

IIIB. Central Nervous System

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Chapter 6 (Mosby)

Chapters in Katzung: 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31

I. Anxiolytics, Sedatives and Hypnotics

A. Key Objectives

1. To understand the stages of central nervous system depression as they pertain to the actions of these agents.
2. To understand the classification of central nervous system depressants.
3. To understand the theories relating to the biochemical mechanism of action of anxiolytics, sedatives and hypnotics, with particular emphasis of the barbiturates and benzodiazepines.
4. To understand the effects of these agents on the cardiovascular, respiratory and central nervous systems.
5. To know the advantages and disadvantages of each class relative to the others.
6. To appreciate why new drugs are being developed in this area.

B. Introduction and Definitions

1. Be able to define the following:

anxiolytic- Drugs that decrease anxiety without significant effects on CNS function (sedation).

sedation - Relief of anxiety accompanied by decreases in motor activity, coordination and mental acuity.

hypnosis - Increased tendency to sleep but readily awakened.

anesthesia - Sleep induction, with awakening dependent on the elimination of drug.

2. Know the primary drugs and drug classes used to treat anxiety and sleep disorders.

Benzodiazepines- chlordiazepoxide, diazepam, alprazolam, flurazepam, triazolam, midazolam, clonazepam.

Barbiturates- pentobarbital, phenobarbital, thiopental.

Miscellaneous- chloral hydrate, meprobamate, paraldehyde, ethanol, buspirone.

3. Understand the clinical and pharmacological differences between ethanol, barbiturates and benzodiazepines.

Benzodiazepines- Bind only a certain subset (α_1 , α_2 , α_3 , and α_5 . Most common: α_1 α_2 - diazepam sensitive) of GABA-receptors and increase their affinity to GABA. Because of the selectivity of benzodiazepines to certain GABA receptors, their effects as CNS depressants are less generalized. Are clinically employed as anxiolytics, hypnotics, anticonvulsants and muscle relaxants.

Barbiturates- Attach to GABA-receptor coupled chloride channel and prolong the time that the channel is open when the receptor is exposed to GABA. All GABA-receptors have the chloride channel so the barbiturates effects are more generalized and diffuse CNS depressants. Clinically used as anticonvulsant (grand mal), anxiolytic, hypnotic and general anesthetic.

Ethanol- The intoxication produced by ethanol is believed to be caused by ethanol interacting with GABA receptors. Ethanol produces this effect by modification of ion flux through chloride channels activated by GABA, thereby potentiating the inhibitory effects of GABA. No unique medicinal value, but used for its sedative property and ability to impart a feeling of well being.

C. Ethanol

1. Understand the metabolism of ethanol, its effects on major organs systems, contraindications for its use, and the acute and chronic toxicities associated with this substance.

Ethanol undergoes zero-order kinetics (i.e., the rate of metabolism is relatively constant, regardless of the concentration in the blood). CNS effects: Impairment of vision and muscle coordination, lengthens reaction time, decrease anxiety, remove inhibitions, increase appetite. G.I. effects: increases salivation and gastric secretion, decreases intestinal motility, irritation of mucosa, nausea and vomiting. Respiration: little effect at low doses, then decrease at anesthetic doses. C.V.: vasodilatation, decrease in blood pressure at anesthetic doses. Hepatic/Renal: cirrhosis, increase in microsomal enzyme activity, increase in urine flow and volume due to inhibition of ADH. Contraindications include hepatic disease, renal disease, ulcers, epilepsy, and the use of any other CNS depressant. Acute toxicity is marked by hypothermia, decrease respiration, and possibly pneumonia or coma. Chronic toxicity is marked by withdrawal symptoms such as restlessness, tremor, fear, hallucinations, and convulsions.

2. Know the mechanism of action of disulfiram, its acute toxicity and primary use.

Disulfiram is used in the management of ethanol abuse. The drug is not a cure for alcoholism but rather is a deterrent to ethanol consumption. Ethanol is initially metabolized to acetaldehyde by alcohol dehydrogenase. Disulfiram interferes with the hepatic oxidation of acetaldehyde. This enzymatic inhibition results from the drug's ability to compete with nicotinamide adenine dinucleotide (NAD) for binding sites on aldehyde dehydrogenase. This results in the build up of acetaldehyde levels, which induces unpleasant effects like dizziness, vomiting, increased heart rate or unconsciousness.

D. Barbiturates

1. Understand the mechanism of action of the barbiturates.

Barbiturates attach to GABA-receptor coupled chloride channels and prolong the time that the channel is open when the receptor is exposed to GABA. All GABA-receptors have the chloride channel so the barbiturates are general/diffuse CNS depressants.

- Understand the concept of physical redistribution as it pertains to the action of barbiturates.
Barbiturates diffuse across all membranes and distribute throughout the body. They are highly protein bound and thus subject to drug interactions. Redistribution accounts for the differences in the duration of action of the barbiturates.
- Know the effects of barbiturates on major organ systems, with particular emphasis on hepatic function.
Effects on CNS: complete and diffuse depression, paradoxical excitement.
Effects on respiration and CV: no effect up to anesthetic doses, at anesthetic doses they cause decreased resp. and blood press.
Effects on hepatic function: causes an increase in microsomal enzyme activity and increased porphyrin synthesis.
- Be able to list the primary uses of the barbiturates.
Phenobarbital- (long duration) anticonvulsant [less lipid soluble so it takes longer to redistribute throughout the body]
Pentobarbital- (intermediate duration) hypnotic "truth serum"
Thiopental- (ultra short duration) fixed anesthetic
- Know the most common side effects and toxicities associated with barbiturates and the steps taken to treat an acute overdose.
Side effects and toxicities of barbiturates: sedation, ataxia and motor incoordination up to decreases in respiration and blood pressure at overdose levels. Coadministration of any CNS depressant is contraindicated and can cause death. Absolutely contraindicated in intermittent porphyria patients.

E. Benzodiazepines

- Know the primary use of the following benzodiazepines:

chlordiazepoxide - anxiolytic $T_{1/2} = 30h$
 diazepam – anxiolytic, anticonvulsant, muscle relaxant $T_{1/2} = 150h$
 alprazolam – anxiolytic/hypnotic $T_{1/2} = 15h$
 flurazepam – hypnotic $T_{1/2} = 100h$
 triazolam – hypnotic $T_{1/2} = 5h$
 midazolam - anxiolysis, and amnesia $T_{1/2} = 1-5h$
 clonazepam –anticonvulsant $T_{1/2} = 50h$
 flumazenil – benzodiazepine antagonist $T_{1/2} = 1h$

- Be able to describe the biochemical mechanism of action of the benzodiazepines.
Cause CNS effects by binding only a certain subset (α_1 , α_2 , α_3 , and α_5) of GABA-receptors and increasing their affinity for GABA. Because of the selectivity of benzodiazepines to certain GABA receptors, their effects as CNS depressants are less generalized.
- Know the chief effects of the benzodiazepines on the major organ systems, as well as their primary side effects and toxicities.
CNS effects: incomplete depression, muscle relaxant, anticonvulsant, hypnotic, paradoxical excitement. (tolerance develops to sedative, hypnotic and anticonvulsant actions)
Respiratory, CV, GI effects: no significant direct effects.
Side effects and toxicities: sedation, ataxia, amnesia. High potential for abuse. Withdrawal seen especially w/ short acting agents. (idiosyncratic- nightmare, irritability, anxiety, seizures)

F. Other Agents

Understand the advantages and disadvantages of the following in terms of treating anxiety:

Meprobamate: good anxiolytic, muscle relaxant, and hypnotic commonly used in elderly. Adverse effects similar to barbiturates.

Chloral hydrates: rapid onset and short duration hypnotic used in children. Toxicities same as barbiturates & is irritating to GI.

Paraldehyde: rapid onset and short duration hypnotic given as an enema to relieve EtOH withdrawals. Irritating to GI.

Antipsychotics-Antidepressants-Antihistamines: Sedation a side effect with many of these due to anticholinergic and antihistaminic effects. Seldom used as primary therapy for anxiety, although a useful side therapy for some patients.

Beta-blockers: Decrease somatic symptoms of anxiety-enough for some patients. Not thought to have centrally-mediated anxiolytic action.

Bupirone: Anxiolytic, not a CNS depressant, partial agonist at 5-HT_{1A} site. Slow onset of action - 1-2 weeks & dysphoric instead of euphoric.

G. Current Trends

Understand the clinical and pharmacological rationales for the continued development of anxiolytics and hypnotics.

H. Some Important Drugs

1. Benzodiazepine anxiolytics, hypnotics and antagonists

ALPRAZOLAM
CLONAZEPAM
DIAZEPAM
FLUMAZENIL (antagonist)
FLURAZEPAM
TRIAZOLAM

2. Barbiturate sedatives-hypnotics and anesthetics

PENTOBARBITAL
PHENOBARBITAL
THIOPENTAL

3. Miscellaneous sedative-hypnotics

CHLORAL HYDRATE
ETHANOL
MEPROBAMATE
PARALDEHYDE

4. Non-depressant anxiolytic

BUSPIRONE

5. Treatment of alcoholism

DISULFIRAM

II. Antiepileptics

A. Key Objectives

1. To understand the different types of seizures and the drug classes most effective in their management.
2. To understand the proposed mechanisms of actions of antiepileptics.
3. To appreciate the more common side effects and toxicities encountered with antiepileptic therapy.
4. To gain a sense for the types of antiepileptics being developed.

B. Introduction and Definitions

1. Know the physiological and clinical differences between partial and generalized seizures and be able to cite examples of each.

Partial seizures: Usually no loss of consciousness, a partial or focal seizure is the more common type of epilepsy and is caused by a disorder of a neuron population usually in a specific site on one side of the brain. The most difficult to control. Examples: 1) *Simple Partial Seizures*- Elementary symptomatology, such as cortical focal and Jacksonian March - may experience confusion, jerking movements, tingling, or odd mental and emotional events, such as *deja vu*, mild hallucinations, or extreme responses to smell and taste.

2) *Complex Partial Seizures*- Complex symptomatology such as Psychomotor (emotional outburst) can result in loss of judgment, involuntary or uncontrolled behavior. Emotions can be exaggerated, and some sufferers appear to be drunk. After a few seconds, some may begin to perform repetitive movements, such as chewing or smacking of lips.

3) *Secondarily Generalized Seizures:* In some cases, simple or complex partial seizures evolve into generalized seizures.

Generalized seizures: Always involves the loss of consciousness, is caused by disturbances of nerve cells in more diffuse areas of the brain than with partial seizures and therefore have a more serious affect on the patient. Examples: 1) *Absence (Petit Mal) Seizures.* Petit mal or absence seizures are brief (3 to 30 seconds) and may consist of only a short cessation of physical movement and loss of attention. They may even pass unnoticed by others. Petit mal may be confused with simple or complex partial seizures; in petit mal, however, a person loses consciousness and may experience attacks as often as 50 to 100 times a day.

2) *Tonic-Clonic (Grand Mal) Seizures.* The first stage of a grand mal seizure is called the *tonic phase*, in which the muscles suddenly contract, causing the patient to fall and lie rigidly for about 10 to 30 seconds. Some people experience a premonition or aura before a grand mal or tonic-clonic seizure; most, however, lose consciousness without warning. Spasms occur for about 30 seconds to a minute as the seizure enters the *clonic phase*, when the muscles begin to alternate between relaxation and rigidity. After this phase, the patient may lose bowel or urinary control. The seizure usually lasts a total of two to three minutes, after which the patient remains unconscious for a while and then awakens to confusion and extreme fatigue

3) *Status Epilepticus* (either absence or tonic-clonic) unremitting successive seizures.

2. Know the primary drugs and drug classes used to treat epilepsy.

1. Generalized Tonic-Clonic
Valproic Acid---Carbamazepine---Phenobarbital---Phenytoin→Primidone---Lamotrigine
2. Absence (petit mal)
Ethosuximide---Valproic Acid→Lamotrigine→Trimethadione→Clonazepam→Acetazolamide
These agents often administered with phenytoin, phenobarbital or primidone to prevent precipitation of Grand Mal
3. Status Epilepticus
Diazepam→Lorazepam→Phenobarbital→ Phenytoin→General Anesthetic
4. Partial seizures
Carbamazepine→Phenytoin→Valproic Acid→Phenobarbital→Felbamate→
Any of above in combination with GABA-pentin, Lamotrigine, or vigabatrin

3. Know the characteristics of therapy, especially as they pertain to the drug interactions and chronic toxicity.
(See below)

C. Mechanisms of Action

Be able to define, at the biochemical and cellular levels, the proposed mechanisms of action of:

Hydantoins (Phenytoin), Carbamazepine, Valproic Acid, Lamotrigine and Felbamate

Prolong inactivation of Na⁺ channels, reducing ability of neurons to fire at high frequencies

Succinimide-Ethosuximide, Trimethadione and Valproic Acid

Inhibit T-type Ca⁺ channels in neurons

Vigabatrin and Tiagabine

Inhibit GABA transaminase (vigabatrin) or GABA uptake (tiagabine), increasing brain levels of this inhibitory amino acid

Barbiturates and Benzodiazepines

Enhance GABAergic activity by increasing receptor response to neurotransmitter

GABA-pentin

Enhances depolarization-induced GABA release

Acetazolamide

Inhibits carbonic anhydrase, increasing brain CO₂ which increases seizure threshold

D. Drugs Used to Treat Grand Mal, Status Epilepticus, and Partial Seizures

Be able to match the following agents with the types of seizures they are used to treat, their chief side effects and toxicities and potential for drug interactions:

Hydantoins-Phenytoin: (a drug of choice for Grand Mal)

Side effects and toxicities: Ataxia, Nausea and vomiting, Hyperplasia of the gums, Hirsutism, Blood dyscrasias.

Drug interactions: Phenytoin competes for plasma protein binding sites with a variety of drugs, including anti-inflammatory agents and some hypnotics. When coadministered with such agents there is a possibility that the blood levels of free phenytoin will increase, leading possibly to adverse effects and toxicities not previously observed at that dose. Conversely, blood levels of phenytoin may drop if it is administered with drugs, such as phenobarbital and carbamazepine that induces microsomal enzyme activity.

Barbiturates-

Side effects and toxicities of barbiturates: sedation, ataxia and motor incoordination up to decreases in respiration and blood pressure at overdose levels.

Drug interactions The potential for drug interactions is similar for phenobarbital and primidone. These include modifying the metabolism and thereby altering the blood levels of other drugs, particularly antiepileptic agents. Blood levels of phenobarbital and primidone, or the adjunctive therapy, may be increased or decreased depending on the level of competition for plasma protein binding sites and microsomal enzymes. Adjustment in dosage may be required to maintain seizure control when combining these agents with other drugs. Coadministration of any CNS depressant is contraindicated and can cause death. Absolutely contraindicated in intermittent porphyria patients.

Phenobarbital: (a drug of choice for Grand Mal)

Long duration anticonvulsant -less lipid soluble so it takes longer to redistribute throughout the body. Abrupt withdrawal can precipitate status epilepticus.

Primidone: (a drug of choice for Grand Mal)

Frequently effective in patients not responding to phenytoin or phenobarbital
Converted to phenobarbital and phenylethylmalonamide (PEMA)
Parent as well as products active as antiepileptics

Often given in combination with phenytoin, NEVER with phenobarbital
Side effects include ataxia, nausea and vomiting

Benzodiazepines-Diazepam and Clonazepam:

May be effective in Grand Mal but for only 2-3 weeks due to tolerance
One of the most effective drugs in infantile myoclonus, but again tolerance is a problem
Drug of choice for treatment of status epilepticus (i.v.)
Side effects and toxicities: sedation, ataxia, amnesia. High potential for abuse. Withdrawal seen especially w/ short acting agents. (idiosyncratic- nightmare, irritability, anxiety, seizures)

Valproic Acid: [Petit Mal (Absence)]

Side effects include nausea and vomiting, Hepatotoxicity in children. Also effective in Grand Mal so, unlike other agents, may be used alone to treat Petit Mal.
Drug Interactions Valproic acid modifies the blood levels of phenobarbital, phenytoin, and carbamazepine by altering the metabolism of these agents. In particular, valproic acid dramatically increases the likelihood of adverse effects to the barbiturates.

E. Drugs Used to Treat Petit Mal (Absence) Seizures

Know the chief side effects, toxicities and potential for drug interactions for the following:

Oxazolidinediones-Trimethadione: (treating petit mal epilepsy only when other medications are found to be unsatisfactory)

Adverse effects Sedation and hemeralopia are the most common adverse effects associated with trimethadione. It is also known to cause blood dyscrasias, and it is sometimes toxic to the kidney and liver. These potential toxicities have relegated trimethadione to a backup role in the treatment of petit mal seizures. It must be used with caution because of the potential for fatal toxicities.

Drug interactions There are no significant interactions between trimethadione and other medications.

Succinimides-Ethosuximide: (Petit mal only)

Adverse effects: Anorexia, nausea, and vomiting are the chief adverse effects associated with ethosuximide. Adverse CNS effects include sedation, lethargy, and dizziness. Less frequently encountered are parkinsonian-like symptoms, skin reactions, and blood dyscrasias.

Drug interactions: When administered with valproic acid, the clearance of ethosuximide is slowed. Beyond this, ethosuximide has no significant interaction with other agents.

Acetazolamide: (Petit mal only, tolerance develops)

Mild potassium sparing diuretic. Some sedation, minimal side effects, toxicities and interactions

Valproic Acid: [Petit Mal (Absence)]

Side effects include nausea and vomiting, Hepatotoxicity in children. Also effective in Grand Mal so, unlike other agents, may be used alone to treat Petit Mal.

Drug Interactions Valproic acid modifies the blood levels of phenobarbital, phenytoin, and carbamazepine by altering the metabolism of these agents. In particular, valproic acid dramatically increases the likelihood of adverse effects to the barbiturates.

F. Current Trends

Understand the clinical and pharmacological rationales for the continued development of antiepileptic medications.

3. Partial

CARBAMAZEPINE
PHENYTOIN
VIGABATRIN
GABAPENTIN
LAMOTRIGINE
FELBAMATE
TIAGABINE

G. Some Important Drugs

1. Grand mal

CARBAMAZEPINE
CLONAZEPAM
DIAZEPAM (Status)
PHENOBARBITAL
PHENYTOIN
PRIMIDONE
VALPROIC ACID

2. Petit mal (absence)

ACETAZOLAMIDE
ETHOSUXIMIDE
TRIMETHADIONE
VALPROIC ACID

III. General Anesthetics**A. Key Objectives**

1. To understand the characteristics which determine the potency of general anesthetics and their rate of induction.
2. To understand the relationship between minimum alveolar concentration (MAC) and the Ostwald coefficient.
3. To understand the signs and stages of general anesthesia.
4. To appreciate the pharmacological and clinical differences among the inhalational anesthetics and between these and fixed anesthetics.
5. To understand the rationale for preanesthetic medications.

C. Absorption and Elimination of General Anesthetics

Understand the variables that influence the rates of induction and emergence from general anesthesia.

The depth of anesthesia is directly related to the partial pressure or tension of free anesthetic in the brain. The time required to attain equilibrium between the partial pressure of an anesthetic in the brain, blood and lungs (rate of induction) is directly related to the lipid solubility of the anesthetic, as is the time required to eliminate the anesthetic (rate of emergence). Potency and efficacy are DIRECTLY related to the lipid solubility (Ostwald coefficient) of the anesthetic. More lipophilic = higher Ostwald coefficient = Slower induction and recovery

D. Anesthetic Potency

Understand the concept of minimum alveolar concentration (MAC) and its relationship to the Ostwald coefficient.

The relative potency of an inhalational anesthetic (MAC value) is the concentration in the inspired air at equilibrium (when partial pressure is the same in lungs, brain and blood) at which there is no response to a skin incision in 50% of patients. The numerical value of MAC is INVERSLY related to the lipid solubility (Ostwald coefficient) of an inhalational anesthetic. High Ostwald → Low MAC Low Ostwald → High MAC

E. Signs and Stages of General Anesthesia

Be able to characterize the four stages of general anesthesia and their importance.

Stages of Anesthesia

- Stage 1 - Analgesia Stage: From administration to loss of consciousness
- Stage 2 - Delirium Stage: From loss of consciousness to regular respiration
- Stage 3 - Surgical Stage: From regular respiration to respiratory arrest
- Stage 4 - Medullary Paralysis Stage: From respiratory arrest to death

F. Comparison of Inhalational Anesthetics

Know and understand the chemical and pharmacological relationships among the major anesthetics.

Agent	Type	MAC & Ostwald Coeff.	Rate of Induction & Emergence	Muscle Relaxation	Effect on C.V. System	Toxic Effect on Liver and Kidney
Nitrous oxide	Gaseous	>100 0.47	Rapid	None	No arrhythmias	None
Halothane	Volatile	0.8 2.3	Slow	Very good	Sensitizes heart to CA's	Hepatotoxic
Enflurane	Volatile	1.7 1.8	Slow	Very good	No arrhythmias, does not sensitize heart	Hepatotoxic
Isoflurane	Volatile	1.40 1.40	Slow	Very good	No arrhythmias, does not sensitize heart to CA's	None
Methoxyflurane	Volatile	0.16 12.0	Very slow	Excellent	Sensitizes heart to CA's	Hepatotoxic and nephrotoxic

G. Preanesthetic Medications

Understand the rationale for using preanesthetic medications in general, and the use of the following in particular:

Anxiolytics/hypnotics: benzodiazepines – Reduce preoperative anxiety and speed-up induction.

Analgesics: opiates – Ease preoperative and postoperative pain. Calming effect that eases induction also.

Antiemetics: phenothiazines - Reduce postoperative nausea and vomiting frequently associated with volatile anesthetics.

Anticholinergics: scopolamine, glycopyrrolate - Mainly counteract bradycardia and inhibit irritational secretions. May reduce nausea and vomiting.

H. Fixed Anesthetics

1. Know advantages and disadvantages of fixed or I.V. anesthetics as compared to inhalational agents.

Advantages over General Anesthetics:

- Quick, easy, smooth induction and lack of adverse effects on the heart, liver and kidneys.

Disadvantages:

- Slow elimination

2. Know the uses and side effects of ketamine, thiopental, innovar and propofol.

Ketamine (Dissociative Anesthesia)
 Related to phencyclidine
 Blocks glutamate receptor ion channels
 Excellent analgesia and amnesia
 Poor muscle relaxation
 Slow awakening with hallucinations

Innovar (Droperidol and Fentanyl)

Also known as neuroleptanalgesia
 Cause state of indifference, but no sleep
 Good for x-rays, burn dressings, etc.
 Decreases respiration and blood pressure
 Some nausea and vomiting

Thiopental

Rapid and pleasant induction
No analgesia, in fact hyperalgesia
Profound decrease in resp. at anesthetic doses
Difficult to control level of anesthesia
Often used with Nitrous oxide

Propofol

Similar to barbiturates, except a more rapid recovery
Causes significant decrease in blood pressure

I. Some Important Drugs

1. Fixed anesthetics

INNOVAR
KETAMINE
MIDAZOLAM
PROPOFOL
THIOPENTAL

2. Gaseous anesthetics

NITROUS OXIDE

3. Volatile anesthetics

ENFLURANE
ISOFLURANE
HALOTHANE
METHOXYFLURANE
DESFLURANE
SEVOFLURANE

IV. Local Anesthetics

A. Introduction

What is the general mechanism of action of local anesthetics (LA)?

Local anesthetics stabilize nerve membranes by depressing sodium conductance, thereby slowing the propagation of the action potential.

What are the primary clinical uses of LA?

Some local anesthetics, such as cocaine and benzocaine, are effective topically because they penetrate mucous membranes. Procaine is an example of an agent useful only for infiltration anesthesia or spinal block. Some agents such as lidocaine, mepivacaine, or bupivacaine, are used for infiltration, peripheral nerve block, or epidural block. Local anesthetics are useful in surgical procedures that are not extensive. They are of greatest use for outpatient surgery. Their use eliminates the need for the extensive postanesthesia care required with general anesthetics. Hemorrhoidectomy and transurethral resection of the prostate are examples of procedures that lend themselves to regional local anesthetic block.

B. Basic Pharmacology of LA

How are LA administered? Local anesthetics are applied topically or injected near the nerve to be blocked

Understand the factors that influence absorption of LA from the site of administration.

The status of the circulatory system and the chemical properties of the anesthetic.

What is the role of vasoconstrictor agents in the clinical use of LA?

Vasoconstrictors, such as epi, are given to prolong anesthesia and lower systemic toxicity.

Be able to classify LA as either esters or amides.

Esters: BENZOCAINE, PROCAINE, TETRACAINE, COCAINE, BUTAMBEN PICRATE, CHLOROPROCAINE.

Amides: BUPIVACAINE, LIDOCAINE, MEPIVACAINE, PRILOCAINE, ETIDOCAINE

Be able to describe the differences in drug distribution and metabolism between amide and ester LA.

Esters: Metabolized by plasma cholinesterase...occurs rapidly producing a short duration of action. . . .Higher allergy potential. . .

Lower potential for toxicity as it clears faster.

Amides: Liver metabolism...patients with liver disease will experience the effect of the agent 2 times longer. . . Lower allergy potential. . . Higher potential for toxicity as it clears slower

C. Clinical Pharmacology of LA

What are clinical bases for adding a vasoconstrictor agent to a LA? To prolong the duration of action and reduce systemic effects.

D. Toxicology

Be able to describe the toxic effects of LA on:

central nervous system- Lightheadedness, Dizziness, Visual and auditory disturbances (difficulty focusing and tinnitus), Disorientation, Drowsiness. . . all the way up to → Muscle twitching, Convulsions, Unconsciousness, Coma, Respiratory depression and arrest, Cardiovascular depression and collapse.

peripheral nervous system- Local anesthetic solutions are very acidic and cause tissue irritation when injected. Commercial anesthetic solutions are manufactured with low pH (5-6) to enhance shelf life. Addition of epinephrine to an anesthetic lowers the pH even more. Very high doses of anesthetics can produce irreversible conduction block in less than 5 minutes.

cardiovascular system- myocardial depression, cardiac dysrhythmias and cardiotoxicity in pregnancy. Several of the anesthetics also have negative inotropic effects on cardiac muscle leading to hypotension. Symptoms include: Chest pain, Shortness of breath, Palpitations, Lightheadedness, Diaphoresis, Hypotension, Syncope.

hemopoietic system- Methemoglobinemia has been reported which at low levels (1-3%) can be asymptomatic, but higher levels (10-40%) may be accompanied by any of the following: Cyanosis, Cutaneous discoloration (gray), Tachypnea, Dyspnea, Exercise intolerance, Fatigue, Dizziness and syncope, Weakness.

E. Some Important Drugs

BENZOCAINE (GENERIC, OTHERS)
BUPIVACAINE (MARCAINE, SENSORCAINE)
BUTAMBEN PICRATE (BUTESIN PICRATE)
CHLOROPROCAINE (NESACAINE)
COCAINE (GENERIC)
DIBUCAINE (GENERIC, NUPERCAINAL)
DYCLONINE (DYCLONE)
ETIDOCAINE (DURANEST)
LIDOCAINE (GENERIC, XYLOCAINE, OTHERS)
MEPIVACAINE (GENERIC, CARBOCAINE, OTHERS)
PRAMOXINE (TRONOTHANE, PRAX)
PRILOCAINE (CITANEST)
PROCAINE (GENERIC, NOVOCAIN)
TETRACAINE (PONTOCAINE)

V. Skeletal Muscle Relaxants

A. Introduction

What are the two major therapeutic groups concerning drugs that affect skeletal muscle function?
Non-depolarizing(competitive) agents and Depolarizing agents.

B. Basic Pharmacology of Neuromuscular Blocking Drugs

What are the two general classifications for neuromuscular blockers? - Non-depolarizing(competitive) and Depolarizing agents.
Be able to describe the differing routes of elimination of the non-depolarizing neuromuscular blockers.
They are eliminated primarily via the urine.

Which non-depolarizing blockers are relatively longer vs. shorter in duration? (See chart)

What is the major depolarizing skeletal muscle blocker? → SUCCINYLCHOLINE

C. Mechanism of Action

What are mechanisms of actions for nondepolarizing blockers?
They act as competitive antagonists at the neuromuscular nicotinic receptor

What are the two phases of block that may accompany the use of depolarizing drugs?
Because they are agonists, the initial effects are muscle fasciculation or contraction followed by relaxation. The neuromuscular nicotinic receptors thus "blocked" via depolarization.

D. Clinical Pharmacology of Neuromuscular Blocking Agents

What is the role of neuromuscular blockade as a part of surgical anesthetic protocols?

They are used as an adjunct to anesthesia to facilitate easy intubation and incision.

Be able to describe the cardiovascular effects of the neuromuscular blockers. (See chart)

	D-TUBOCURARINE	METOCURINE	PANCURONIUM	SUCCINYLCHOLINE
Type	Competitive	Competitive	Competitive	Depolarizing
Site of action junction	N-M junction and ganglion	N-M junction and ganglion	N-M junction	N-M junction and ganglion
Enters CNS	No	No	No	No
Crosses placenta	Negligible	—	—	—
Effect on				
Histamine release	+++	++	+	++
Heart rate	Decrease	Decrease	Increase	Decrease
Blood pressure	Decrease	Decrease	Increase	Increase or decrease
Potency altered by pH	Yes	No	No	No
Other effects				1. Increase intraocular pressure 2. K ⁺ release from muscle leading to electrolyte imbalance
Duration of action	20 min Residual effects 2-4 hours	20 min	20 min	20 min
Metabolism and excretion	1. urinary 2. bile Some metabolism	1. urinary 2. bile Some metabolism	Hepatic metab	Hydrolyzed by plasma and liver cholinesterases
Uses	Surgery MS diagnosis	Surgery More potent than D-tubocurarine	Surgery	Surgery Electroconvulsive therapy

Be able to discuss the interactions of neuromuscular blockers with anesthetics, antibiotics, local anesthetic and antiarrhythmic agents. (See chart below)

EFFECTS	COMPETITIVE	DEPOLARIZING
Action at receptor	Antagonist	Agonist
Effect on motor end plate depolarization	None	Partial persistent depolarization
Initial effect on striated muscle	None	Fasciculation
Muscles affected first	Small muscles	Skeletal muscle
Muscles affected last	Respiratory	Respiratory
Effect of AchE inhibitors	Reversal	No effect or increased duration
Effect of Ach agonists	Reversal	No effect
Effect on previously administered D-tubocurarine	Additive	Antagonism
Effect on previously administered succinylcholine	No effect of antagonism	Tachyphylaxis or no effect
Effect of halothane	Increase potency	Decrease potency
Effect of antibiotics	Increase potency	Decrease potency
Effect of Ca ⁺⁺ channel blockers	Increase potency	Increase potency

Name conditions in which neuromuscular blockers can be particularly dangerous. → asthma, ulcers,

E. Other Uses of Neuromuscular Blockers

Be able to describe the other uses of neuromuscular blockers.

→ Used in electroconvulsive shock therapy, the diagnosis of multiple sclerosis (tubocurarine), and in the diagnosis of pain from nerve root compression masked by muscle spasm.

F. Some Important Drugs

1. Neuromuscular blocking drugs

ATRACURIUM (TRACRIUM)
DOXACURIUM (NUROMAX)
GALLAMINE (FLAXEDIL)
METOCURINE (METUBINE IODIDE)
PANCURONIUM (PAVULON)
PIPERCURONIUM (ARDUAN)
SUCCINYLCHOLINE (ANECTINE, OTHERS)
TUBOCURARINE (GENERIC)
VECURONIUM (NORCURON)

VI. Pharmacological Management of Parkinsonism and Other Movement Disorders

A. Parkinsonism

Abnormalities in what part of the brain are associated with Parkinsonism. → Nigrostriatal and basal ganglia dopamine Pathways.

What are general presenting symptoms of Parkinsonism? Tremor, rigidity, bradykinesia, and mask-like expression.

What neurotransmitters are considered important in the pathophysiology of Parkinsonism? DOPAMINE

What drug classes may induce Parkinsonism? Antipsychotics, MPTP, -any drug that can disrupt dopamine pathways.

Be able to describe the chemical relationships between L-DOPA and dopamine and the basis for the pharmacological advantage of L-DOPA administration vs. dopamine administration.

L-DOPA is a dopamine precursor that is able to cross the BBB.

What are the neural locations of D1 and D2 receptors and which are most important in the actions of the dopamine receptor agonists?

D1A and D2 represent the major subtypes expressed in the striatum of the adult brain. Within the striatum, these two subtypes are differentially distributed in the two main neuronal populations that provide direct and indirect pathways between the striatum and the output nuclei of the basal ganglia. Movement disorders, including Parkinson disease and various dystonias, are thought to result from imbalanced activity in these pathways.

Be able to describe the pharmacokinetics of L-DOPA in the presence and absence of CarbiDOPA.

L-Dopa in the absence of CarbiDOPA has a shorter $T_{1/2}$ = 1-3h with >95% decarboxylated in periphery and excreted in the urine. However, in the presence of CarbiDOPA the $T_{1/2}$ is longer and the total amount of L-DOPA needed is lower. CarbiDOPA blocks amino acid decarboxylase(AADC) in the periphery thus increasing the amount of L-DOPA available for the brain.

Be able to describe adverse effects seen with L-DOPA administration, including gastrointestinal, cardiovascular, dyskinesias and behavioral effects, and fluctuations in response.

SIDE EFFECTS

Early:

GI - nausea and vomiting - v. common
CV - postural hypotension - v. common
hypertension, esp. w/ sympathomimetics
arrhythmia, tachycardia

Neuroendocrine - decreased prolactin secretion

Long-term:

Motor - fluctuations in efficacy
"On-Off" - symptoms reappear periodically
"Wearing Off" - effects don't last as long
Can be improved by a "drug holiday"
Neurological - abnormal movements: dystonia, dyskinesias, chorea, etc. - v. common
Psychic - Hallucinations, paranoia, mania, anxiety, depression
Neuroendocrine - renewed sexual interest and behavior

What are "drug holidays" with respect to L-DOPA administration?

Stop taking L-DOPA for a time – better response when it is started again.

What is the nature of the drug interaction between L-DOPA and vitamin B6?

Pyridoxine (vitamin B₆), can accelerate the peripheral inactivation of levodopa

Be able to describe contraindications for the use of L-DOPA.

Contraindications/Precautions: Narrow-angle glaucoma, MAOI therapy, malignant melanoma, cardiovascular disease, pulmonary disease, bronchial asthma, occlusive cerebrovascular disease, renal disease, hepatic disease, endocrine disease, affective disorders, major psychoses, cardiac arrhythmias, acute myocardial infarction, peptic ulcer disease, tartrazine dye hypersensitivity.

Be able to describe the pharmacological basis for the action of bromocriptine or other agonists. What are pergolide and pramipexole?

Dopamine Agonists: BROMOCRIPTINE, PERGOLIDE, PRAMIPEXOLE

Mechanism: Agonist at D₂ and other dopamine receptors.

Use: in patients with “on-off” or whose symptoms are not controlled by L-DOPA.

Side effects: nausea, vomiting, postural hypotension, hallucinations

What is the role of the monoamine oxidase B inhibitor (MAOB) selegiline (deprenyl) in the therapy of Parkinsonism?

MAO Inhibitors: SELEGELINE

Mechanism: MAO-B inhibitor, blocks catabolism of dopamine

Use: Adjunct to L-DOPA, increases efficacy, decreases L-DOPA dose, decreases “on-off” effect.

Describe the use of amantadine in the treatment of Parkinsonism.

Antiviral: AMANTIDINE

Mechanism: Unknown

May release dopamine and/or have anticholinergic properties

Use: adjunct to L-DOPA, only in uncontrolled patients.

Side Effects: mainly anti-cholinergic,

What are the centrally active antimuscarinic drugs that are useful in the treatment of Parkinsonism?

Anticholinergics: TRIHEXYPHENYDYL, BENZTROPINE, PROCYCLIDINE

Mechanism: Block actions of striatal interneurons. Generally less effective than L-DOPA.

Side effects: constipation, urinary retention, mental confusion, hallucinations

Clinical: reserved for L-DOPA resistant patients.

Antihistamines: DIPHENHYDRAMINE

Used primarily for their anticholinergic actions

B. Spasmolytic Drugs

What is clinical spasticity? State of hypertonicity over the normal tone of a muscle, with heightened deep tendon reflexes.

Be able to describe how drug therapy may improve some of the symptoms of spasticity. (see chart)

By what mechanism may diazepam (Valium) diminish spasticity? What neurotransmitter receptor is involved? (see chart)

By what mechanism may baclofen, a GABA-mimetic drug, diminish spasticity? How does the efficacy of baclofen compare to diazepam or dantrolene? (see chart)

How does dantrolene reduce spasticity? (see chart)

Table 6.8 Attributes of Drugs for the Treatment of Spasticity

	BACLOFEN	DIAZEPAM	DANTROLENE
Mechanism	GABA _B agonist: inhibits release of excitatory transmitters, increases threshold for excitation	Augments GABAergic transmission	Inhibits release of Ca ²⁺ from sarcoplasmic reticulum
Site of action	Spinal cord	Spinal and supraspinal	Muscle
Adverse effects	Drowsiness, insomnia, weakness, dizziness, ataxia, confusion	Sedation Ataxia	Generalized muscle weakness Hepatotoxicity
Uses	Spinal cord injury Multiple sclerosis	All types of spasticity Spinal cord injury Cerebral palsy	Paralysis Cerebral palsy Multiple sclerosis

What is the role of dantrolene in the treatment of malignant hyperthermia? It treats it!

How is Botox used in the relief of muscle spasm?

Botulinum toxin type A is a parenteral toxin. It is used to treat strabismus and blepharospasm associated with dystonia. Botulinum toxin type A works by blocking neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering nerve terminals, and inhibiting the release of acetylcholine. Botulinum toxin type A's paralytic effect helps reduce the excessive, abnormal contractions associated with blepharospasm.

How long do the effects of Botox last?

Weeks to months.

C. Some Important Drugs

1. Antimuscarinics

BENZTROPINE (COGENTIN)
TRIHENXYPHENIDYL (ARTANE, OTHERS)

2. Dopamine agents

CARBIDOPA (LODOSYN)
L-DOPA (DOPAR)
CARBIDOPA/L-DOPA (SINEMET)
BROMOCRIPTINE
PERGOLIDE
PRAMIPEXOLE (MIRAPEX)

3. Others

AMANTADINE (SYMMETREL)

4. SELEGILINE (DEPRENYL)

5. Spasmolytics

BACLOFEN (LIORESAL)
DANTROLENE (DANTRIUM)
DIAZEPAM (GENERIC, VALIUM, OTHERS)

6. BOTOX

VII. Antipsychotics and Lithium

A. Key Objectives

1. Understand the indications for these drugs.
2. Understand the dopamine theory of schizophrenia; data supporting and refuting.
3. Understand mechanisms and sites of action proposed for therapeutic effectiveness and for side effects.
4. Know side effects.

B. Introduction to Antipsychotics

Understand the terms:

neuroleptic- A term coined to refer to the effects on cognition and behavior of antipsychotic drugs, which produce a state of apathy, lack of initiative and limited range of emotion and in psychotic patients cause a reduction in confusion and agitation and normalization of psychomotor activity.

Antipsychotic- A drug that is effective in the treatment of psychosis. Antipsychotic drugs (also called neuroleptic drugs and major tranquilizers) are a chemically diverse (including phenothiazines, thioxanthenes, butyrophenones, dibenzoxazepines, dibenzodiazepines and diphenylbutylpiperidines) but pharmacologically similar class of drugs used to treat schizophrenic, paranoid, schizoaffective and other psychotic disorders, acute delirium and dementia and manic episodes (during induction of lithium therapy), to control the movement disorders associated with Huntington disease, Gilles de la Tourette's syndrome and ballismus and to treat intractable hiccups and severe nausea and vomiting.

Antischizophrenic- Drugs effective in the treatment of schizophrenia.

C. Major Classes of Antipsychotics

1. Know the following by generic name only (trade name):

Phenothiazines: chlorpromazine (Thorazine), thioridazine (Mellaril) and fluphenazine (Prolixin)
 Butyrophenones: haloperidol (Haldol)
 Dibenzodiazepine: clozapine (Clozaril)
 Other

2. Understand differences between these drug classes with regard to affinity for dopamine receptors, and side effects.

CHEMICAL CLASS		CLINICAL POTENCY	EPS LIABILITY	SEDATIVE EFFECT	HYPOTENSIVE ACTIONS	ANTICHOLINERGIC EFFECTS
Drug/Presumed Site of Action		DA	DA	Histamine	α -Adrenergic	Ach
Chlorpromazine	Aliphatic phenothiazine	low	moderate	high	high	moderate
Fluphenazine	Piperazine phenothiazine	high	high	low	v. low	moderate
Thiothixene	Thioxanthene	high	moderate	moderate	moderate	moderate
Haloperidol	Butyrophenone	high	v. high	low	v. low	low
Clozapine	Dibenzodiazepine	moderate	v. low	high	v. low	v. low
Risperidone	Benzisoxazole	high	low	low	v. low	low

Mechanism of Action- True mechanism unknown
 All antipsychotics are antagonists of the D₂-dopamine receptor
 Serotonin receptors and/or novel D₂-like receptors may be involved
 Pharmacokinetics- IM, IV, PO, Highly lipophilic, Extensive hepatic metabolism

D. Therapeutic Effects and Side Effects

1. What are effects in positive and negative symptoms of schizophrenia?
 Positive symptoms: Hallucinations, Delusions, Disorganized, illogical, or incoherent thought
 Negative symptoms: Flat or inappropriate affect, Social isolation or withdrawal

2. Understand side effects: mild and severe; overdose.

Initial - sedation
 In normal persons - dysphoria, disinterest, blunted affect
 In schizophrenics-Positive symptoms improve over weeks-Months of treatment, Negative symptoms are less affected
 Antiemetic - CTZ

Side Effects

Short-term: Extrapyramidal effects: Parkinsonian, symptoms (tremor, bradykinesia), dystonia, perioral tremor,
 Endocrine alterations - increased prolactin, Release, gynecomastia, amenorrhea, Antihistaminergic effects (sedation)
 Orthostatic hypotension (α -adrenergic), Anticholinergic effects (dry mouth, etc.), Delirium or agitation, Cardiovascular alterations, Ocular - blurred vision, retinitis pigmentosa, Decreased seizure threshold, Poikilothermy-can lead to hypothermia, Neuroleptic malignant syndrome

Long Term: Tardive dyskinesia (stereotyped abnormal movements and facial disfigurement), - frequently irreversible Perioral Tremor, Blood dyscrasias - agranulocytosis can occur with clozapine and some phenothiazines - must curtail drug usage.

3. Appreciate reasons for choosing one drug vs. another. (see chart)

4. What drugs may be useful in treatment of chronic multiple tics (Tourette's Syndrome)?

Clonidine, Haloperidol, Pimozide - Phenothiazines, particularly fluphenazine, may be effective alternatives to haloperidol and pimozide.

E. Lithium (Li)

1. Understand proposed mechanism of action.

Mechanism: (not very clear) May affect ion transport, the serotonin system, or the PI cascade.

2. Indications for use.

Manic episodes of bipolar affective disorder.

3. Side effects: mild and severe.

Side Effects: Low Therapeutic Index, tremor - most common, treat with propranolol, thyroid enlargement, polydipsia and polyuria, EEG alterations, leukocytosis, edema, acne,

Overdose: tremor, nausea, vomiting, diarrhea, sedation

In severe cases: ataxia, confusion, coma, arrhythmias, hypotension, albuminuria, death,

F. Some Important Drugs

1. Antipsychotics

CHLORPROMAZINE (THORAZINE)
CLOZAPINE (CLOZARIL)
OLANZAPINE (ZYPREXA)
FLUPHENAZINE (PROLIXIN)
HALOPERIDOL (HALDOL)
LOXAPINE (LOXITANE)
MOLINDONE (MOBAN)
QUETIAPINE (SEZOQUEL)
RISPERIDONE (RISPERIDAL)
SERTINDOLE (SERLECT)
THIORIDAZINE (MELLARIL)
THIOTHIXENE (QUETIAPINE)

2. Mood stabilizers

CARBAMAZEPINE
DIVALPROEX
LITHIUM
VALPROIC ACID

VIII. Antidepressant Agents

A. Key Objectives

1. Understand the 2 types of mood disorders (bipolar and unipolar) and their drug treatments.

Bipolar- periods of depression alternating with periods of mania or hypomania. Treatment: Lithium, Carbamazepine, Valproic acid. Treat the acute depression with antidepressants and the acute mania phase with antipsychotics.

Unipolar- Usually just depression. Treat with MAO-I's, TCA's, Heterocyclics, and SSRI's.

2. Know the 4 classes of antidepressants and examples of each (TCA's, MAO-I's, Heterocyclics, SSRI's).

3. Know the indications for the antidepressants.

Panic disorder (TCAs, MAOIs and SSRIs)

Obsessive-compulsive disorder (SSRIs).

Enuresis (TCAs)

Chronic pain (TCAs)

Eating disorders (SSRIs)

4. Understand proposed mechanisms of action for therapeutic effects and side effects for each of the 4 classes of antidepressants.

5. Know the side effects, mild and severe, for each class. (see outline)

6. Understand the pharmacological data that implicate neurotransmitter abnormalities that may be associated with mood disorders.

7. Understand the clinical advantages of the serotonin-selective reuptake inhibitors (SSRI's).

Lack many of the side effects and potential toxicities of other antidepressants.

8. Understand the criteria for selecting one drug or class over another. ?Webcai?

9. Know about the most important drug-food and drug-drug interactions of these drugs. (see outline)

10. Know the symptoms of overdose and the treatments. (see outline)

B. Outline of Antidepressants

1. Monoamine oxidase inhibitors (MAO-I's)

phenelzine (Nardil)
tranylcypromine (Parnate)
moclobemide (RIMA)

Mechanism: increase synaptic availability of norepinephrine and serotonin by blocking their catabolism.

Side effects: dry mouth, constipation, headache, drowsiness, postural hypotension, weight gain, sexual dysfunction.

Overdose: unusual but can cause seizures, shock, delirium, and hyperthermia.

Potentiate the action of other sedatives such as alcohol

Potentially fatal "serotonin syndrome" if administered with an SSRI.

Treat OD: Supportive, phenothiazines with alpha adreno-blocking → chlorpromazine.

** Food interactions- tyramine containing foods.

2. Tricyclic antidepressants (TCA's)

amitriptyline (Elavil)
imipramine (Tofranil)
desipramine (Norprami)
doxepin (Sinequan)
clomipramine (Anafranil)

Mechanism: inhibit the reuptake of norepinephrine and/or serotonin. Are also potent antagonists at various receptors including cholinergic, histaminergic and alpha-adrenergic receptors.
Side effects: sleepiness, tremor, insomnia, anticholinergic effects, orthostatic hypotension, arrhythmias, seizures, weight gain, sexual dysfunction.
Overdose: Life threatening, coma, respiratory depression, delirium, seizures, hyperpyrexia, bowel and bladder dysfunction, cardiac effects.
Treat OD: Sodium Bicarbonate, propranolol, phenytoin, ?Physostigmine?

3. Heterocyclics → Mechanism: varies but probably involves increased synaptic availability of norepinephrine or serotonin.

amoxapine (Asendin) - antidopaminergic activity, Used in psychotic depression, Causes EPS and tardive dyskinesia.
bupropion (Wellbutrin) - mechanism involves blockade of dopamine reuptake. Side effects: dizziness, sweating, aggravation of psychosis, seizures.

trazodone (Desyrel) - very sedating
nefazodone (Serzone)
venlafaxine (Effexor)
mirtazepine (Remeron)
maprotiline (Ludiomil)

Pharmacokinetics

Route of Administration: Oral
Relatively long half-life - once daily dosing
exceptions: trazodone, venlafaxine, bupropion
All have active metabolites
Metabolism and Excretion - varies

4. SSRI's

fluoxetine (Prozac)
sertraline (Zoloft)
paroxetine (Paxil)
fluvoxamine (Luvox)

Mechanism: inhibit serotonin reuptake. Can inhibit reuptake of NE at high doses.
Side effects: anxiety-insomnia-tremor-GI symptoms-rashes-weight loss or gain decreased libido-sexual dysfunction.
Overdose: Low risk of fatal overdose.
Adverse drug interactions: MAOIs - 5-HT syndrome
Dispositional interactions: Paroxetine and fluoxetine are metabolized by CYP2D6, nefazodone and fluvoxamine by CYP3A4.

C. Some Important Drugs

1. Monoamine oxidase inhibitors

ISOCARBOXAZID (MARPLAN)
PHENELZINE (NARDIL)
TRANLYCPROMINE (PARNATE)
MOCLOBEMIDE

2. Tricyclic drugs

AMITRIPTYLINE (GENERIC, ELAVIL, OTHERS)
CLOMIPRAMINE (ANAFRANIL)
DESIPRAMINE (NORPRAMIN, PERTOFRANE)
DOXEPIN (GENERIC, SINEQUAN, OTHERS)
IMIPRAMINE (GENERIC, TOFRANIL, OTHERS)
NORTRIPTYLINE (AVENTYL, PAMELOR)
PROTRIPTYLINE (VIVACTIL)
TRIMIPRAMINE (SURMONTIL)

3. SSRI's

FLUOXETINE (PROZAC)
PAROXETINE (PAXIL)
SERTRALINE (ZOLOFT)
FLUOXAMINE (LUVOX)

4. Heterocyclic

AMOXAPINE (ASENDIN)
BUPROPION (WELLBUTRIN)
MAPROTILINE (LUDIOMIL)
NEFAZODONE (SERZONE)
VENLAFAXINE (EFFEXOR)

MIRTRAZAPINE (REMERON)
MAPROTILINE (LUDIOML)

IX. Opioid Analgesics and Antagonists

A. Basic Pharmacology of Opioid Analgesics:

You should be able to discuss the mechanism of action of these agents, including shared features with the endorphins.

Which parts of the brain are most likely sites of analgesic action of opioids?

- Presynaptic and postsynaptic spinal actions-
 - IPSP's
 - Inhibition of neurotransmitter release
- Pain-modulating descending pathways-
 - Periaqueductal Grey matter (PAG)
 - Rostral Ventral Medulla (RVM)

Opioid receptors:

At least three different receptor types:

- ì (mu)
- ä (delta)
- ê (kappa)

- All are G-protein coupled and at least 2 subtypes of each have been cloned
- Close Ca²⁺ channels, reducing evoked transmitter release (presynaptic)
- Open K⁺ channels, hyperpolarizing membranes (postsynaptic)

- Different receptor types may play distinct roles in modulation of sensory input. Activation of ì (mu) receptors produces the analgesic, sedative, and euphoric effects of opiates, as well as most of their untoward side effects. Activation of ê (kappa) receptors may contribute to analgesia, but primarily results in dysphoria.

- Other sites - PCP and ó (sigma) - may contribute to dysphoric effects of opiates. (Note that the sigma site is NOT an opioid receptor!)

What are the definitions of tolerance and physical dependence?

Tolerance: The need for higher doses in order to have the same effects. Starts with 1st dose, clinically apparent in 2-3 weeks.

Physical dependence: physiological requirement for the substance in order to avoid withdrawal symptoms.

Be able to describe CNS effects of opioids, which are: analgesia, euphoria, sedation, respiratory depression, cough suppression, miosis, truncal rigidity, and nausea and vomiting (CTZ).

Be able to discuss peripheral effects: Arterial and venous dilation, Constipation, Biliary colic (cholinergic), Renal blood flow, Renal function, Uterine tone, ADH, PRL, Somatotropin release, LH release, Flushing (histamine), Sweating (histamine), Rash and Itching (histamine).

B. Clinical Pharmacology

What are the major clinical uses of opioid analgesics?

- Acute or Chronic Pain-analgesic
 - no apparent maximal dose
 - less effective for neuropathy (adjuvant analgesics such as Imipramine)
- Acute pulmonary edema-
 - Decrease sensation of crisis
- Cough-
 - Antitussive
- Diarrhea-
 - Decrease GI motility
- Anesthesia/preoperative meds-
 - Anesthetic sparing

Be able to discuss specifics concerning application of opioids to treatment of cancer pain, obstetrical applications, renal and biliary colic.

- Opioids are used clinically in all of the above conditions, as well as acute pulmonary edema, cough, diarrhea and anesthesia. Use of opioids in analgesia is indicated for *severe, constant* pain rather than intermittent pain.

Discuss opioid use in acute pulmonary edema, cough suppression, diarrhea and in anesthesia.

Pulmonary edema- reduces patient anxiety as well as reduced preload and afterload.

Cough- only used in low synthetic doses.

Diarrhea- synthetic opioid surrogates are used that are selective for GI to decrease motility w/out CNS effects.

Anesthesia- used for analgesic, anxiolytic, and sedative effects.

What are the major toxic effects of opioid analgesics?

Respiratory depression - 1° cause of death

Dysphoria

Nausea and vomiting

Constipation

Seizures (high doses - may be μ -mediated)

Be able to discuss the nature of tolerance, physical and psychological dependence associated with opioid agonists.

Tolerance: Euphoria (days), Respiratory depression (days), analgesia, sedation, nausea (weeks to months), cough suppression, Antidiuresis. Cross tolerance to other opioids also.

Minimal or No Tolerance: Miosis, constipation, seizures.

Physiological Dependence-

Abstinence syndrome: dysphoria, rhinorrhea, lacrimation, yawning, chills,

Vomiting, diarrhea, anorexia, insomnia, anxiety, hostility.

- Time of onset and duration depends on the drug.
- After withdrawal, no tolerance but craving can persist.

Psychological Dependence-

Initially, drug use is pleasurable.

With physiological dependence - need drug to feel "normal".

Important issue for opiate abuse.

Should NOT be used as a rationale for withholding adequate pain control.

What are the approaches to diagnose and treat opioid overdose? What is the role of naloxone? Naltrexone?

Diagnostic aids: known addict, needle marks, miosis, brought to clinic by friends that use drugs. Coma?

Treatment of Overdose - Use an opiate antagonist. (Can precipitate withdrawal symptoms.)

NALOXONE - IM or IV 1 - 2 hr duration

NALTREXONE - Oral T_{1/2} = 10 hrs

What are the major contraindications and cautions in the clinical use of opioids?

Contraindications:

Head injuries - vasodilatation intracranial pressure

Pregnancy - fetal addiction

Impaired pulmonary function

Hepato- or renal compromised patients

Endocrine disorders -Addison's disease, Hypothyroidism

Be able to discuss the major pharmacological properties of morphine, heroin, methadone, meperidine, fentanyl, codeine, oxycodone, diphenoxylate, loperamide, dextromethorphan, naloxone, naltrexone and tramadol.

High Efficacy Analgesics

MORPHINE

METHADONE (longer acting ~6 hrs; plasma t_{1/2} ~24 hrs)

MEPERIDINE (med. acting 2-4 hrs, antimuscarinic)

FENTANYL (short acting 1-1.5 hrs)

SUFENTANYL (short acting 1-1.5 hrs)

ALFENTANIL (very short acting 15 - 45 min)

Low to Medium Efficacy Analgesics

CODEINE

HYDROCODONE

OXYCODONE

PROPOXYPHENE (v. low efficacy)

TRAMADOL (propoxyphene-like metabolites; inhibits NE and 5-HT re-uptake)

Antidiarrheals
LOPERAMIDE

Antitussives
CODEINE
DXTROMETHORPHAN

Drugs of Abuse
HEROIN

Pharmacokinetics/Disposition of Opioids
Routes of Administration
Parenteral - IV, IM, SC
Oral - 1st pass metabolism
Rectal - avoids 1st pass
transdermal - fentanyl
Distribution
Protein bound - varies by compound
vary in ability to cross blood-brain barrier
Metabolism and Excretion
Morphine glucuronidated
M-6G more potent than morphine
2° hepatic metabolism
Some metabolites are psychoactive (e.g., normeperidine)
Excreted by kidney

DRUG INTERACTIONS:
Pure agonists with mixed ag-antags
analgesia
can precipitate withdrawal symptoms
Sedative-hypnotics
sedation and respiratory depression
Antipsychotics
sedation and respiratory depression
risk of seizures
MAOIs
risk of hyperpyrexia
hypertension

Be familiar with the pharmacokinetics and pharmacodynamics of the pure opioid antagonist drugs naloxone and naltrexone.
NALOXONE - IM or IV 1 - 2 hr duration
NALTREXONE - Oral T_{1/2} = 10 hrs

C. Some Important Drugs

1. Analgesic opioids

ALFENTANIL (ALFENTA)
BUTORPHANOL (STADOL)
CODEINE SULFATE OR PHOSPHATE
DEZOCINE (DALGAN)
FENTANYL (SUBLIMAZE)
HYDROMORPHONE (GENERIC, DILAUDID)
LEVORPHANOL (LEVO-DROMORAN)
MEPERIDINE (GENERIC, DEMEROL)
METHADONE (GENERIC, DOLOPHINE)
MORPHINE SULFATE (GENERIC, OTHERS)
NALBUPHINE (GENERIC, NUBAIN)
OXYCODONE (GENERIC)
OXYMORPHONE (NUMORPHAN)
PENTAZOCINE (TALWIN)
PROPOXYPHENE (GENERIC, DARVON OPULVULES, OTHERS)
SUFENTANIL (SUFENTA)
TRAMADOL (ULTRAM)

2. Analgesic combination

CODEINE/ACETAMINOPHEN (GENERIC, TYLENOL, OTHERS)
CODEINE/ASPIRIN (GENERIC, EMPIRIN, OTHERS)
HYDROCODONE/ACETAMINOPHEN (GENERIC, NORCET, VICODIN, LORTAB, OTHERS)
OXYCODONE/ACETAMINOPHEN (GENERIC, PERCOCET, PERCODAN, TYLOX, OTHERS)
OXYCODONE/ASPIRIN (GENERIC, PERCODAN)
PROPOXYPHENE/ASPIRIN (DARVON COMPOUND-65, OTHERS)

3. Antitussives

CODEINE (GENERIC, OTHERS)
DXTROMETHORPHAN (GENERIC, BENYLIN DM, DELSYM, OTHERS)

4. Antidiarrheal

Diphenoxylate
Loperamide

5. Antagonists

Naloxone
Naltrexone
Nalmefine

X. Drugs used in treatment of dementia

A. Basic Pharmacology

Know the mechanism of action of drugs used to treat dementia.

They are cholinesterase inhibitors and muscarinic modulators.

Does this mechanism affect the disease process?

No. It is only a symptomatic treatment.

How effective are these drugs in relieving dementia symptoms?

They are effective in slowing the progress of dementia associated with Alzheimer's.

Does disease severity affect efficacy?

The more demented the patient, the less help these agents are in slowing the progress.

What side effects are associated with these drugs?

Besides the expected increases on Parasympathetics, tacrine is hepatotoxic.

What dispositional interactions are associated with tacrine?

? Abnormal thinking, anxiety, agitation, confusion, hostility, depression, insomnia?

Agents Used:

TACRINE
DONEPEZIL

XI. Drug Abuse

A. Introduction

Be able to define psychic dependence, physical dependence, addiction, tolerance, metabolic tolerance, and functional tolerance.

Psychological dependence is manifested by compulsive drug-seeking behavior in which the individual uses the drug repetitively for personal satisfaction, often in the face of known risks to health. **Physiologic dependence** is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. **Addiction** is usually taken to mean a state of physiologic and psychological dependence, but the word is too imprecise to be useful. **Tolerance** signifies a decreased response to the effects of the drug, necessitating ever-larger doses to achieve the same effect. Tolerance is closely associated with the phenomenon of physiologic dependence. It is largely due to compensatory responses. **Metabolic tolerance** is due to increased disposition of drug after chronic use. **Functional tolerance** is from compensatory changes in receptors, effector enzymes or membrane actions.

B. Opiates and Opioids

What are the most commonly abused drugs in this group? Morphine, Heroin, and Oxycodone.

What is the method of administration of these agents? IV

What are the symptoms of opiate withdrawal?

Abstinence syndrome: **major dysphoria**, rhinorrhea, lacrimation, yawning, chills, Vomiting, diarrhea, anorexia, insomnia, anxiety, hostility.

What are some examples of serious complications that may be associated with opiate dependence? (see above)

Be able to describe the treatment options for management of opiate dependencies.

Treat with a substitute agent and then slowly taper the dose. Methadone and clonidine.

C. Barbiturates and Other Sedatives

What are the major drug categories in this section? (see above)

What are the effects seen with increasing doses of these drugs? (see above)

What is the main pharmacokinetic classification of barbiturates and benzodiazepines? (see above)

What are the patterns of drug abuse with sedatives? (see above)

What are withdrawal symptoms seen with sedatives?

The old DT's for EtOH - Convulsions associated with withdrawal are the most serious.

Be able to discuss treatment principles as applied to sedative abuse.

Treat with a substitute agent and then slowly taper the dose.

D. Stimulants

What are the major stimulant drugs of abuse? Cocaine and Amphetamines.
Be able to discuss the patterns of amphetamine abuse.

Initially euphoria and alertness then following days of abuse paranoid schizophrenic

Know the patterns of cocaine abuse. (Same as above?) Withdrawal- depression, exhaustion, hunger and sleepiness.

What are pharmacological approaches that are being considered for long-term treatment of stimulant abuse?

Treat the initially with antipsychotics then for long term –Despramine, carbamazepine, bromocriptine, amantadine, clonidine, buprenorphine, and bupropion.

E. Hallucinogens

What are the major drugs in this section? LSD, PCP, mescaline, psilocybin.

What is the neurotransmitter system that may be most affected by LSD? Serotonin

What receptor system may be involved in the mediation of the effects of phencyclidine (PCP)? Opioid sigma receptor.

What are adverse effects (psychological and physical) associated with the use of hallucinogens?

Psychological -Decreased hearing, visual illusions, distortion of time, memory impairment, altered moods, poor judgment.

Physical- Pupillary dilation, hyperactive SNS, tremor, and increased heart rate.

F. Marijuana

What is the active cannabinoid in marijuana? THC - tetrahydrocannabinol

What are the main characteristics of cannabis intoxication? Euphoria, laughter, time distortion, and sharpened vision, then increased pulse rate and reddening of conjunctiva.

What are health hazards that may be associated with marijuana use?

Similar to cigarette smoking - invasive fungal infections also.

What are therapeutic uses for cannabis? Treatment of Nausea and vomiting and to decrease intraocular pressure in glaucoma.

G. Inhalants

What are the categories of inhalants that are subject to abuse?

Nitrous oxide, ether and chloroform, industrial solvents, aerosol propellants, and organic nitrites.

Know the clinical aspects of abuse of nitrous oxide, ether and chloroform, industrial solvents and organic nitrites.

What is the toxicity of chloroform? Liver and kidney damage.

H Some Important Drugs:

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| 1. Central Nervous System Depressants
ALCOHOL
BARBITURATES
BENZODIAZEPINES |
| 2. Stimulants
CAFFEINE
NICOTINE
COCAINE
AMPHETAMINE |

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| 3. Hallucinogens
LSD
MESCALINE
PSILOCYBIN
PHENCYCLIDINE
KETAMINE |
| 4. MARIJUANA |
| 5. Inhalants
NITROUS OXIDE
ETHER
CHLOROFORM |