricyclic antidepressants

- The choice of anti-depressants depends on the incidence of adverse effects
- For example, a patient which is very agitated or anxious, a TCA like amitriptyline that facilitates more sedation can be preferable

II. Selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI)

- SSRI has become the most commonly used drug for treatment of depression and some anxiety disorders

	Selective Serotonin Reuptake Inhibitors (SSRI)	**Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)**
Mechanism	Block SERT	Block NET and SERT
Compared to TCA	As effective but fewer side effects Increase alertness (taken in the morning)	No action on other receptors, thus fewer side effects
Effect	Take 1-2 months for maximum effect, not for acute treatment	
Clinical use	First-line depression First line OCD Bulimia nervosa Anorexia nervosa Panic disorder	Major depressive disorder Diabetic neuropathy Generalized anxiety disorder Fibromyalgia Menopausal flushing
Toxicities	Nervousness Dizziness Insomnia Male sexual dysfunction	
Drugs	**Fluoxetine**[1] (most common) **Fluvoxamine** **Sertraline**[2]	**Duloxetine** **Venlafaxine**

[1]Causes more drug interactions than other SSRIs
[2]Often preferred in elderly

CLINICAL CORRELATION

Prozac

- Prozac is a brand name for fluoxetine and is often referred to as the "happy pill" in daily life
- It is commonly used to treat depression

III. Other antidepressive drugs

- Most of the following drugs has partial activity on more receptors than are mentioned

Drug class	Mechanism	Positive	Negative	Drug
Serotonin Reuptake Inhibitors (SRI)	Antagonist at $5HT_{2A}$	No anticholinergic effects Minimal cardiac conduction	Sedation[1] Orthostatic hypotension	**Trazodone**
Serotonin modulator and stimulator (SMS)	Selective SERT	Very safe in comorbidities like renal and hepatic insufficiency		**Vortioxetine**
Noradrenaline reuptake inhibitors (NRI)	Inhibit reuptake at NET		The least effective antidepressant	**Reboxetine**
Noradrenaline dopamine reuptake inhibitors (NDRI)	Inhibit reuptake at DAT, NET, SERT	Few anticholinergic side effects Little sedation Rarely cardiovascular effects or sexual dysfunction[2]	Agitation Insomnia Nausea Weight loss	**Bupropion**
Atypical antidepressants	Blocks 5HT-2 and 5HT-3 receptors Increase central NE	Better tolerated and fewer side effect than TCA	Elevated hepatic enzymes Agranulocytosis	**Mirtazapine**
Monoamine oxidase inhibitors (MAO-I)	Irreversible inhibition of monoamine oxidase (MAO-A) [3]	Alternative therapy in failure of response	Many drug interactions Hypertensive crisis (Avoid tyramine containing food)[4]	**Isocarboxazid**

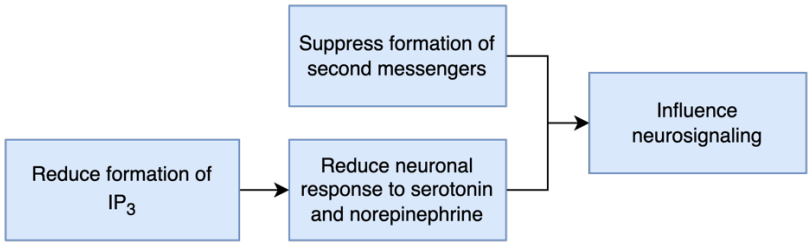
[1]Used when sleep disturbances are one of the worst symptoms
[2]Can be beneficial for patients suffering from sexual dysfunction caused by the other drugs
[3]Enzyme responsible for degradation of norepinephrine, dopamine, and serotonin
[4]Can increase the risk of hypertensive crisis

2.6.3 - Mood Stabilizing Drugs

- Drugs that aim to reduce mood swings in patients with bipolar disorder
- Lithium is the most commonly used mood stabilizing drug

I. Lithium

- Lithium is a drug that reduces both manic and depressive symptoms, but it is more effective in the manic phase

<table>
<tr><th></th><th colspan="2">Lithium</th></tr>
<tr><td>Mechanism</td><td colspan="2">Not well understood, but believed to suppress formation of second messengers and inositol triphosphate
 
</td></tr>
<tr><td>Effect</td><td colspan="2">Stabilizing from “above”
Calming effect in manic patients, and mild antidepressive effect</td></tr>
<tr><td>Onset</td><td colspan="2">Onset is days or weeks, and adjunct therapy is indicated until maximum response to lithium</td></tr>
<tr><td>Clinical use</td><td colspan="2">Bipolar disorders, especially with recurrent manic episodes
Anti-suicidal effect
Enhance effectiveness of antidepressants</td></tr>
<tr><td rowspan="2">Toxicity</td><td colspan="2">Narrow therapeutic index[1]</td></tr>
<tr><td><u>Lithium overdose (increased levels)</u>
First symptom: nausea and vomiting
Neurotoxicity and cardiotoxicity</td><td><u>Side effects (therapeutic levels)</u>
Drowsiness
Weight gain
Hand tremor
Polyuria
Hypothyroidism</td></tr>
<tr><td>Interactions</td><td colspan="2">NSAIDS and diuretics decrease lithium clearance</td></tr>
<tr><td>Contraindications</td><td colspan="2">Teratogenic, can cause Epstein’s anomaly</td></tr>
</table>

[1]There is a low margin of toxicity, and serum concentration should always be monitored

II. Other mood-stabilizing drugs

- Some drugs are thought to have an equal or greater efficiency and to be better tolerated than lithium
- These drugs are covered more thoroughly in an earlier chapter.

	Mechanism	Indications in mood-stabilizing	Stabilizer
Carbamazepine	Inhibits sodium channels	Second choice stabilizers	From “above”
Valproate	Inhibits sodium channels and enhance GABA	Manic episodes	From “above”
Lamotrigine	Inhibits sodium channels and decrease glutamate release	Depressive episodes	From “below”

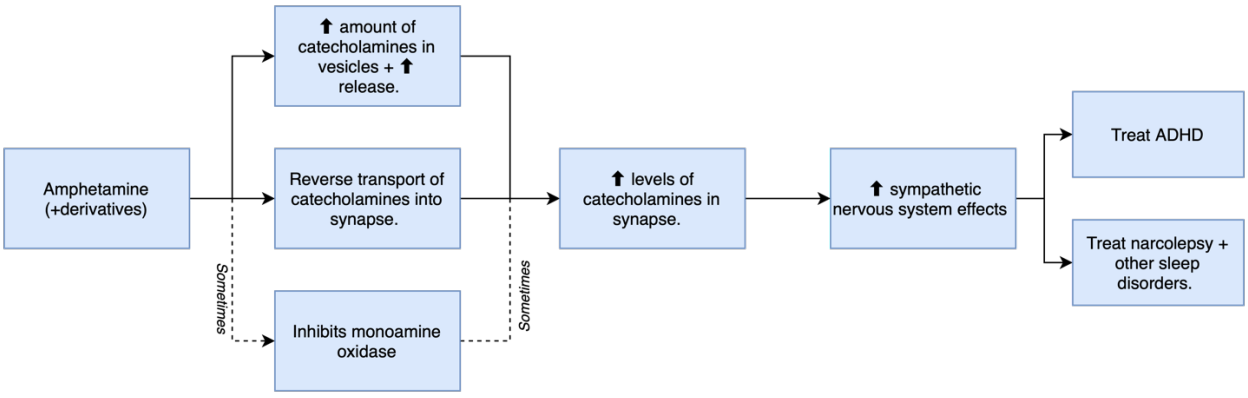
2.7 – Central Nervous System Stimulants

- Stimulants are substances that enhance neural activity, increasing attention, alertness, and energy level. They usually work by increasing release or blocking reuptake of neurotransmitters, e.g. dopamine or norepinephrine, in the brain.

2.7.1 – Sympathomimetics

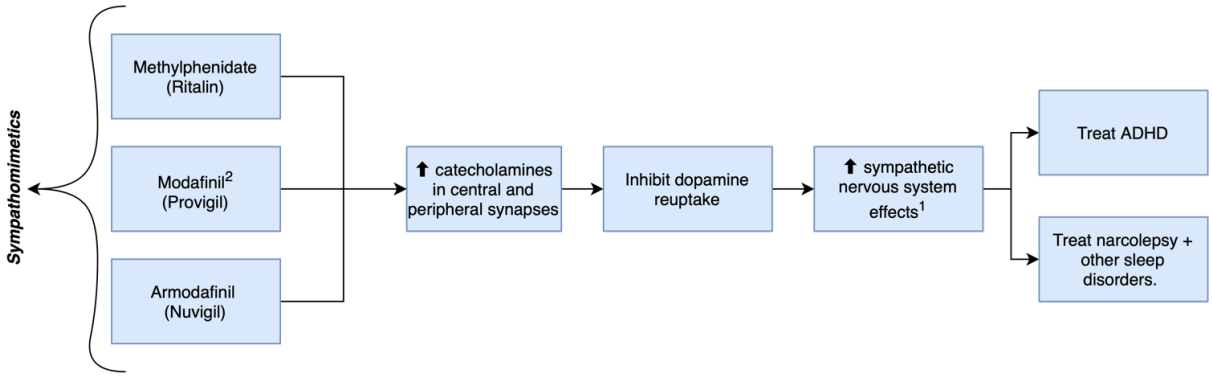
- Used to treat ADHD, narcolepsy, obstructive sleep apnea and shift work sleep disorder.

I. Amphetamine - see also 4.2.1



II. Sympathomimetics increasing catecholamines

- Substances that produce effects similar to the sympathetic nervous system.



[1] Less irritability, anxiety and anorexia than amphetamine.

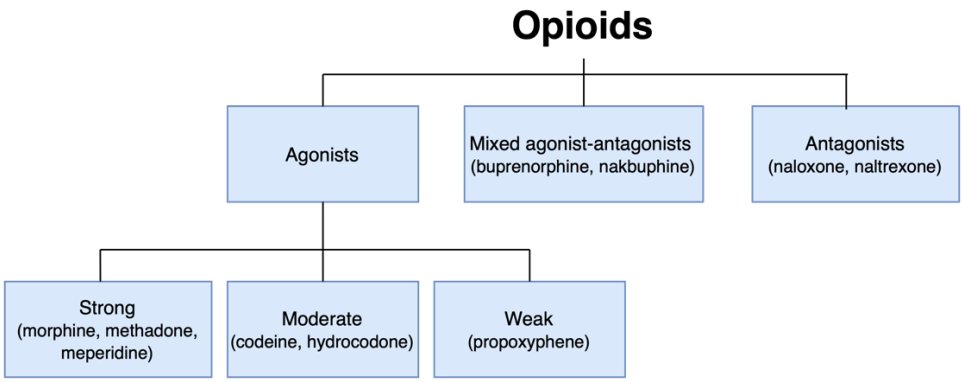
[2] Not approved for ADHD treatment in children.

III. Other sympathomimetics

	Mechanism	Clinical	Risk factors
Atomoxetine	Norepinephrine reuptake inhibitor	Treat ADHD	- Cardiovascular risks - Decrease weight gain and growth in children - Potential for drug abuse
Phentermine (amphetamine derivative)	Sympathomimetic mechanisms stimulating satiety center.	Appetite suppressant (obesity treatment)	

2.7.2– Opioids

- Opioids interact with opioid receptors in the brain and the body to relieve pain and produce feelings of euphoria and relaxation. They include substances like morphine, oxycodone, and fentanyl.



I. Opioids and pain

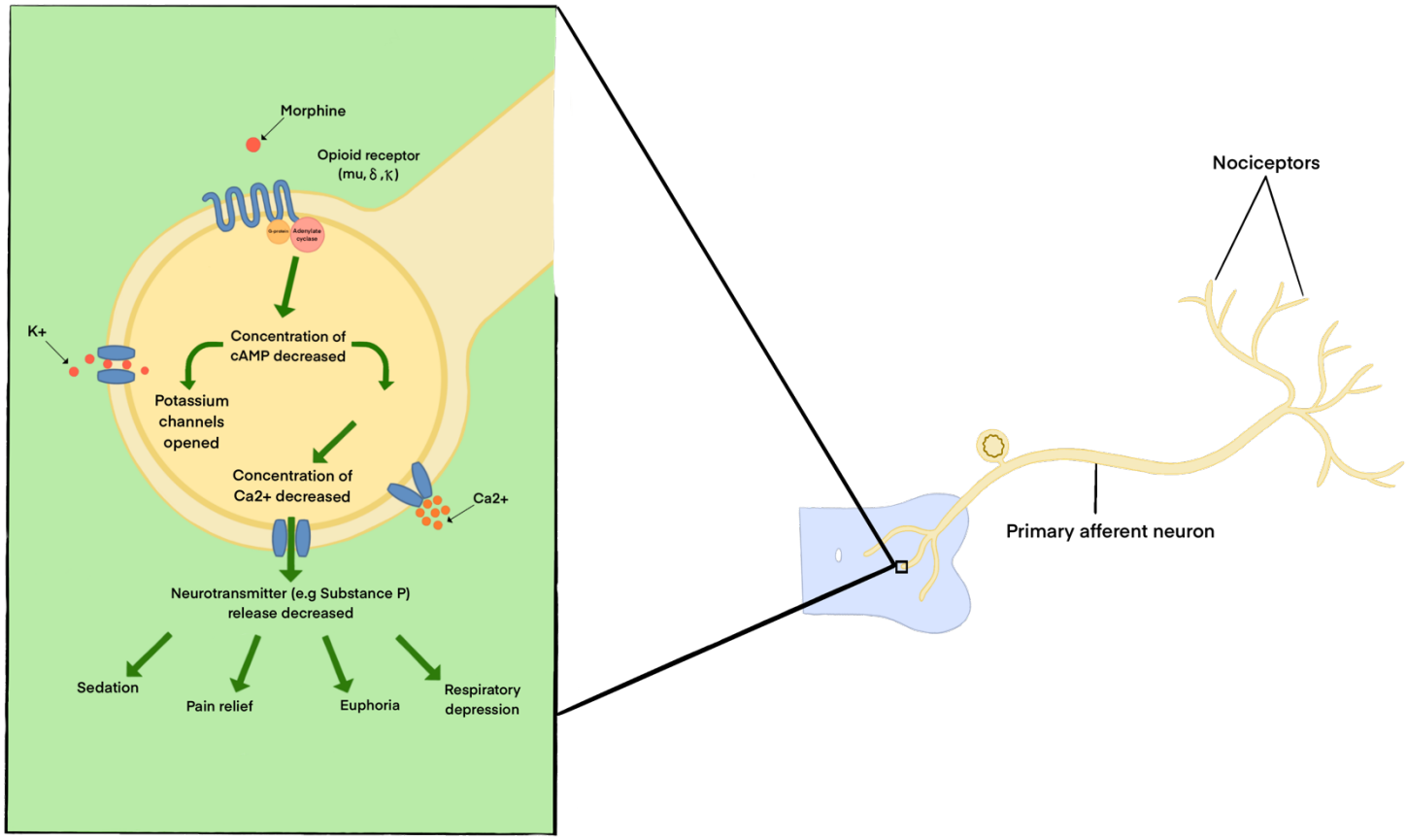
- Pain is an uncomfortable and emotional experience alerting an individual to actual or potential tissue damage. Analgesics are a symptomatic treatment of pain.
- Opioid analgesics act in the spinal cord and brain to inhibit the neurotransmission of pain.
- Opioid receptors: μ (mu), δ (delta) and κ (kappa); mostly μ clinically

II. Classification

- Strong agonists: well tolerated, relieve severe pain.
- Moderate agonists: submaximal doses used for moderate/mild pain + NSAIDs.
- Mixed agonist-antagonist: varying combinations lead to various degree of affinity.
- Antagonists: no analgesic effects

III. Tolerance

- Chronic or long-term administration of opioids will decrease the pharmacological effects, leading to increased doses necessary for the same analgesic



CLINICAL CORRELATION

Opioid allergy

- An allergy to opioids is not uncommon. It can present in various ways, e.g. skin reactions, respiratory symptoms, GI symptoms, swelling or cardiovascular symptoms.
- Usually, a patient who is allergic to one opioid can use an **opioid from a different chemical class**.
- E.g. fentanyl could probably be used in a patient allergic to codeine.

2.7.3 – Opioid Agonists

I. Strong opioids

- Equivalent analgesic effects, but differ in pharmacokinetic properties, adverse effects and uses.
- Opioid agonists have respiratory depression and sedation as adverse effects.

	Route of administration	Duration	Active metabolite	Clinical (pain related to...)	Adverse effects
Morphine	Oral (larger doses), Parenteral	4h	6-glucuronide	Trauma, MI, cancer PULMONARY EDEMA?	Nausea Constipation
Fentanyl	Parenteral, transdermal, sublingual, buccal	1h	No	Chronic pain, augment anesthesia	Truncal rigidity
Remifentanyl	IV	4 min (ultrarapid onset)	No	Anesthesia (short procedures)	
Meperidine	Oral, Parenteral	3h	Normeperidine	Obstetric or postsurgical	Seizures, tremor
Methadone	Oral, Parenteral	8h	No	Chronic, treat opioid addiction	
Oxycodone	Oral	4h	No	Acute and chronic	
Hydromorphone	IM, IV, subcutaneous, rectal, oral.	4h	3-glucuronide (a little 6-glucuronide)	Acute and chronic	

II. Moderate opioid agonists

- Used at submaximal doses in combination with an NSAID.

	Mechanism	Clinical	Toxicities
Codeine	μ-receptor agonist	Always combined with NSAIDs: - mild to moderate pain - diarrhea - cough (codeine)	(less than the strong opioids) - Respiratory depression - Constipation - Addiction liability
Hydrocodone			

III. Other opioid agonists

	Mechanism	Clincial	Toxicities
Tramadol	μ-receptor agonist + inhibits reuptake of serotonin and norepinephrine	Used orally to manage chronic pain Only partially inhibited by naloxone	Minimal opioid toxicities - Increased seizure risk (in combination with antidepressants) - increased risk of suicidality
Tapentadol	μ-receptor agonist + Inhibits reuptake of norepinephrine		
Dextromethorphan	weak μ-receptor agonist + NMDA blocker	Anti-cough medication	Toxic in overdose
Diphenoxylate	μ-receptor agonist in GI smooth muscle	Oral administration Treatment of diarrhea	Chronic ingestions: -> anticholinergic side effects (diphenoxylate)
Loperamide (Imodium)		*Do not use in diarrhea with fever!*	-> cardiac toxicity (loperamide)

CLINICAL CORRELATION

Loperamide/Imodium

- To be allowed to go scuba diving, one should not be sick, however, whilst traveling people might experience a stomach bug and wish to avoid stomach issues during diving.
- This is not recommended, as Loperamide/Imodium **might not work underwater.**
- Should also be avoided as it can have sedative effects, therefore should not be used whilst diving.

IV. Mixed opioid agonist-antagonist

- Agonist/antagonist activity at μ-receptors + agonist/antagonist activity at κ-receptors.

	Buprenorphine	**Butorphanol**	**Nalbuphine**	**Pentazocine**
Route of admin.	Sublingual	Parenterally (+nasal)	Parenterally	IM (IV + subcut.+ oral)
Clinical	Sedation	Postoperative pain + migraine induced pain	Moderate pain	Sedation Child delivery
Receptors	κ- + δ- antagonist μ-partial agonist	κ-agonist μ-antagonist/agonist (weak)	κ-agonist μ-antagonist (weak)	κ-agonist μ-antagonist (weak)

2.7.4 – Opioid Antagonists

- Naltrexone and naloxone are competitive opioid receptor antagonists.
- Used for treatment of opioid overdose, alcohol and opioid dependence, and opioid-induced constipation.

	Naloxone	**Naltrexone**
Mechanism	Opioid receptor antagonists	
Duration	1-2h	24-36h (can also be used long-term)
Route of administration	IV Nasal spray	Oral
Clinical	- Opioid overdose - Opioid maintenance therapy - Opioid-induced constipation	- Alcohol and opioid dependance - Opioid-induced constipation

2.8 - Test Yourself

1. What is the antidote to benzodiazepines?
a) Naloxone
b) Flumazenil
c) Tramadol
d) Aspirin

2. Which drug is not used in the treatment of generalized tonic-clonic seizures?
a) Valproate
b) Carbamazepine
c) Phenytoin
d) Pregabalin

3. Which local anesthesia can only be used for topical anesthesia?
a) Bupivacaine
b) Lidocaine
c) Prilocaine
d) Cocaine

4. How is the potency of inhalational anesthetics measured?

_____

_____

_____

5. Describe the actions of anticonvulsant drugs?

_____

_____

_____

6. What is the first-line drug for all seizures?
a) Phenytoin
b) Barbiturates
c) Benzodiazepines
e) Valproate

7. What is the first-line drug for depression?
a) SSRI
b) Clozapine
c) TCA
d) Valproate

8. Which phase of bipolar disorder is treated with lithium?
a) Manic phase
b) Depressive phase

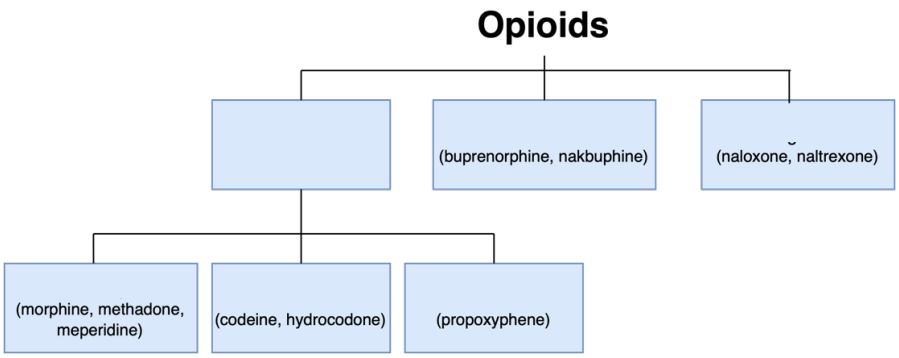
9. Which anesthetic can cause dissociative anesthesia?

a) Propofol
b) Etomidate
c) Barbiturate
d) Ketamine

10. Drag a line between the drug class and the suffix

Benzodiazepines	-Pam
Barbiturates	-Caine
Local anesthetics	-Tal

11) Fill in the correct opioid classification.



12) A patient presents to the doctor experiencing itching, hives and swelling after ingestion an opioid for pain relief. Do the patient have to find another analgesic than opioids to treat their chronic pain?

_____

_____

_____

13) Match the duration of action with the correct strong opioid?

1)	Morphine	a)	4h
2)	Remifentanyl	b)	1h
3)	Methadone	c)	4 min
4)	Fentanyl	d)	8h

14) What other analgesic is moderate opioid agonists usually combined with?

a) Paracetamol

b) NSAIDs

c) Tramadol

d) Local anesthetics

15) Which of the following mixed opioid agonist-antagonists IS NOT an κ-receptor agonist?

a) Buprenorphine

b) Butorphanol

c) Nalbuphine

d) Pentazocine

16) Why do first-responders use naloxone instead of naltrexone when treating an opioid overdose?

a) Naloxone can be administered as a nasal spray.

b) Naloxone has a short half-life and may need repeated doses.

c) Naltrexone has high oral bioavailability and is used long-term to treat opioid addicts.

d) All of the above

Section 3 – Drugs for Neurodegenerative Diseases

3.1 – General About Neurodegenerative Diseases

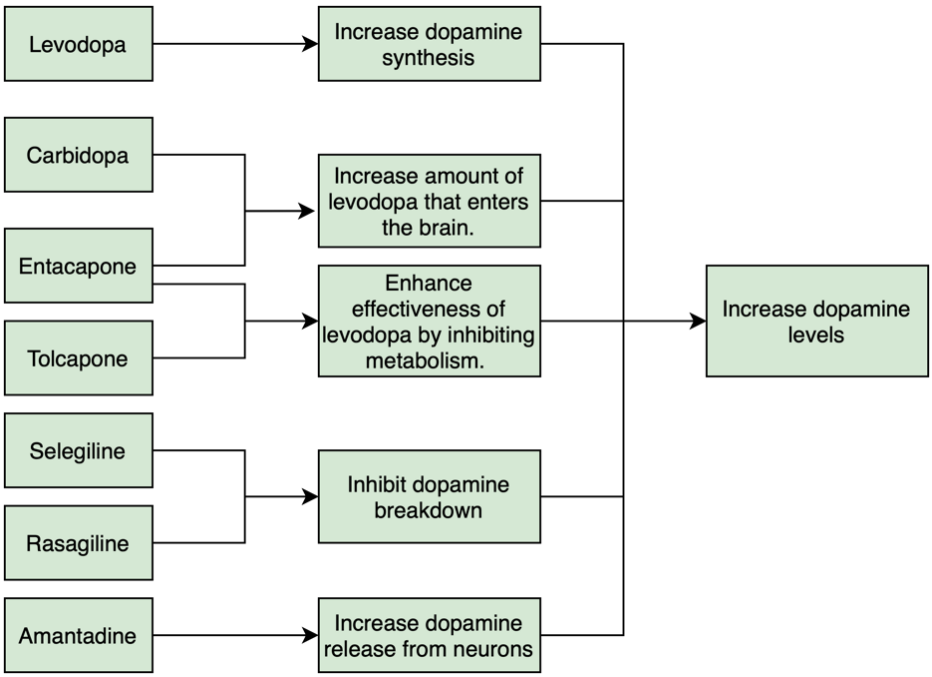
- Neurodegenerative diseases are characterized by loss of function in groups of neurons in different parts of the CNS.
- They are pathological, progressive, and with unknown etiology. However, they are suggested to be caused by environmental factors, autoimmunity, or inheritance.
- There is limited research on neurodegenerative diseases, however, there are newly introduced drugs on both Parkinson and Alzheimer disease.
- Drugs from different chemical classes are used to treat different symptoms of the diseases.

3.2 – Parkinson Disease

- Resting tremor, rigidity, bradykinesia, gait problems and postural instability are typical symptoms of parkinsonism.
- This results from extensive degeneration of dopaminergic neurons in substantia nigra, which leads to loss of dopamine production in the brain.

3.2.1– Drugs that Increase Dopamine Levels

- Increasing the dopamine levels will not prevent or stop the progression of the disease, but it will help avert the symptoms.
- Dopamine itself cannot cross the blood-brain barrier to a significant extent by itself and can therefore not be used.

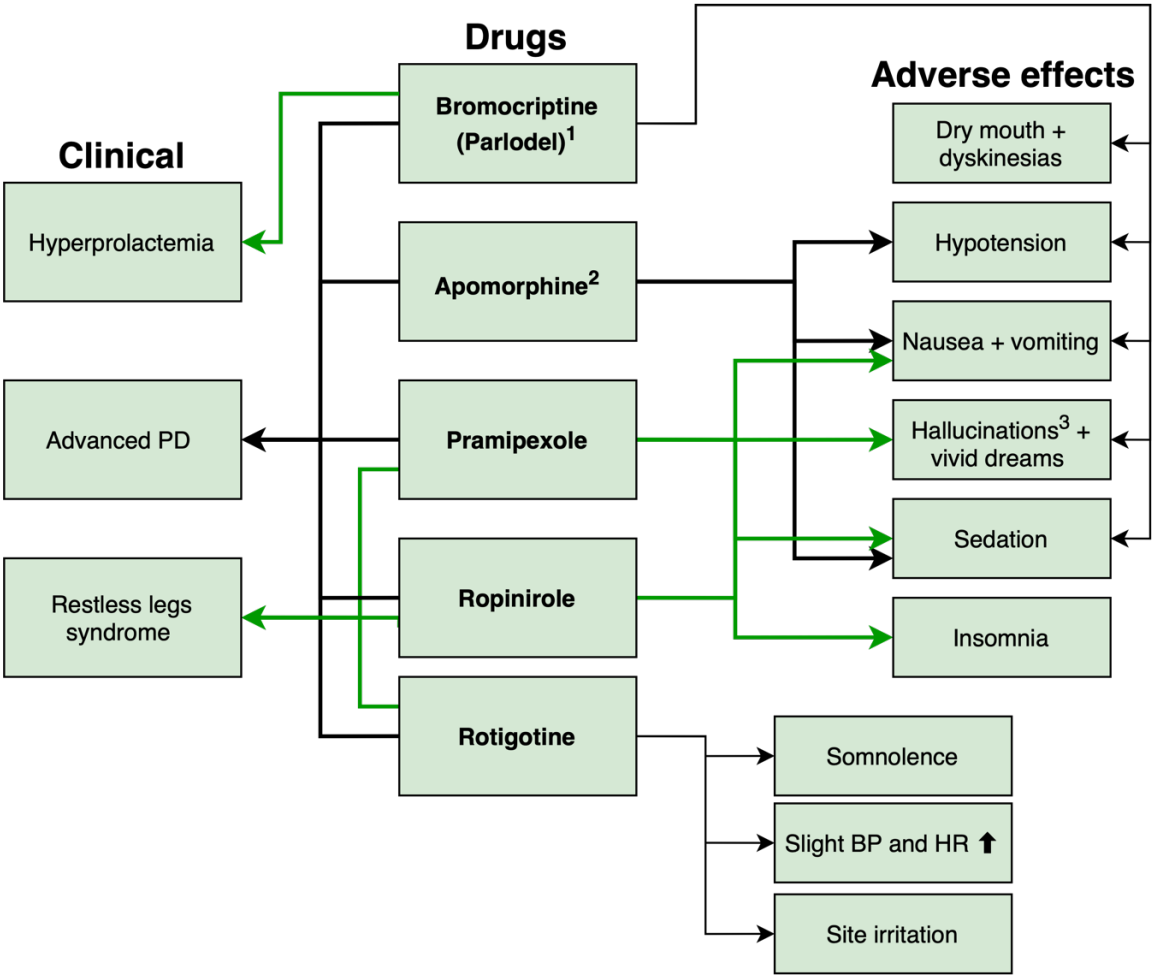


3.2.2 – Dopamine Receptor Agonists

- Activate dopamine receptors directly.
- Useful in advanced cases of Parkinson´s (almost no neurons left) as they do not need a functional dopaminergic neuron to produce an effect.

	D_1	D_2	D_3
Apomorphine	Dopamine receptor agonist		
Bromocriptine (Parlodel)[1]	Antagonist	Agonist	-
Pramipexole	-	Agonist	Agonist
Ropinirole	-	Agonist	-
Rotigotine	-	Agonist	Agonist

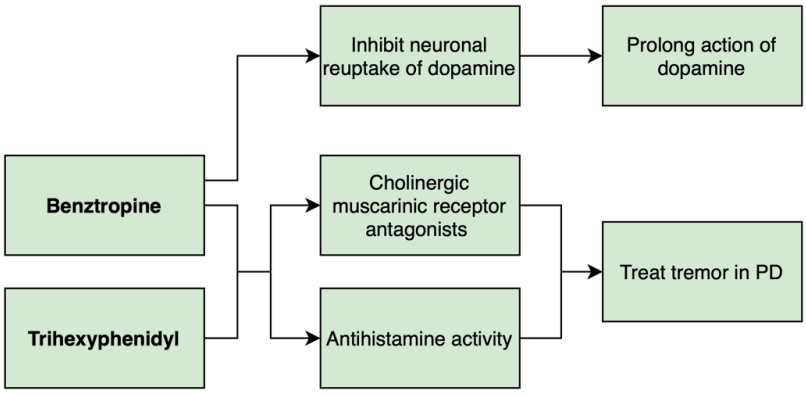
[1] Ergot alkaloid (same class as LSD)



[1] A formulation can be used for diabetes 2
[2] For acute intermittent hypomobility in PD
[3] Pimavanserin (antipsychotic) is used for treating the hallucinations associated with PD or the treatment of PD.

3.2.3 – Cholinergic Receptor Antagonists (antimuscarinic agents)

- Dopaminergic drugs are generally more effective, but antimuscarinic agents may be helpful in combination.
- Reduce tremor in PD.

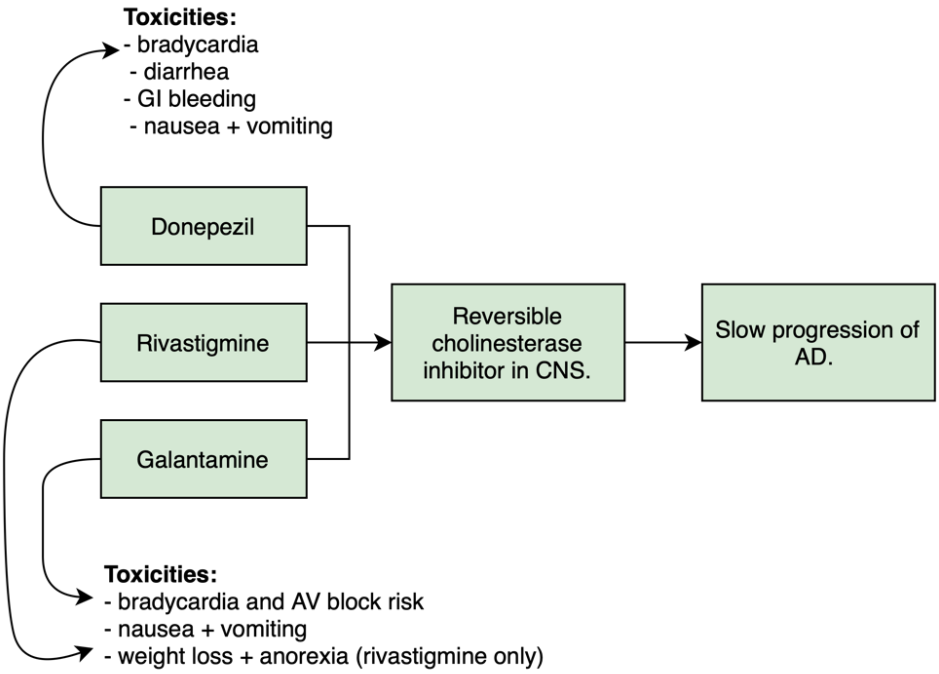


3.3 – Alzheimer Disease

- Neurodegenerative disease of unknown etiology, characterized by progressive cognitive impairment (especially memory and cognition), severe disability, and dependence.

3.3.1 – Central Acetylcholinesterase Inhibitors

- Used to improve the cholinergic neurotransmission.
- Does not change course of disease, only slows the cognitive deterioration.
- Mechanism of AChE is covered in pharmacology booklet 1.



3.3.2 – Other Agents

	Mechanism	Clinical	Toxicities
Caprylidene	Metabolized into ketone bodies -> replace depleted glucose levels	Dietary supplement Age-associated memory impairment and AD.	- diarrhea - other GI symptoms
Memantine	Noncompetitive NMDA-receptor antagonist	Dementia of AD	- confusion - dizziness + headache - drowsiness - insomnia

CLINICAL CORRELATION

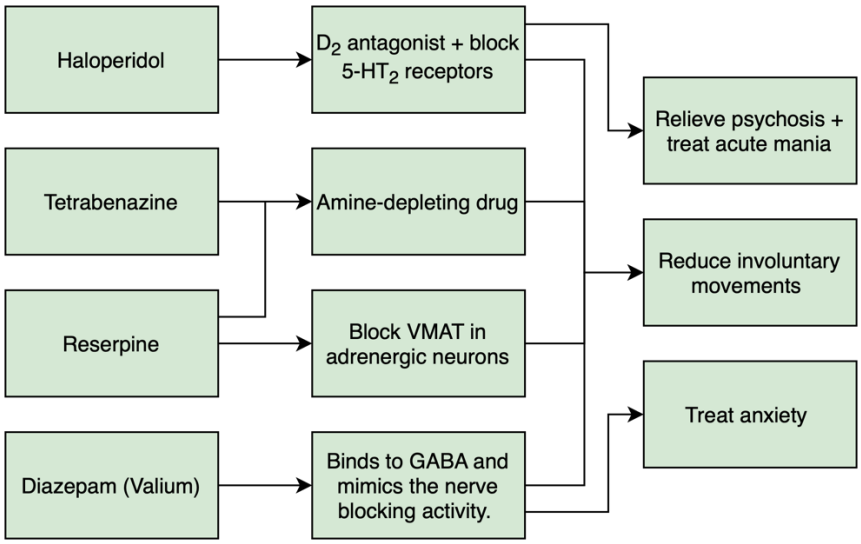
Pseudobulbar affect

- **Dextromethorphan** is a drug with significant antitussive effects
- Combined with **quinidine** (antiarrhythmic), dextromethorphan can be used in the treatment of **pseudobulbar affect.**
- Pseudobulbar affect includes outbursts of uncontrollable crying or laughter in inappropriate settings, often seen in AD, MS and ALS.
- Dextromethorphan inhibits NMDA receptors that are involved in regulating emotional expression. Quinidine inhibits the CYP2D6 enzyme which metabolizes dextromethorphan, resulting in an increase of the drug.

3.4 – Huntington Disease

- An autosomal dominant disorder with involuntary "dancing" movements (chorea) and often psychosis or dementia.
- The GABA function in the brain is diminished and the dopaminergic functions enhanced.

3.4.1 – Drugs



3.4.2 – Adverse effects

	Adverse effects
Haloperidol	Extrapyramidal dysfunction.
Tetrabenazine	Less troublesome adverse effects - Depression - Hypotension - Sedation
Reserpine	Less troublesome adverse effects - Sedation - Severe psychiatric depression (high doses) - Hypotension
Diazepam (Valium)	- hallucinations - delusions - frequent falls

3.5 – Multiple Sclerosis (MS)

- MS is a chronic autoimmune disorder that affects the CNS
- It is characterized by inflammation, damage to the myelin sheaths, and disruption of nerve impulses. This results in a wide range of symptoms, including fatigue, muscle weakness, numbness, and coordination problems.
- The disease can either have a relapsing or progressive development.

	Mechanism	Clinical
Dalfampridine	Block potassium channels ⟶ enhanced conduction in damaged nerves.	Improve walking
Fingolimod	↓ the number of lymphocytes circulating in PNS and CNS, by binding the sphingosine 1-phosphate S1P receptor.	↓ rate of relapses and slow progression of disease.
Interferon beta (β)-1b	↓ the immune response that Is directed against myelin.	↓ frequency of relapses + ↓ number of new lesions
Prednisone	Corticosteroids used to relieve inflammation.	↓ duration of relapse + ↓ MS flare symptoms.
Teriflunomide[1]	↓ formation of overactive immune cells → ↓ inflammation and ↓ damage to CNS nerves.	↓ rate of relapses and slow progression of disease.
Dimethyl fumarate	Activate the nuclear factor (erythoid-derived)-like-2 (NFR-2) transcriptional pathway.	↓ stress, demyelination and nerve cell inflammation.

[1] risk of hepatic toxicity

3.6 – Amyotrophic Lateral Sclerosis (ALS)

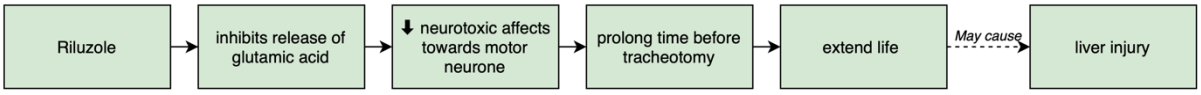
- ALS = Lou Gehrig disease
- Progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord, causing weakness, muscle wasting and lead to respiratory failure.
- Cause/etiology unknown.
- Current treatment is mostly symptomatic.

3.6.1 – Gabapentin

	Mechanism	Clinical	Toxicities
Gabapentin (antiepileptic)	Structural analog of GABA, does not activate GABA receptors directly.	Slow muscle strength decline + Nerve pain	- Dizziness - Sedation - Ataxia - Nystagmus

3.6.2 – Riluzole

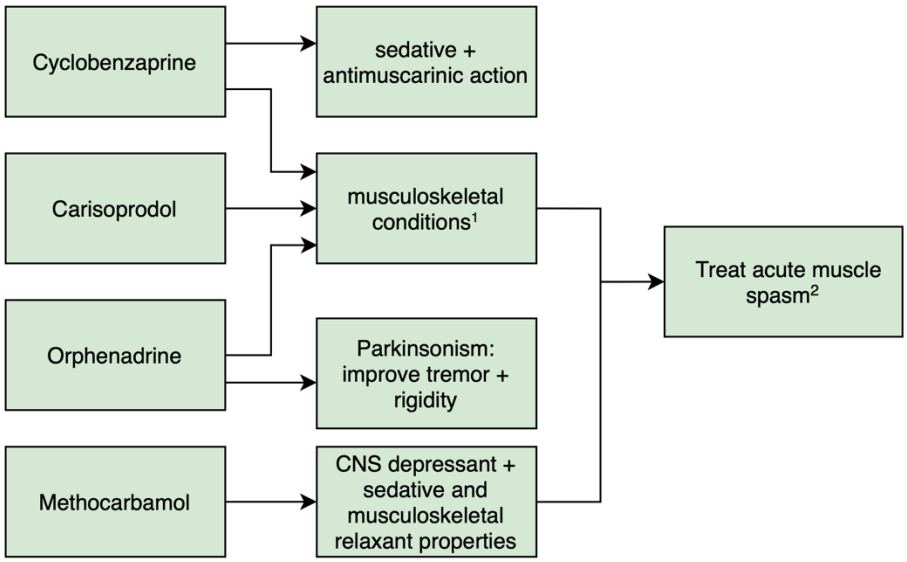
- Riluzole is the only drug that is specifically approved for ALS.



3.7 – Antispastic Drugs

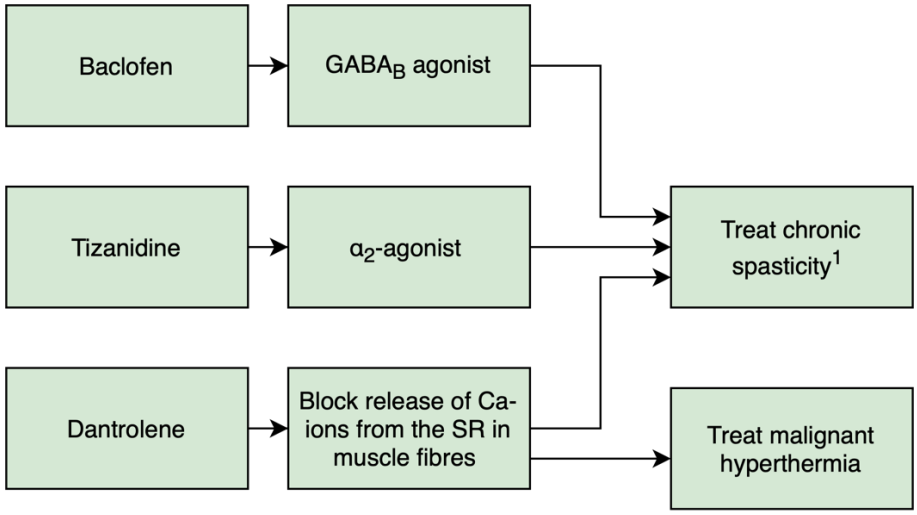
- Antispastic drugs/muscle relaxants treat abnormally, severe, elevated skeletal muscle tone, spasms, caused by neurologic disease or injury.

3.7.1 – Treatment of Acute Spasticity



[1] not effective in muscle spasm resulting from CNS diseases
[2] these drugs are only used in short-term treatment.

3.7.2 – Treatment of Chronic Spasticity



[1] due to e.g. MS

CLINICAL CORRELATION

Malignant hyperthermia

- This emergency can be triggered by general anesthesia protocols (succinylcholine or tubocurarine).
- This is a severe condition including rapid temperature rise, muscle stiffness, tachycardia, tachypnea, sweating and altered mental status.
- It is characterized by a **massive release of calcium** from the sarcoplasmic reticulum of skeletal muscles.
- **Dantrolene** is given to block calcium release.

3.7.3 – Other Antispatic Drugs

	Mechanism	Clinical	Toxicities
Botulinum toxin A (BOTOX)	Produced by Clostridium Botulinum Block release of Ach -> inhibits neuromuscular transmission.	- Urinary incontinence - Reduce pain caused by severe spasm - Treat localized spasm (e.g. of eyes or face) - Parkinson disease symptoms - Cosmetic: reduce facial wrinkles	- Dry mouth - Dysphagia - Paralysis

3.8 – Test Yourself: Neurodegenerative Diseases

1) Match the drug with the correct mechanism of increasing dopamine levels:

1) Selegiline	a) Increase dopamine synthesis
2) Levodopa	b) Increase amount of levodopa that enters the brain
3) Carbidopa	c) Increase dopamine release from neurons
4) Amantadine	d) Inhibit dopamine breakdown

2) Why are dopamine receptor agonists (e.g. apomorphine) useful in advanced cases of Parkinson's?

a) They provide immediate relief from symptoms.
b) They do not need a functional dopaminergic neuron to produce an effect.
c) They slow down progression by protecting dopaminergic neurons from further damage.
d) They never cause side effects.

3) Which dopamine receptor agonists are D_2 and D_3 receptor agonists?

a) Pramipexole and Rotigotine
b) Rotigotine and Ropinirole
c) Bromocriptine and Pramipecole
d) Bromocriptine only

4) Which toxicity is seen only in rivastigmine, not the other central acetylcholinesterase inhibitors?

a) bradycardia
b) nausea + vomiting
c) GI bleeding
d) weight loss + anorexia

5) Fill in the blanks in the information about Huntington Disease:

- An autosomal dominant disorder with involuntary "dancing" movements (_____) and often psychosis or dementia.
- The GABA function in the brain is _____ and the dopaminergic functions _____.

6) Which of the MS drugs have a risk of hepatic toxicity

a) Prednisone
b) Fingolimod
c) Teriflunomide
d) Interferon beta-1b

7) Fill in the blanks:

	Clinical
Dalfampridine	_____
	↓ rate of relapses and slow progression of disease.
Interferon beta (β)-1b	↓ frequency of relapses + ↓ number of new lesions
	↓ duration of relapse + ↓ MS flare symptoms.
Teriflunomide[1]	↓ _____ and slow progression of disease.
Dimethyl fumarate	↓ stress, demyelination and nerve cell inflammation.

8) Which drug is the only drug that is specifically approved for treating ALS (Lou Gehrig disease)?

_____

_____

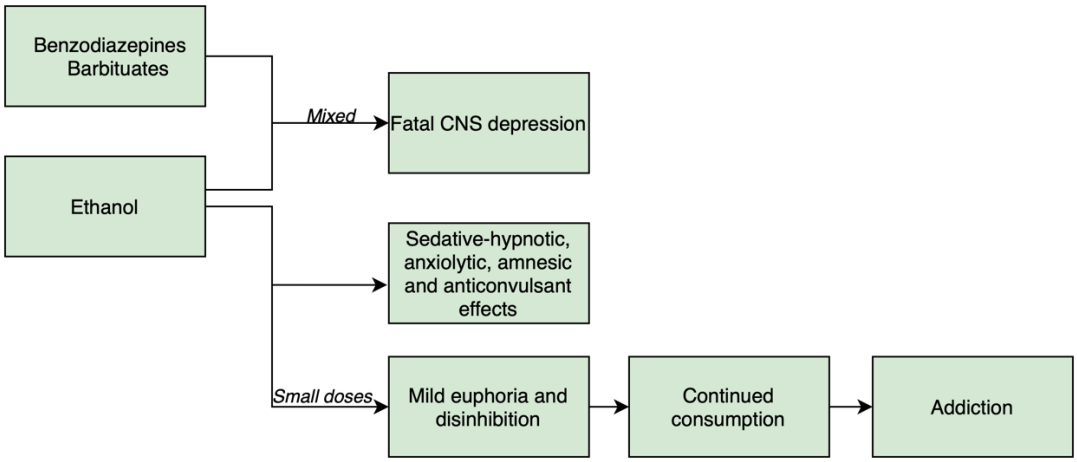
9) Which drug treats chronic spasticity?

a) Cyclobenzaprine
b) Baclofen
c) Orphenadrine
d) Methocarbamol

4.1 – Central Nervous System Depressants

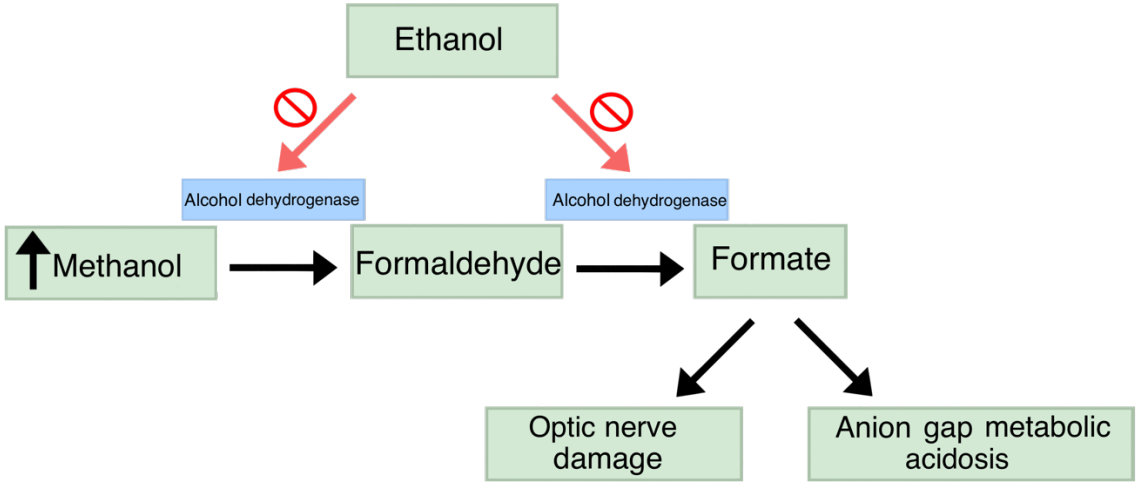
4.1.1 – Alcohols and Glycols

I. Effects



II. Methanol toxicity

- Methanol is a toxic form of alcohol; it can lead to optic nerve damage and anion gap metabolic acidosis.
- Methanol toxicity is treated with ethanol. Ethanol has a greater affinity for alcohol dehydrogenase and will more easily saturate it, this prevents the formation of formaldehyde and formate from methanol.

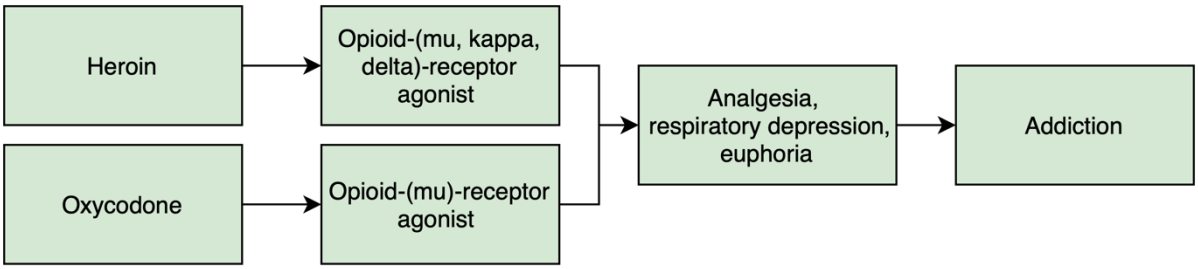


4.1.2 – Barbiturates and Benzodiazepines

- Sedative-hypnotic agents to treat anxiety disorders, insomnia, and other conditions.
- Long-term use leads to dependence.
- Withdrawal symptoms are similar to alcohol withdrawal.

	Flunitrazepam ("roofies"/Rohypnol)	**Pentobarbital**	**Gamma-hydroxybutyrate (GHB)**
GABA receptor	$GABA_A$ (benzodiazepam)	$GABA_A$ (barbiturate)	$GABA_B$
Taste?	No	Bitter	Salty
Clinical	Drowsiness, anterograde amnesia, impaired motor skills	Induce sleep, cause sedation	CNS depressant
"Date rape" drug?	Yes	No	Yes
Risk	Addiction, cognitive decline	Respiratory and cardiovascular depression	Death due do CNS depression when mixed with alcohol

4.1.3 – Opioids

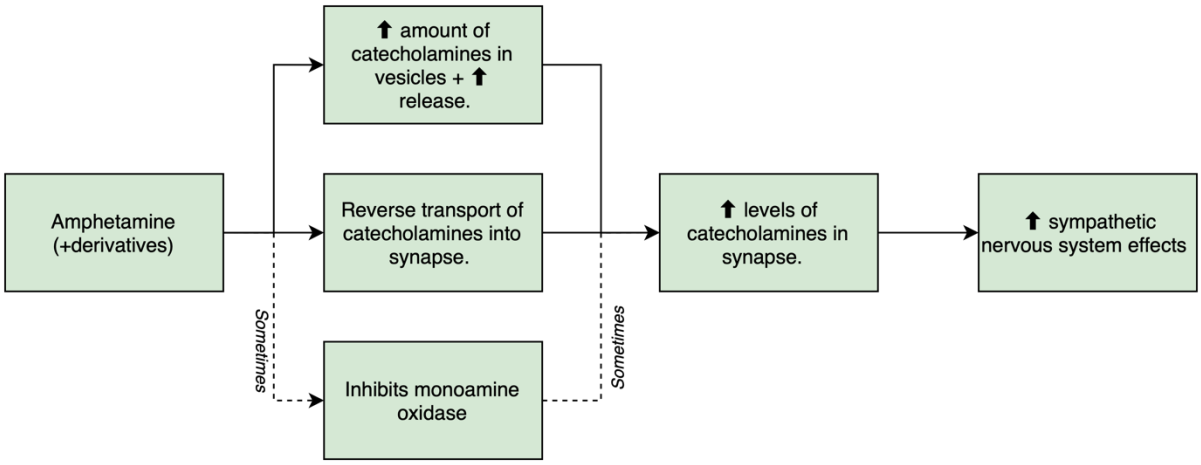


4.2 – Central Nervous System Stimulants

- Increase concentration of norepinephrine and dopamine in dopaminergic synapses. Mimic effects of the sympathetic nervous system.

4.2.1 – Amphetamine and its derivatives

I. Mechanism

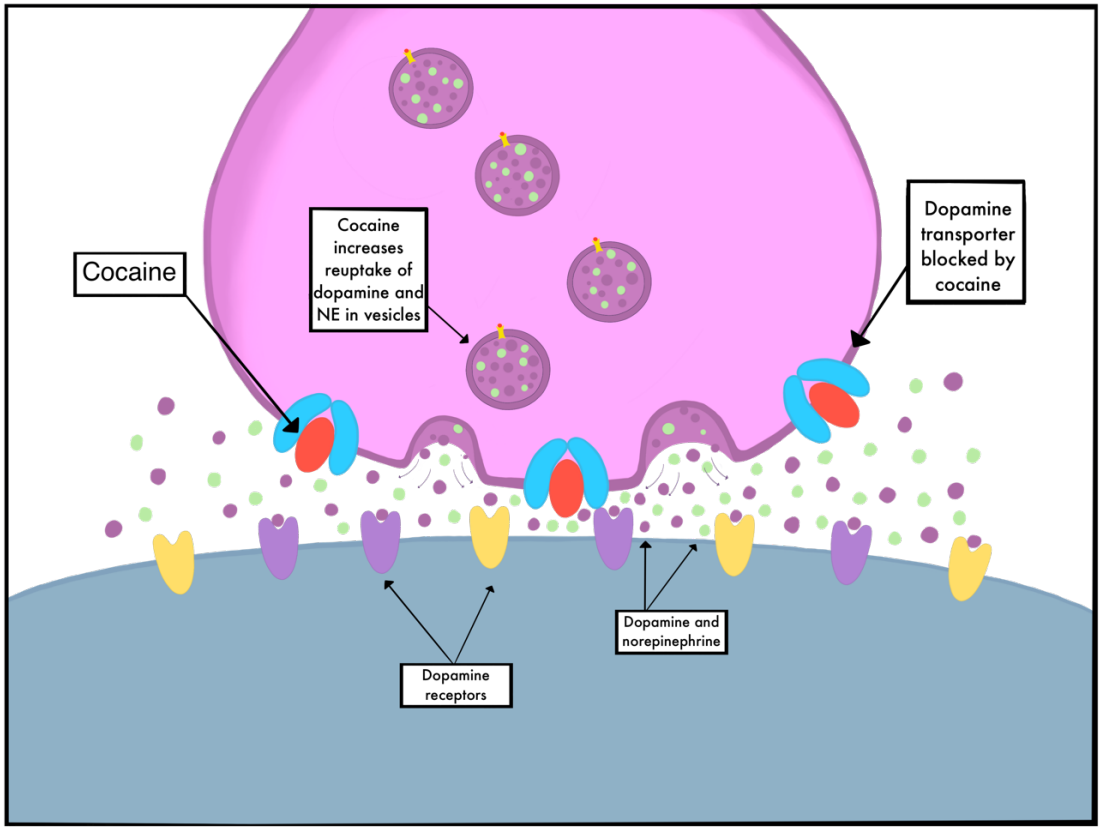


II. Clinical aspect

	Clinical	Drug abuse
Amphetamine	Medical indications for ADHD, obesity, narcolepsy and other sleep disorders. No specific antidote.	- Central and peripheral effects, e.g. euphoria - Sympathomimetic effects
Metamphetamine		*Crystal meth:* - Euphoria - Cheap - Easy production
3,4-methylene-dioxy-methamphetamine (MDMA)	PTSD + other mental health conditions	- Euphoria - Hallucinogenic properties - Sexual enhancer

4.2.2 – Other stimulants

	Clinical	Drug abuse	Toxicities
Cocaine	Psychostimulant Local anesthetic	- Euphoria - Self-confidence - Mental alertness	- Alter tactile sensations - Cheyne-Stokes respiration - Cardiovascular, pulmonary, and neural toxicity
Nicotine	Treating dependence	- Mild euphoria ++ - Pharmacokinetic tolerance	- Excessive CNS stimulation - Cardiac toxicity - Respiratory paralysis
Caffeine	IV to treat apnea in neonates Prevent fatigue	- Euphoria - Hallucinogenic properties - Sexual enhancer	- Cardiovascular, respiratory and neoplastic disease



One can see that cocaine blocks dopamine reuptake transporters, resulting in dopamine and norepinephrine stimulating the dopamine receptors longer. Cocaine also increases the reuptake of dopamine and NE into the vesicles that are released into the synapse with dopamine receptors.

4.3 – Other Psychoactive Drugs

4.3.1 – Cannabis and its Derivatives

- THC (tetrahydrocannabinol) is the main psychoactive compound in cannabis, causing the "high" sensation. It binds to cannabinoid receptors in the brain and body, which affect mood, pain perception, and appetite.

<table>
<tr><th></th><th>Mechanism</th><th>Clinical</th><th>Toxicities</th></tr>
<tr><td>Marijuana</td><td rowspan="3">THC regulate neurotransmitter release
-> Modulate activity of acetylcholine, dopamine and serotonin</td><td>Headache, insomnia, chronic pain</td><td rowspan="3">- Drug dependance
- Mild euphoria followed by a depressive phase
- Impairment of judgement and reflexes</td></tr>
<tr><td>Dronabinol</td><td>Treat nausea (cancer chemotherapy)</td></tr>
<tr><td>Nabilone</td><td>Stimulate appetite (AIDS or anorexic patients)</td></tr>
</table>

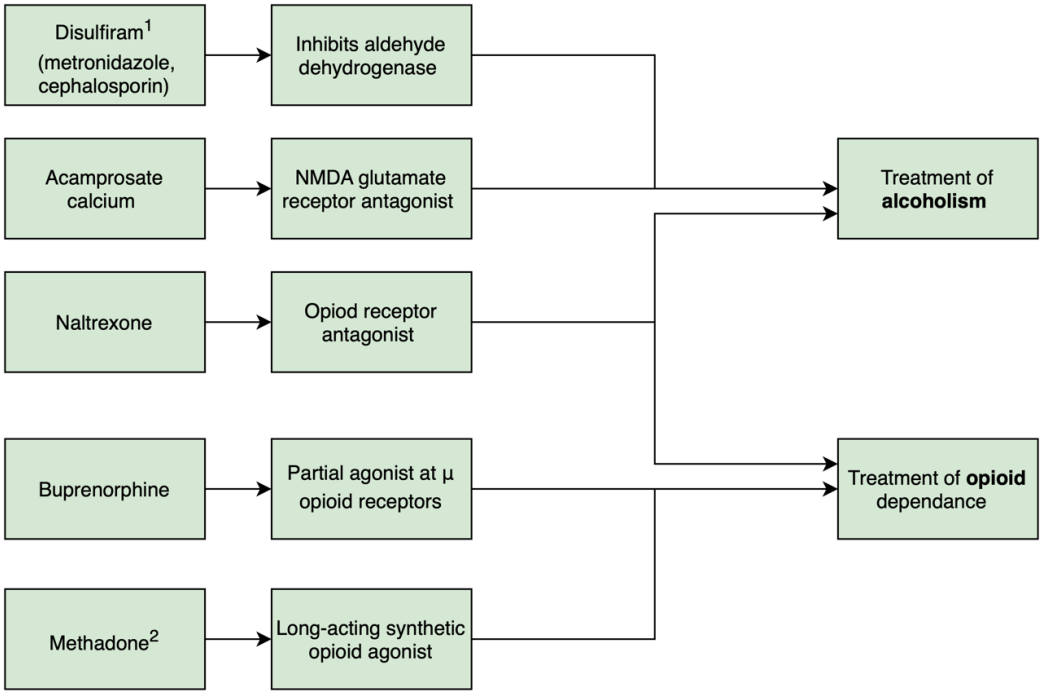
4.3.2 – Hallucinogens

- Hallucinogens are psychoactive drugs that can alter perception, mood, and consciousness, leading to hallucinations, distortions of reality, and changes in thought patterns.
- They primarily work by binding to serotonin receptors in the brain which leads to altered neurotransmitter activity and communication between neurons.

	LSD (Lethargic acid diethylamide)	**Mescaline Psilocybin**	**PCP (Phencyclidine)**
Hallucinations	Yes	Yes	Yes
Cause delirium	No	No	Yes
Origin	Synthetic	Cactus Mushroom	As an anaesthetic (later removed)
Administration	Oral	Oral	Usually inhaled
Duration	12h	6h	3-48h
Mechanism	Not understood	Not understood	Block glutamate NMDA-receptors

4.4 – Drugs for Treating Drug Dependence

- Drug dependence is diagnosed on a patient's history, psychological assessment, physical examination findings, and laboratory findings.

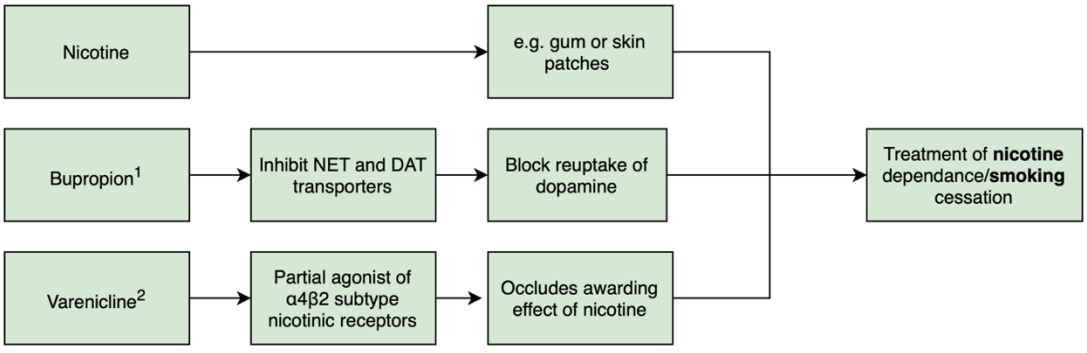


[1] When mixed with ethanol causes unpleasant effects like nausea, palpitations, dyspnea (++)
[2] Especially treat heroin addiction

CLINICAL CORRELATION

Opioid Overdose and Naloxone

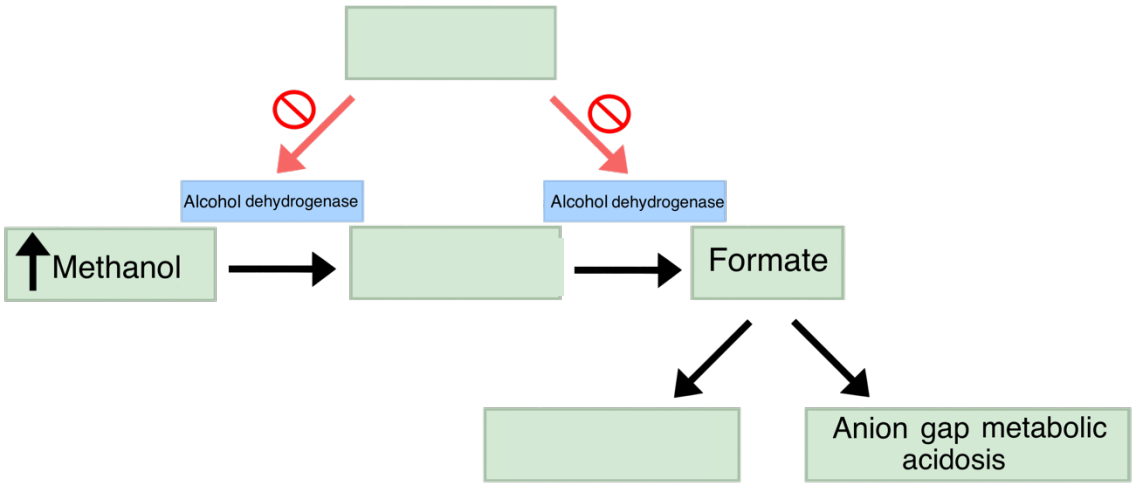
- If a patient in an opioid overdose experience respiratory failure or other life-threatening symptoms, **naloxone** should be administered (IV or intranasally).
- Naloxone is a competitive opioid antagonist and will displace the opioid from the receptors. This will quickly restore normal breathing and consciousness.



[1] May induce seizures
[2] Causes neuropsychiatric side effects

4.5 – Test yourself

1) Fill in the blanks:



2) Why is Flunitrazepam ("roofies"/Rohypnol) used as a "date rape drug"?
a) causes memory loss and sedation
b) causes euphoria, making victims susceptible to coercion
c) tasteless and fast onset
d) increases libido and lowers inhibition
e) all of the above

3) What does THC stand for?
a) Trihydrocannabinol
b) Tetrahydrocannabidiol
c) Terpenehydrocannabinol
d) Tetrahydrocannabinol

4) How do hallucinogens work?

_____

_____

_____

5) Which hallucinogen/s can cause delirium?
a) LSD
b) Mescaline
c) Psilocybin
d) PCP
e) all of them


studyaid