Pharmacology of the CNS

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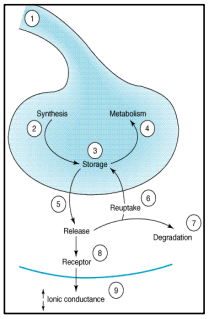
Central Nervous System (CNS)

- The CNS comprises the brain and the spinal cord and controls motor function, the ANS and the endocrine system.
- The CNS is an extremely complex network of interconnecting neuronal pathways.
- Each neuron comprises a cell body (soma) and an axon, which forms a connection or synapse to a postsynaptic cell.
- The cell bodies also have neural projections (dendrites) that can terminate on the cell body itself, on the cell body of another nerve or on the presynaptic terminal of a third neuron that is making neuronal connection to a postsynaptic cell.

Drug Action in the CNS

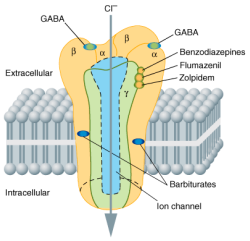
- Drugs have therapeutic effects in various CNS disorders , and some drugs such as anesthetics and non-medical drugs such as alcohol, caffeine, nicotine, etc modify normal CNS function.
- For drugs to affect the CNS, they must first traverse the blood-brain barrier.
- Drugs act in the CNS by affecting the action of the neurotransmitter at the postsynaptic terminal either by interfering with the synthesis, storage, release, re-uptake or the degradation of the neurotransmitter.



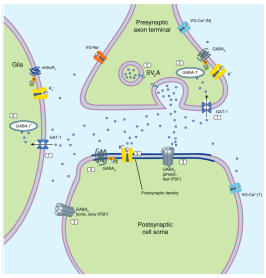
Neurotransmitters of the CNS

- A number of different neurotransmitter systems are involved in neuronal communication within the CNS.
- These include
  - **γ-aminobutyric acid (GABA)**
  - **Glutamate,**
  - **Glycine,**
  - **5-HT (Serotonin)**
  - **Dopamine**
  - **Histamine etc**

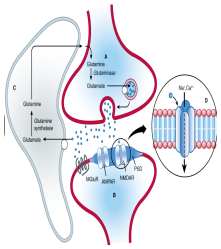
- GABA is the major inhibitory neurotransmitter within the CNS in the terminal endings of GABAergic neurons.
- It activates $GABA_A$ receptors which opens Cl^- channels resulting in Cl^- entry and cell Hyperpolarization, thereby reducing the postsynaptic neuronal excitability and neurotransmitter release by the postsynaptic neuron.



- Clinically relevant drugs such as benzodiazepines (e.g. diazepam) target $GABA_A$ receptors and enhances the action of GABA.
- These are used as anxiolytic, sedative, and anticonvulsant drugs.



- **Glutamate** is one of the most abundant excitatory neurotransmitters in the brain that bind to ligand-gated Na^+ and Ca_2^+ channels and activate them.
- These lead to the entry of Na^+ and Ca_2^+ in the postsynaptic neuron causing membrane depolarization and increases cell excitability.
- Drugs like **Ketamines** block these receptors and are used as general anesthetics.



- **Dopamine** inhibits Central neurons by opening K^+ Channels leading to hyperpolarization.
- Dopamine agonists are used in the treatment of Parkinson's disease and antagonist use in Schizophrenia.

Neurodegenerative Disorders

- These include
  - Stroke
  - Parkinson Disease, &
  - Alzheimer's Disease.
  - Hutington's chorea,
  - Motor neuron disease, &
  - Creutzfeldt-Jako Disease
- These diseases result from irreversible neuronal death usually due to stroke, glutamate excitotoxicity, oxidative stress and apoptosis.

Stroke

- Stroke leads to brain ischemia that result in rapid cell death in the hypoxic area followed by a slower neurodegenration in the vicinity.
- The ischemia causes depolarization of neurons, leading to the release of glutamate that results in excitotoxicity that damages the cell membrane.
- This blocks the functioning and a drop in ATP resulting in a malfunctioning of Ca_2^+, and Na^+-K^+ pumps .
- The drug **Ateplase** can improve blood flow and reduce further damage; however can make matters worse if the stroke is due to hemorrhage rather than clot formation.

Parkinson's Disease

- Parkinson's disease is a neurodegenerative disorder that involves selective destruction of dopaminergic neurons in the basal ganglia resulting in abnormality of motor functions including bradykinesia (slow movement) rigidity, resting tremor and a lot of other movement disturbances such as difficulty in performing voluntary movements (hypokinesia).
- The symptoms of the Parkinson's disease can be ameliorated by therapeutic intervention, however, the neurodegeneration is not reversed.

Pathogenesis of Parkinson's Disease

- The motor symptomps are due to a specific loss of doperminergic neurons in the nigrostriatal pathway, which constitute the main link in the extrapyramidal motor system involved in fine motor control.
- The Excessive activity of the intrinsic cholinergic fibers of the striatum, unchecked by dopamine, is likely to be involved in the tremor.
- The imbalance between these two systems is the main cause of Parkinson's disease.

- This result in the damage of dopaminergic neurons is caused by excitotoxity, oxidative stress and apoptosis.
- In Parkinson's disease, the destruction of dopaminergic fibers projecting from the substantia nigra to the coprpus striatum impairs the fine control exerted by the basal ganglia which is exacerbated by a resulting enhancement in the action of striatal cholinergic neurons

Treatment of Parkinson's Disease

- Levapoda is the main drug used against Parkinson's disease.
- It is orally administered with a selective extracerebral decarboxylase inhibitor such as carbidopa or bensarazide.
- These greatly decreases the effective dose by reducing peripheral metabolites and reduces peripheral adverse effects such as nausea, postural hypotension etc.
- Some dopamergic drugs such as bromocriptine, carbegoline etc which are direct acting drugs are used but have peripheral side effects which can be reduced with dopamine antagonist such as doperidone.

Alzheimer's Disease

- This is an age-related disease associated with the loss of neurons and shrinkage of the brain tissue, particularly in the hippocampus and basal forebrain.
- There is lost of cholinergic fibers and therefore anticholinesterase drugs such as donepezil are used for treatment.
- The treatment can only help slow the progress of the disease but cannot reverse the situation

Anxiolytics, and Hypnotics

- Anxiety is a condition associated with excessive excitatory neurotransmission in the CNS that is clinically characterized by nervousness and apprehension concerning a variety of activities or events and is a reaction to stress or altered circumstances (e.g. bereavement).
- It is also associated with a state of sympathetic arousal (e.g. sweating, headache, and restlessness).

- The manifestation of anxiety is a result of a complex interaction between different brain structures.
- A number of neuronal pathways, involving GABA, Serotonin (5HT), and NE are implicated in modulating anxiety and provide a rational basis for treatment.
- Anxiolytics are used in the treatment of anxiety state and hypnotics are used for insomnia.

Drug Treatment

- Drug treatment of sleep disorders (hypnotics) and acute anxiety states (anxiolytics) is dominated by benzodiazepine (BDZs).
- In general, these drugs will induce sleep when given in high doses at night and will provide sedation and reduce anxiety when given in low, divided doses during the day.
- BDZs have anxiolytic, hypnotic, muscle relaxant, anticonvulsant and amnesic actions caused mainly by the enhancement of GABA-mediated inhibition in the CNS

Commonly used Benzodiazepines

- Anxiolytics
  - Diazepam which is long acting and used in premedication and in epilepsy
  - Lorazepam, medium acting and used in premedication.
- Hypnotics
  - Temazepam, medium acting is used to avoid daytime sedation
  - Lormetazepam, and nitrazepam are medium acting applied for problematic early morning waking and for daytime anxiolytic effect

Pharmacological Actions of Benzodiazepines

- BDZs cause
  - A decrease in anxiety
  - A sedative effect
  - Sleep induction
  - A reduction in muscle tone, &
  - An anticonulsant effect.
- Their clinical use depends on the duration of action; short-acting drugs are preferred as hypnotics to avoid sedative action throughout the day.

Mechanism of Action of BDZs

- Benzodiazepines act by binding to $GABA_A$ receptors and enhance the action of GABA, increasing the affinity for its site on GABA-activated Cl^- channels.
- BZDs are GABA agonists with overall actions in the CNS being the general enhancement of neuroinhibitory actions of GABA.
- Competitive antagonsists of BZDs such as Flumazenil can be used to treat BZDs overdose.

Pharmacokinetics of BZDs

- BZDs are lipid soluble and generally well absorbed from the gut and readily distributed to the brain.
- Most bind strongly to plasma proteins.
- Some are metabolized to active agents with longer plasma half-lives.
- The final excretory product of most BZDs is the glucuronide.
- Slower metabolism and increased half-lives necessitate lower doses in elderly persons.

Unwanted Effects of BZDs

- These include
  - Confusion
  - Forgetfulness, &
  - Loss of motor control
- These effects combine to affects
  - Complex task such as driving
  - Respiratory functions in combination with alcohol
- Generally BZDs are very safe on their own but users leads to dependence and develop withdrawal syndrome both physically and psychologically.

Drugs Acting at Serotonergic (5HT) Receptors

- 5HT cell bodies are located in the ralphe nuclei of the midbrain and project to many areas of the brain, including those involved in anxiety (hyppocampus, amygdala, frontal cortex).
- 5HT antagonists therefore are useful anxiolytic drugs.
- Buspirone, a $5HT_{1A}$ partial agonist has anxiolytic effects by acting as antagonist at postsynaptic 5HT1A sites in the hyppocampus.
- Buspirone is not sedative and does not cause dependence

$5HT_{1A}$ Agonists

- $5HT_{1A}$ receptors occur extensively in the cerebral cortex and amygdala.
- They are auto-inhibitory presynaptic receptors and their activation results in decreased firing of the serotonergic neurons on which they occur.
- $5HT_{1A}$ receptor agonists have mainly inhibitory effects.
- The main drugs are
  - **Buspirone**
  - **Gepirone, &**
  - **ipsapirone**

Pharmacological Actions and Mechanism of Action

- $5HT_{1A}$ agonists reduce anxiety but do not cause the sedation and motor incoordination observed with BZDs.
- The drugs work by activating the presynaptic 5HT1A autoreceptors, particularly in the dorsal raphe nucleus of the midbrain.
- The drugs also reduce the activity of some noradrenergic neurons and thus decreas arousal reactions, but do not induce sleep.
- However, there is a delay of several days before clinical effects are observed.

Unwanted Effects

- These include
  - Nausea
  - Nervousness
  - Restlessness
  - Headache, &
  - Light-headedness.
- The possibility of developing dependence and withdrawal is low.

Beta-Blockers

- Anxiety of often associated with overactivation of the sympathetic nervous system.
- This is manifested in symptoms such as sweating, tremor, palpitations and diarrhea, which can arise during social situations.
- Propranolol and atenolol antagonize the peripheral actions of Norepineprine and Epinephrine.
- This reduces the physiological response to activation of the sympathetic nervous system.
- They have no effects on the CNS and therefore are abused in some competitive sports and performing arts

Barbiturates

- Barbiturates are far more depressant than BZDs, because at higher doses they increase the Cl^- conductance directly and decrease the sensitivity of the neuronal postsynaptic membrane to excitatory transmitters.
- Barbiturates were extensively used but are now obsolete as hypnotics and anxiolytics because they readily lead to psychological and physical dependence, induce microsomal enzymes and relatively small overdosages may be fatal.
- In contrast, huge overdose of BZDs have been taken without serious long-term effects.
- Barbiturates (e.g. thiopental) remain important in anesthesia and are still used as anticonvulsants(e.g. phenobarbital)

Local Anesthetics

- Local anesthetics such as Amides (lidocaine, prilocaine, ropivacaine, levobupivacaine, & bupivacaine) and Esthers (Cocaine, benzocaine, tetracaine, & procaine) are used to prevent pain by causing a reversible block of conduction along nerve fibers.
- Most are weak bases and penetrate the nerve in non-ionized form.
- Once inside the axon, some ionized molecules form and these block the Na+ channels, preventing generation of the action potentials

- All nerve fibers are sensitive to local anesthetic, but in general, small diameter fibers are more sensitive than large fibers.
- Thus a differential block can be achieved where the small pain and autonomic fibers are blocked, while coarse touch and movement fibers are spared.
- Local anesthetic vary widely in their potency, duration of action, toxicity and ability to penetrate mucous membranes.
- Local anesthetic depress other excitable tissues (e.g. myocardium) if the concentration in the blood is sufficiently high, but their main unwanted systemic effects involved the CNS.

Drugs used as Local Anesthetics

- **Lidocaine** is the most widely used agent.
- It acts more rapidly and is more stable then other local anesthetics.
- When given with epinephrine, its action last about 90 min.
- **Prilocaine** is similar to lidocaine, but is more extensively metabolized and is less toxic in equipotent doses.
- **Bupivacaine** has a slow unset (up to 30 min) but has a very long duration of action, up to 8 hrs when used for nerve blocks.
- It is used for spinal anesthesia and during labour.

- **Benzocaine** is neutral , water-soluble , local anesthetic of low potency.
- It is in surface anesthesia for non-inflamed tissue of the mouth and pharynx.
- **Tetracaine** and cocaine are more toxic drugs with restricted use
- Hypersensitivity reactions may occur with local anesthetics, especially with procaine and other esters.

General Anesthetics

- General anesthesia is the absence of sensation associated with a reversible loss of consciousness.
- General anethetics facilitates surgery with much reduced distress to the patient.
- There are two broad categories of anesthetics:
  - Inhalation anesthetics (gases or volatile liquids), &
  - Intravenous agents.
- Numerous agents ranging from inert gases to steroids produce anesthesia in human, but only a few are used clinically

Clinical Use of General Anesthetics

- Historical Anesthetics include
  - Ether
  - Chloroform
  - Cyclopropaine
  - Ethylchloride, &
  - Trichlorethylene.
- Inhalation anesthetics include : nitrous oxide, halothane, isolurane, enflurane, desflurane and sevoflurane
- Intravenous Anesthetics are thiopental. Propofol, etomedate, and ketamine.

Action of General Anesthetics.

- Anesthetics depress all excitable tissues including central neurons, cardiac, smooth, and striated muscle.
- However, these tissues have different sensitivities to anesthetics and the areas of the brain responsible for consciousness such as the spinal cord, the thalamic nuclei, the cerebral cortex and the reticular activation system are the most sensitive
- Thus, it is possible to administer anesthetic agents at concentrations that produce unconsciousness without unduly depressing the cardiovascular and respiratory centers or the mycardium.
- However for most anesthetics, the margin of safety is small.

Medication Methods

- General anesthetics usually involves the administration of different drugs for:
- **Premedication**
  - To relief anxiety (benzodiazepines)
  - Reduction of secretions and vagal reflexes (antimuscarinics)
  - Pain relief (opioid analgesics)
- **Induction of anesthesia** (intravenous agents&
- **Maintenance of anesthesia** (Inhalation anesthetics),

- Premedication has two main aims:
  - The prevention of the parasympathomimetic effects of anesthesia (bradycardia, bronchial secretions etc), &
  - The reduction of anxiety or pain.
- Premedication is often ommitted for minor operations.
- If necessary, the appropriate drugs (e.g. hyoscine) are given intravenously at induction.
- Induction is most commonly achieved by the intravenous injection of **thiopental** or **profofol.**
- Unconsciousness occur within seconds and is maintained by the administration of an inhalation anesthetic such as **desflurane or isoflurane.**
- **Nitric Oxide** causes sedation and analgesia, but it is not sufficient alone to maintain anesthesia

- During the induction of anesthesia, distinct stages occur with some agents, especially ether.
  - Stage I is analgesic state
  - Stage II is excitement due to the inhibition of reticular neurons, &
  - Stage III is the stage of surgical anesthesia.
- The depth of the surgical anesthesia depends on the amount of the drug administered.
- These stages are not obvious with currently used anesthetics

Antipsychotic Drugs (Neuroleptics)

- Schizophrenia is a syndrome characterized by specific psychological manifestations, delusions thought disorders and behavioural disturbances.
- It is caused by developmental abnormalities involving the medial temporal lobe (parahippocampal gyrus, Hippocampus and amygdala), temporal and frontal lobe cortex
- Schizophrenia can be a genetically determined illness, but there is also implicating intrauterine events and obstetric complications,

Action of Neuroleptic Drugs

- Neuroleptic drugs control most of the symptomes of Schizophrenia.
- They have most effects on the positive symptomes such as hallucinations and delusion.
- Negative symptomes such as social withdrawal and emotional apathy, are less affected by the neuroleptic drugs.
- About 30% of patients show only limited improvement and 7% of patients show no improvement, even with prolonged treatment.

- The neuroleptics are all antagonists at dopamine receptors.
- This indicates that Schizophrenia ia associated with increased activity the dopaminergic mesolimbic and mesocortical pathways
- In agreement with this idea, amphetamine, which causes dopamine release can produce a psychotic state in normal individuals.
- In Schizophrenics, there is a great occupancy of D_2 receptors, implying greater dopaminergic stimulant.

- Neuroleptic drugs require several weeks to control the symptoms of schizophrenia and most patience will require maintenance treatment for several years.
- Relapses are common even in drug-maintained patients and more than two third of the patients relapses within one year if they stop drug treatment.
- Unfortunately, neuroleptic drugs also block dopamine receptors in the basal ganglia resulting in movement disorders such as parkinsonism, acute distonic reaction, motor restlessness, and tardive dyskinesia,

- Some atypical drugs such as clozapine, resperidone, clanzapine, olanzapine quetiapine, and amisulpride are relatively free of side effects are also applied as neuroleptic drugs.
- In the pituitary gland, dopamine acting on D_2- receptors inhibit prolactin release.
- This effect is blocked by neuroleptics, and the resulting increase in prolactin release result endocrine side effecst such as galactorrhea, menstrual irregulaties, impotence and weight gain.

Receptor blocking effects of Neuroleptics

- Many neuroleptics have Muscarinic receptor an d a-adrenoceptor blocking effects and causes autonomic effects including postural hypotension, dry mouth, blurred vision, and constipation.
- The potency of individual drugs in blocking autonomic receptors, and therefore their peripheral side effects, depends on the chemical class in which they belong which can either be propylamine, piperidine or piperazine.

Drugs Used in Affective Disorders-Antidepressants

- Affective disorders are characterized by a disturbance of the mood associated with alterations in behavior, energy, appetite, sleep and weight.
- The extreme range from intense excitement and elation (mania) to severe depression states.
- In depression, which is much more common than mania, a person becomes persistently sad and unhappy.
- Depression is common and, although it can cause people to kill themselves.

Pathophysiology

- The neurological basis of depression is based on the monoamine theory which states that in depression there is a functional deficit of the transmitters NE and 5-HT in the forebrain and in the mania, there is a functional excess of these transmitters.
- Antidepressants therefore act on NE/5-HT nerve endings.

- In support of monoamine theory are the following observations.
  - Inhibition of NE or 5-HT re-uptake improves mood.
  - Inhibition of monoamine oxidase (MAO: which metabolizes NE and 5-HT) has an antidepressant effect.
  - **Reserpine**, which depletes monoamine stores in the nerve endings, causes depression.

- Against the monoamine theory are the following observations
  - The sympathomimetic drugs cocaine and amphetamine lack an antidepressant action.
  - Some drugs (e.g. iprindole) have an antidepressant effect in the absence of clear effects of NE/5-HT transmission
  - There is a 2-4 week delay in the onset of the clinical action of antidepressant drug, despite immediate effects on neurotransmission
  - There are inconsistent changes in NE and 5-HT receptor densities and in turnover of amine transmitters in depressed patients.

Drugs used in Affective disorders

- There are two categories of drugs used to treat affective disorders which are:
  - Those used to treat unipolar depression, namely the true antidepressant, and
  - Those used to treat bipolar depressants
- These drugs include
  - NE/5-HT reuptake inhibitors
  - Monoamine Oxidase inhibitors, &
  - Atypical antidepressants

- NE/5-HT reuptake inhibitors are
  - Tricyclic
    - Amitriptyline
    - Imipramine
    - Dosulepin, &
    - Lofepramine
  - Others
    - Nefazodone, &
    - Venlafaxine
  - Specific serotonin re-uptake inhibitors, &
    - Fluxetine, &
    - citalopram

- Monoamine Oxidase Inhibitors are
  - Moclobemide
  - Phenelzine, &
  - Isocarboxazid
- Atypical antidepressants are drugs that do not block amine re-uptake and include
  - Mitrazapine, &
  - trazodone

Mechanism of Action
a. Monoamine Reuptake Inhibitors

- Inhibition of reuptake raises the concentration of the transmitter in the synaptic cleft and increases stimulation of the postsynaptic receptors.
- The selectivity for NE or 5-HT reuptake depend on the drug type.
- Some of these drugs inhibit MAO within nerve endings.
- The cytosolic concentration of NE/5-HT increases and more leak out into the synaptic cleft.
- There are two MAO isoezymes (A & B) which have selective drugs and some are non-selective.
- MAO binds covalently to the enzyme and thus have long duration of action

Mechanism of Action
b. Atypical Antidepressants

- They have less well characterized mechanism of action on monoamine transporters and receptors.
- Trazodone have weak5-Ht uptake inhibition and antagonism of 5-HT receptors.
- Bupropion has dopamine and NE reuptake inhibition.
- Mianserine and mirtazepine have α_2-adrenoceptor antagonsim and iprindole has dopamine reuptake inhibition

Pharmacokinetic Aspects

- They are given orally and are well absorbed in the GI tract.
- The half-lives vary from 24 to 96 hrs.
- The drugs are very lipid soluble and well absorbed by the mouth.
- The bind strongly to the plasma and tissue components, resulting in large volume of distribution.
- These drugs are tertiary amines with two methyl groups attached to side chain nitrogen.
- Removal of one of these methyl groups yields active drugs.
- These drugs are subsequently conjugated with glucuronic acid and long half-lives and dosage can often be once daily.

Unwanted Effects

- These drugs are dangerous in overdose.
- They are chemically related to antipsychotic phenothiazine and many have a similar spectrum of side effects due to receptor block:
  - **Antimuscarinic actions:** dry mouth, constipation, blurred vision, and urinary retention.
  - **Antihistamine effect:** sedation
  - **α-adrenoceptor block:** hypotension
- Other effects include
  - Nausea and vomiting
  - Sexual dysfunction

Atypical antidepressants

- These include agents that block serotonin reuptake but also 5-HT_2 receptor antagonists (**trazodone, nefazodone**)
- Side effects include sedation, hypotension and reflex tachycardia.
- **Bupropion** inhibits NE and dopamine reuptake and is a 5-HT_{1A} receptor agonists.
- Its side effects include dizziness, anxiety and seizures.

- These have fewer adverse effects than other antidepressants.
- The drugs have little or no activity on amine uptake.
- They generally cause fewer autonomic side effects and, because they are less cardiotoxic, they are less dangerous in overdosage.
- Mirtazapine and trazodone are sedative antidepressant.
- Mirtazapine has α_2-adrenoceptor blocking activity and, by blocking inhibitory α_2-autoreceptors on the central noradrenergic nerve endings.
- It may increase the amount of NE in synaptic cleft.

Monoamine Oxidase Inhibitors (MAOIs)

- MAO metabolize biogenic amines and occurs in two isoforms, both metabolizing dopamine.
- MAO_A metabolizes serotonin and NE outside storage vesicles, thus increasing the building blocks for new neurotransmitter synthesis into synaptic vesicles.
- MAO_B is selective foe phenylethylamine

- Some MAO inhibitors are non-selective (e.g. **phenelzine** and **tranylcypromine**) and patients who are prescribed these drugs should refrain from consuming food and drinks high in tyramine (e.g. cheese, wine).
- Medications such as nasal decongestants should also be avoided with MAOIs as these drugs will augment sympathetic activity at peripheral terminals in response to tyramine which indirectly causes the release of NE.

Side Effects of MAOIs

- Side effects include dry mouth, tremor, blurred vision, headache, hypertension and CNS stimulation.
- More selective and reversible inhibitors of MAO_A (e.g. **moclobemide, brofaromine, toloxatone** and **cimoxatone**), have more tolerable side effects and are used for depression

Drugs used for bipolar depression (Mood Stabilizers)

- Lithium carbonate is used in the treatment of bipolar effective disorders but also for the treatment of acute mania.
- It requires weeks to months to reduce manic episodes.
- At the biochemical level, lithium inhibits inositol monophosphatase, which disrupts the formation of the second messenger inositol, 1, 4, 5-triphosphate (IP_3) and as result protein kinase C activation thereby decreasing postsynaptic sensitivity to neurotransmitters (e.g. serotonin).

- This mimics Na_+ thus modifying cell membrane potential and ionic balance.
- It causes CNS toxicity and in large concentrations, renal damage.
- Its low therapeutic index makes it essential to monitor its plasma concentration.
- Lithium has a narrow therapeutic window and major adverse effects including polyuria, hyperthyroidism, and weight gain.
- Toxicity is manifested in the form of nausea, vomiting, diarrhea, confusion, convulsion and death.
- Anticonvulsants have been used in the treatment of mania (**carbamazepine, valproate**)

Clinical Use of Antidepressants

- They are use primarily to treat depression but are also used effectively in some anxiety disorders: panic disorder (citalopram), obsessive compulsive disorder, bulimia.
- The combination of an atypical agent with serotonin receptor inhibitor may be beneficial in antidepressant-resistant patients.
- Tricyclic antidepressants produce varying degrees of sedation, sedative agents being used for anxious patients: less sedative agents for withdrawn patients.
- MAOIs are less effective and subject to more drug interaction than the reuptake inhibtors and are considered second line.

Antiepileptic Drugs

- Epilepsy is a condition in which intermittent abnormal high-frequency firing of localized group of cerebral neurons resulting in seizures.
- The discharge may remain localized or may spread to other regions of the brain.
- Therefore epilepsy is a chronic disease in which seizures result from abnormal discharge of cerebral neurons.
- Seizures have periods of muscle rigidity (tonic) followed by jerking of the body (clonic).

- In childhood, absence of epilepsy, subjects frequently loss consciousness for brief moments without recollection of the events and are non-convulsive.
- The molecular basis involve mutation in various ion channels (sodium channels, $GABA_A$), and an abnormality in the thalamic relay sensory unit resulting in neuronal hyperexcitability.
- Partial syndromes are more common in adults with seizures beginning in particular location (e.g. temporal lobe as a result of stroke).
- This will then spread throughout the brain.
- These seizures are characterized by hallucination, confusion and loss of awareness.

Types of Seizures

- There are two types of seizures: partial and general.
- **Partial seizures** involve repeated jerking of a limb or complex behavioral changes but no loss of consciousness.
- In these cases, the abnormal discharge is localized to the relevant area of the cerebral cortex.
- **Generalized seizures** can take several forms:
  - An initial generalized tonic convulsion followed by jerking of the whole body accompanied by sudden loss of consciousness
  - Episodic transient loss of consciousness, observes mostly in children

- In generalized seizures, the abnormal electrical activity involves the whole brain.
- A state in which generalized convulsions follow each other without consciousness being regained is termed ***status epilepticus*** and is a medical emergency.
- About 70% of those with epilepsy respond well to treatment.

Causes of Epilepsy

- Heredity is an important factor as a cause of epilepsy.
- Damage to the brain (e.g. tumors, asphyxia, infection or head injury) may subsequently cause epilepsy
- Convulsions may be precipitated in epilepsy by several groups of drugs, including phenothiazine, tricyclic antidepressants and many antihistamines

Mechanisms of Action of Anticonvulsants

- The most studies agent is phenytoin which, at therapeutic concentrations, has no effect on transmitter release or on the neuronal response to glutamate or GABA.
- Its anticonvulsant action is as a results of its ability to prevent ***high-frequency repetitive activity***.
- The drug increases the proportion of inactivated sodium channels for many given membrane potentials.
- Phenytoin bind preferentially to inactive (close) sodium channels, stabilizing them in inactivated state and preventing them from returning to the resting (close) state which they must re-enter before they can again open.

- High-frequency repetitive depolarization increases the proportion of sodium channels in the inactivated state and , and because they are susceptible to blockage by phenytoin, the sodium current is progressively reduced until it is eventually insufficient to evoke an action potential.
- Neuronal transmission at normal frequencies is relatively unaffected by phenytoin, because a much smaller proportion of sodium ion channels are in activated state.

- Other drugs such as valproate, in addition increases GABAergic central inhibition but a mechanism involving the stimulation of glutamic acid decarboxylase activity.
- Phenobarbital also increases central inhibition but by enhancing the action of synaptically released GABA at $GABA_A$ receptor-Cl^- channel complex.
- Phenobarbital may also reduce the effect of glutamate on excitatory synapses.

- Absence seizures involve oscillatory neuronal activity between the thalamus and cerebral cortex.
- This oscillations involves Calcium channels in the thalamic neurons, which produce how threshold spike and allow the cells to fire in bursts.
- Drugs that control absences (ethosuximide and valproate) reduce this calcium ion current, dampening the thalamocortical oscillations that are critical in the generation of absence seizures

Drug Treatment

- The major aim of treatment is to reduce neuronal hyper excitability and this is achieved by targeting $GABA_A$, sodium and calcium channels.
- Antiepileptic drugs may need to be taken life-long so the fewer adverse effects the better.
- Treatment with a single drug is preferred b4cause this reduces effects and drug interactions.
- Furthermore, most patients obtain no extra benefit from multiple drug regimens.

- **Carbamazepine** and **valproate** are the first –line drugs in epilepsy because they cause relatively few adverse effect and have least detrimental effect on cognitive functions and behavior.
- Some anticonvulsants especially phenytion, phenobarbital, and carbamazepine are potent liver enzyme inducers and stimulate the metabolism of many drugs e.g. oral contraceptives, warfarin, theophylline etc

Carbamazepine

- Carbamazepine is metabolized in the liver Carbamazepine-10, 11 epoxide, an active metabolite that partly contribute to both its anticonvulsant action and neurotoxicity.
- In contrast to phenytoin, there is a linear increase in serum concentration with dosage.
- Mild neurotoxic effects are common (nausea, dizziness, drowsiness, blurred vision, and ataxia) and often determine the limit of dosage.
- Agranulocytosis is a rather idiosyncratic reaction to carbamazepine.

Phenytoin

- Phenytoin is hydroxylated in the liver by a saturated enzyme system.
- The rate of metabolism varies greatly in different patients, and up to 20 days may be required for the serum level to stabilize after changing the dose.
- Therefore the dose may be increased gradually until signs of cerebullar disturbance occur (nystagmus, ataxia, involuntary movements).
- Once the metabolized enzymes are saturated, a small increase in dose may produce toxic blood levels of the drug
- Other adverse effects include gum hypertrophy, acne, greasy skin, and coarseness of the facial features

Phenobarbital

- Phenobarbital is probably as effective as carbamazepine and phenytoin in the treatment of partial seizures but it is much more sedative.
- Tolerance occur with prolonged use and sudden withdrawal may precipitate status epilepticus.
- Side effects include cerebellar symptomes (e.g. Sedation, ataxia, nystagmus), drowsiness, in adults and hyperkinesia in children.
- **Primidone** is metabolized to active anticonvulsant metabolites, one of which is phenobarbital

Barbiturates

- Family of drugs used for hypnotic, anesthetic and anticonvulsant applications
- ¾ Mechanism probably related to increased GABA-mediated chloride conductance
- ¾ Two members of class commonly used as anticonvulsants:
  - **Phenobarbital**
    - May be administered PO, IM or IV
    - Long half-life (about 100 hours), hepatic metabolism.
    - Strong inducer of microsomal system.
    - Frequently used in infants; less commonly used in adults because of dose-related sedation.
  - **Primidone**
    - Parent drug has anticonvulsant properties, but is
    - metabolized rapidly by the liver to phenobarbital and
    - Toxicity similar to that of phenobarbital

Valproic acid

- Carboxylic acid, structurally distinct from other current classes of anticonvulsants.
- Mechanism uncertain - effective against both partial and primary
- generalized seizures; drug of choice for myoclonic epilepsy
- Oral or IV administration
- Hepatic metabolism, with half life 8-12 hours. Induces metabolism of other anticonvulsants
- Common adverse effects are tremor, weight gain, nausea.
- Most significant risk is hepatotoxicity, which may be fatal. Occurs most
- often in infants under 2 years when taking multiple anticonvulsants

Drugs for primary generalized epilepsy

- **Ethosuccimide**
  - Drug of choice for treatment of absence seizure.
  - Also effective in other forms of primary generalized epilepsy, but not usually effective in partial seizures.
- **Valproic acid**
  - effective in generalized as well as focal epilepsy;
  - Particularly useful when several seizure types are present

New Anticonvulsants

- Because they are new, the clinical indications for these agents are not yet completely defined, and none are currently used as the first treatment for epilepsy.
- **Felbamate** is a new drug for epilepsy but has an unacceptably high rate of drug related aplastic anemia.
- **Lamotrigine** is thought to act by blockade of sodium channels; useful in partial seizures and possibly also in primary generalized seizures.
- Other new drugs include Gabapentin, Tiagabin , Levetiracetam, Zonisamide, and Vigabatrin

Benzodiazepines

- An important anticonvulsant use of benzodiazepines is in setting of urgent treatment of status epilepticus.
- Two agents are frequently used, **diazepam** and **lorazepam**.
- These are particularly suitable because of rapid action after intravenous injection.
- Note that although biological half-life of diazepam is long, duration of action when used IV is short, because activity is terminated by redistribution.
- Oral benzodiazepines are not frequently used alone in primary treatment of epilepsy, although sometimes a useful adjunct in both focal and generalized seizures

Drug Withdrawal

- Abrupt withdrawal of antiepileptic drugs can cause rebound seizures, especially with benzodiazepines and barbiturates.
- However, withdrawal of other drugs in non-epileptic patients does not cause seizures.
- If a patient has been seizure free for 3 to 4 years, gradual withdrawal may be tried.

Opioid Analgesics

- Pain is a subjective experience with both sensory and emotional component arising from actual or potential tissue damage.
- It is frequently a traumatic accompaniment of many diseases and the relief of pain is an important clinical priorities.
- The main pain pathways the spinal cord, the thalamus, and the cortex.
- The main pain relieving drugs are the opioids, which modify both the transmission of pain signals to the brain and the subjective perception of the painful stimulus.

History of Opioids

- Opium is extracted from poppy seeds (*Paper somniforum)*
- Used for thousands of years to produce:
  - Euphoria
  - Analgesia
  - Sedation
  - Relief from diarrhea
  - Cough suppression
- Used medicinally and recreationally from early Greek and Roman times
- Opium and laudanum (opium combined with alcohol) were used to treat almost all known diseases

- Morphine was isolated from opium in the early 1800's and since then has been the most effective treatment for severe pain
- Invention of the hypodermic needle in 1856 produced drug abusers who self administered opioids by injection
- Controlling the widespread use of opioids has been unsuccessful because of the euphoria, tolerance and physiological dependence that opioids produce

Terminology

- "opium" is a Greek word meaning "juice," or the exudate from the poppy
- "opiate" is a drug extracted from the exudate of the poppy
- "opioid" is a natural or synthetic drug that binds to opioid receptors producing agonist effects

Natural opioids occur in 2 places:

- 1) In the juice of the opium poppy (**morphine** and **codeine**)
- 2) As endogenous endorphins
- All other opioids are prepared from either morphine (semisynthetic opioids such as **heroin**) or they are synthesized from precursor compounds (synthetic opioids such as **fentanyl**)

Pharmacological Effects

- **Sedation and anxiolysis**
  - Drowsiness and lethargy
  - Apathy
  - Cognitive impairment
  - Sense of tranquility
- **Depression of respiration**
  - Main cause of death from opioid overdose
  - Combination of opioids and alcohol is especially dangerous.

- **Cough suppression**
  - Opioids suppress the "cough center" in the brain
- **Pupillary constriction**
  - pupillary constriction in the presence of analgesics is characteristic of opioid use
- **Nausea and vomiting**
  - Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting
  - Unpleasant side effect, but not life threatening

- **Gastrointestinal symptoms**
  - Opioids relieve diarrhea as a result of their direct actions on the intestines
- **Other effects**
  - Opioids can release histamines causing itching or more severe allergic reactions including bronchoconstriction
  - Opioids can affect white blood cell function and immune function

Mechanism of action

- Activation of peripheral nociceptive fibers causes release of substance P and other pain-signaling neurotransmitters from nerve terminals in the dorsal horn of the spinal cord
- Release of pain-signaling neurotransmitters is regulated by endogenous endorphins or by exogenous opioid agonists by acting presynaptically to inhibit substance P release, causing analgesia

Primary Effect of Opioid Receptor Activation

- Reduction or inhibition of neurotransmission, due largely to opioid-induced presynaptic inhibition of neurotransmitter release
- Involves changes in transmembrane ion conductance
  - Increase potassium conductance (hyperpolarization)
  - Inactivation of calcium channels
- The three Opioid Receptors are
  - Mu
  - Kappa
  - Delta

Delta Receptor

- It is unclear what delta's responsible for.
- Delta agonists show poor analgesia and little addictive potential
- May regulate mu receptor activity

Mu-Receptor: Two Types

- Mu-1
  - Located outside spinal cord
  - Responsible for central interpretation of pain
- Mu-2
  - Located throughout CNS
  - Responsible for respiratory depression, spinal analgesia, physical dependence, and euphoria

Kappa Receptor

- Only modest analgesia
- Little or no respiratory depression
- Little or no dependence
- Dysphoric effects

Mu and Kappa Receptor Activation

Response	Mu-1	Mu-2	Kappa
Analgesia	★	★	★
Respiratory Depression		★	
Euphoria		★	
Dysphoria			★
Decrease GI motility		★	
Physical Dependence		★	

Mu and Kappa Receptors

DRUGS	MU	KAPPA
Pure Agonists	Agonist	Agonist
Agonist-Antagonist	Antagonist	Agonist
Pure Antagonists	Antagonist	Antagonist

AGONISTS

*Morphine
*Heroin
*Hydromorphone
*Fentanyl
*Codeine
*

General Pharmacokinetics

- LATENCY TO ONSET
- *oral (15-30 minutes)
- *intranasal (2-3 minutes)
- *intravenous (15 – 30 seconds)
- *pulmonary-inhalation (6-12 seconds)
- DURATION OF ACTION – anywhere between 4 and 72 hours depending on the substance in question.
- Metabolism – hepatic via phase 1 and phase 2 biotransformations to form a diverse array of metabolites (eg., morphine to morphine-6-glucuronide).

Morphine

- PHARMACOKINETICS
- Routes of administration (preferred)
  - *Oral
    latency to onset –(15 – 60 minutes)
  - * it is also sniffed, swallowed and injected.
  - * duration of action – (3 – 6 hours)
  - * First-pass metabolism results in poor availability from oral dosing.
  - * 30% is plasma protein bound
- EFFECTS AND MEDICAL USES
  - *symptomatic relief of moderate to severe pain
  - *relief of certain types of labored breathing
  - *suppression of severe cough (rarely)
  - *suppression of severe diarrhea
  - *AGONIST for mu, kappa, and delta receptors.

Hydromorphone

- PHARMACOKINETICS
- *Routes of administration (Preferred)
- *Oral
- *latency to onset (15 – 30 minutes)
- *Intravenous
- *Duration of Action (3-4 hours)
- *Peak effect (30-60 minutes)
- PROPERTIES AND EFFECTS
- * potent analgesic like morphine but is 7-10
- times as potent in this capacity.
- *used fequently in surgical settings for moderate to
- severe pain. (cancer, bone trauma, burns, renal colic.)

Fentanyl

- Pharmacokinetics
- Routes of Administration
  * Oral, and transdermal (possibly intravenous)
  *Highly lipophilic
  *latency to onset (7-15 minutes oral; 12-17 hours transdermal
  *duration of action (1-2 hours oral; 72 transdermal)
  *80 – 85% plasma protein bound
  *90 % metabolized in the liver to inactive metabolites

Other properties
  * 80 times the analgesic potency of morphine and 10 times the analgesic potency of hydromorphone.
  *high efficacy for mu 1 receptors.
  *most effective opiate analgesic

Antagonists

- Naloxone
- Naltrexone

Naltrexone

- PHARMACOKINETICS
- *latency to onset (oral tablet 15-30 min.)
- *duration of action 24-72 hours
- *peak effect (6-12 hours)
- STRUCTURAL DISTINCTION
- *Differs from naloxone insofar as the
- allyl group on the nitrogen atom is supplanted
- by a cyclopromethyl group.
- EFFECTS
- *Reverses the psychotomimetic effects of opiate
- agonists.
- * Reverses hypotension and cardiovascular instability
- secondary to endogeneous endorphins (potent vasodilators)
- *inhibits Mu, Delta, and Kappa receptors.

Aspirin and related NSAIDs

- display a ceiling effect for analgesia (not as effective as opioids)
- can be used in combination with opiate analgesics (summation effect)

History/Actions

Bark of willow tree: Pain relief from chemical in bark, salicin (chemically related to aspirin)

NSAID prototype:
Acetylsalicylic acid (ASA) = aspirin

Action of NSAIDs:
through either selective or non-selective blocking of enzymes involved in the synthesis of prostaglandins

NSAID= non-steroidal anti-inflammatory drug

PROSTAGLANDINS

- Members of group of lipid-derived paracrines

Paracrines:
- chemicals secreted by a cell to act on cells in the immediate vicinity via process of diffusion

- Can be released by all cells in the body

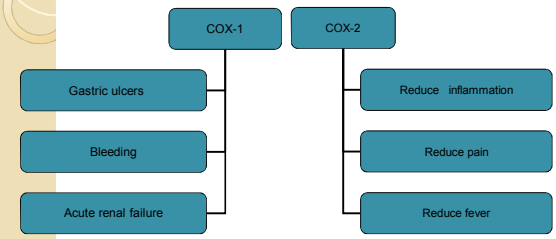
Cyclooxygenase

- An enzyme involved in prostaglandin synthesis
  - **cyclooxygenase-1** (COX-1): beneficial prostaglandins
  - **cyclooxygenase-2** (COX-2): harmful prostaglandins

COX Enzyme:Prostaglandin Effects

	COX-1: beneficial	COX-2: harmful
Peripheral injury site		Inflammation
Brain		Modulate pain perception Promote fever (hypothalamus)
Stomach	protect mucosa	
Platelets	aggregation	
Kidney	vasodilation	

Effects of COX Inhibition by Most NSAIDS



NSAIDs : anti-platelet—decreases ability of blood to clot

Pharmacokinetics:ASA

Absorption: from stomach and intestine

Distribution: readily, into most fluids/tissues

Metabolism : primarily hepatic

- ASA contraindicated for use in children with viral fever –can lead to Reye's Syndrome
- Fatal overdose is possible

Similar pharmacokinetics for ibuprofen and related NSAIDs

Pharmacokinetic Variability of Non-Selective COX-Inhibitors

Name	**Time to peak** (hours)	**½ life** parent ½ life*active
Aspirin	1-2	0.25-0.33 (*3-10 L-H)
Naproxen	2-4	12-15
Oxaprozin	3-5	42-50
****Sulindac (pro-drug)***	2-4	7.8 (*16.4)
Ketorolac (inj)	.5-1	3.8-8.6
Ibuprofen	1-2	1.8-2.5

Selective Cox-2 Inhibitors

- Greater affinity for cyclooxygenase-2
- Decreased incidence of negative effects associated with non-selective COX-inhibitors

Name	Time to peak (hours)	½ life (hours)
Celecoxib	3	11
Rofecoxib	2-3	17

Acetaminophen

N-Acetyl-P-Aminophenol (APAP)

Classification: analgesic, antipyretic, misc.
not an NSAID

Mechanism: inhibits prostaglandin synthesis via *CNS* inhibition of COX (not peripheral)---doesn't promote ulcers, bleeding or renal failure; peripherally blocks generation of pain impulses, inhibits hypothalamic heat-regulation center

APAP Liver Metabolism

1. *Major pathway* —Majority of drug is metabolized to produce a non-toxic metabolite
2. *Minor pathway* —Produces a highly reactive intermediate (acetylimidoquinone) that conjugates with glutathione and is inactivated.

- At toxic APAP levels, minor pathway metabolism cannot keep up (liver's supply of glutathione is limited), causing an increase in the reactive intermediate which leads to hepatic toxicity and necrosis

Pharmacokinetics: APAP

Metabolism: major and minor pathways
Half-life: 1-3 hours
Time to peak concentration: 10-60 min

Treatment for overdose: Acetylcysteine (Mucomyst)