

## **Depression, Anxiety, and Antipsychotics**

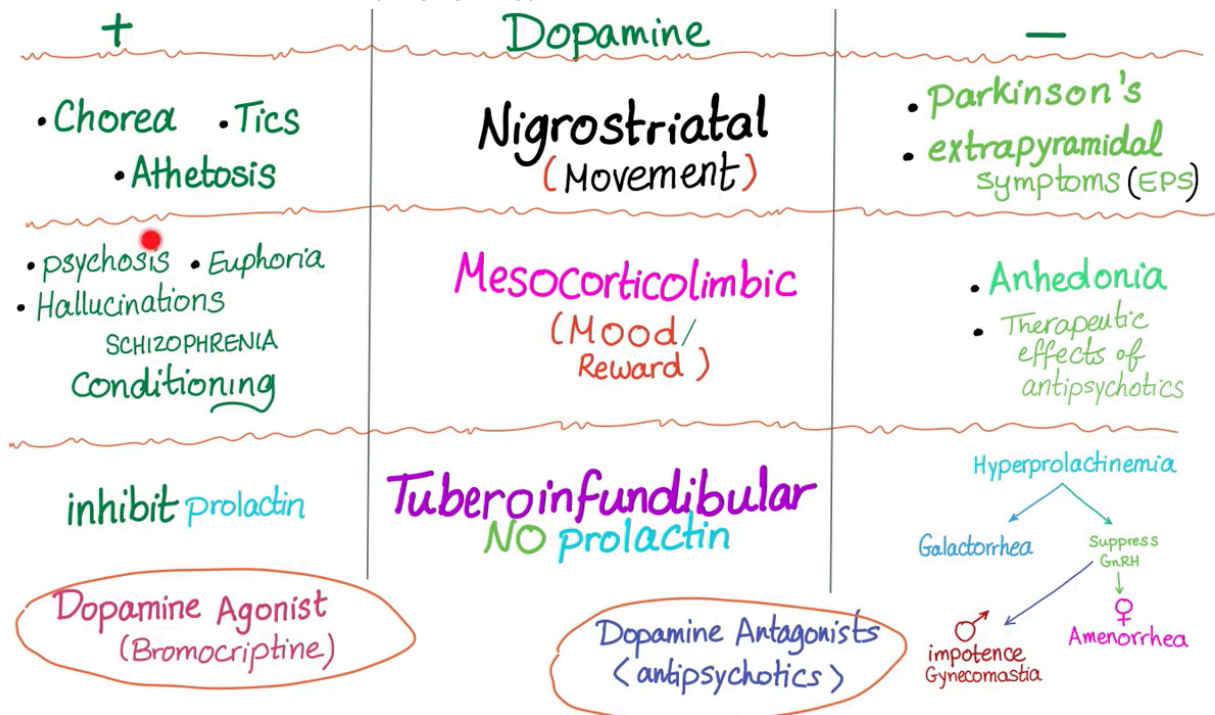
### **Dopamine Pathways**

- Dopamine is a monoamine neuro transmitter
- Catecholamine
- Tyrosine converts to L-dopa which converts to dopamine
- Located in substantia nigra, and ventral tegmental area most often
  - Also found in hypothalamus, olfactory bulb, and retina
- Dopamine pathways
  - Nigrostriatal pathway
  - Mesolimbic pathway
  - Mesocortical pathway
- Acts at G protein coupled receptors
- Dopamine transporter removes dopamine from the synaptic cleft
- Dopamine Functions
  - Movement : Parkinson's disease which has low dopamine
  - Reward
  - Memory
  - Lactation
  - Attention
  - Sleep regulation
  - Nausea
  - Motivation
  - Arousal
  - Many more

### **Dopamine and Neural Pathways**

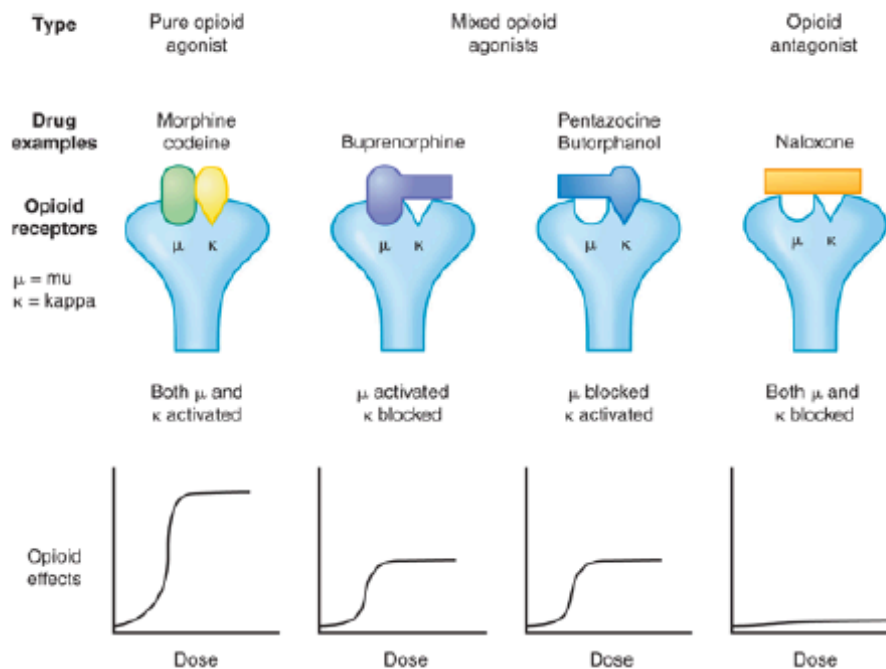
- Nigrostriatal pathway
  - Pars compacta in the substantia Nigra in the midbrain
  - Movement
    - Increase in dopamine:
      - Chorea
      - Athetosis
      - tics
    - Decrease in dopamine:
      - parkinson's,
      - extrapyramidal side effects (antipsychotics)
- Mesocorticolimbic pathway
  - Ventral tegmental impulses flow to the prefrontal cortex, then to the mesolimbic pathway to nucleus accumbens
  - Mood/Reward
  - Increases
    - Seen with cocaine or meth
    - Psychosis
    - Euphoria

- Hallucinations
- Schizophrenia
- Classical operant conditioning
- Decreases
  - Anhedonia
  - Therapeutic effect of Antipsychotics
- Tuberoinfundibular
  - Arcuate N. periventricular nucleus (Hypothalamus) to the pituitary gland secretes prolactin
  - If there is dopamine there is less prolactin
  - Dopamine known as prolactin inhibiting factor
  - Increases
    - Inhibit prolactin
  - Decreases
    - Prolactin inhibited
    - Hyperprolactinemia
    - Galactorrhea (milk from breast)
    - Suppress GnRH
      - Impotence and gynecomastia
      - amenorrhea



## Opioid and Nonopioid

- Natural opioids are 9-14% morphine and 1-2% codeine
- We have developed 12 morphine like drugs
- Best to use narcotic analgesics: Demerol diloride, oxycodone
- Pg 373: 6 receptors in central nervous system opioid effect
- Reduces cough reflex
- Side effects: respiratory depression, constipation, nausea, orthostatic hypotension, sedation, urinary retention



**Figure 25.2**

Types of opioid receptors.

- Migraine Treatment
  - Mild: Tylenol
  - Moderate: serotonin agonist imetrex or regland and a pain med
  - Severe: IM imetrex

## **Pharmacology of Depression**

- Depression affects over 19 million Americans each year.
- Mood Disorders
- Two primary types
  - Depression
    - Major depressive disorder
      - Symptoms that last at least 2 years
    - Dysthymic disorder
      - Adolescence or teens may go through a phase that is not necessarily full depression but need to be watched for

### **Major Depressive Disorder**

- Symptoms of Major Depressive Disorder
  - Suicidal ideation
    - The majority of patients who attempt suicide have major depression
    - Need to assess for a plan
  - Sadness
  - Despondent mood
  - Lack of energy
  - Sleep disturbances
    - Early morning awakening
  - Abnormal eating patterns
  - Feelings of despair, guilt, and hopelessness

### **Postpartum Onset Depression**

- Up to 80% of women experience brief depression during first 2 weeks after baby's birth
- Hormonal shifts and environmental changes contribute

### **Depression**

- Biologic causes
  - Levels and function of neurotransmitters in limbic system
  - Abnormally low levels of norepinephrine, serotonin, dopamine
  - Endocrine system may play a role
- Diagnosis of Depression
  - Rule out medical conditions
    - Certain drugs
    - Medical and neurological conditions
  - Assess alcohol and drug use
  - Assess suicidal thoughts
  - Assess family history
  - Treatment may require both medication and psychotherapy

- Do not want to treat with antidepressants if possibly bipolar, will send patient into a mania. So if there is a lot of substance abuse history or suicide in a family think more bipolar not depression.

### Antidepressants

- Enhance, elevate, or stabilize mood
- Treat all symptoms of major depressive disorder and depressive phases of bipolar disorder
- Restore normal neurotransmitter balances to brain
  - Norepinephrine, serotonin, dopamine
- Nonadherence a problem once patient starts feeling “better”
- Five primary classes
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin–norepinephrine reuptake inhibitors (SNRIs)
  - Atypical antidepressants
  - Monoamine oxidase inhibitors (MAOIs)

### Tricyclic Antidepressants

- Tricyclic antidepressants have been the mainstay for the treatment of depression but have many adverse effects.
- Prototype Drug: Imipramine (Tofranil)
  - Mechanism of action
    - Blocks reuptake of norepinephrine and serotonin into presynaptic nerve terminals
    - Increased action of both neurotransmitters
    - Blocks Ach receptors
  - Indications
    - Off-label uses
      - Adjuvant treatment of cancer or neuropathic pain
      - Overactive bladder
      - ADHD
      - Bulimia
      - Social anxiety disorder
      - Panic disorder
  - Precautions
    - Suicidal tendencies
    - Urinary retention
    - Prostatic hyperplasia
    - Cardiac/hepatic disease
    - Increased intraocular pressure
    - Hyperthyroidism
    - Parkinson’s disease
  - Drug interactions
    - Increased sedation

- Alcohol, barbiturates, benzodiazepines, direct-acting sympathomimetics, other CNS depressants
- Decreased effect
  - Oral contraceptives, clonidine, carbamazepine, indirect-acting sympathomimetics
- Dysrhythmias – thyroid hormone
- Drugs that prolong QT interval – cardiac toxicity
- Phenothiazines and TCAs
- MAOIs
- SSRIs
- Common adverse effects
  - Orthostatic hypotension
  - Dizziness
  - Confusion
  - Drowsiness
  - Diarrhea
  - Dry mouth
  - Increased appetite
  - Jaundice
  - Urinary retention
- Serious adverse effects
  - Seizures
  - Hepatitis
  - Acute renal failure
  - Paralytic ileus
  - Leukopenia

### Selective Serotonin Reuptake Inhibitors

- Selective serotonin reuptake inhibitors are the drugs of choice for treating depression due to their low incidence of serious adverse effects.
- Prototype Drug: Fluoxetine (Prozac, Sarafem)
  - Therapeutic classification
    - Antidepressant, antianxiety agent
  - Pharmacologic classification
    - Selective serotonin reuptake inhibitor (SSRI)
  - Pregnancy category C
  - Mechanism of action
    - Blocks uptake of serotonin at neuronal presynaptic membrane
    - Enhances action of serotonin
    - Stays in the system longer, so if they are irregular with meds, or suddenly stop there is less of an issue
  - Indications
    - Depression
    - Bulimia
    - Pediatric depression
    - Panic attacks

- Contraindications
  - Hypersensitivity
  - Bipolar disorder
- Precautions
  - Cardiac dysfunction
  - Diabetes
  - Seizure disorders
  - Carefully observe pediatric patients
  - Late pregnancy
- Drug interactions
  - Drugs that are metabolized by CYP450
    - TCAs, phenothiazines, atypical antipsychotics, certain antidysrhythmics, benzodiazepines
  - Excessive sedation
    - Other CNS depressants
  - MAOIs
    - Serotonin syndrome or NMS
  - Increased risk of bleeding
    - Warfarin, aspirin, NSAIDs
  - Increased risk of toxicity
    - Phenytoin, digoxin, carbamazepine
  - Increased EPS
    - Certain antipsychotics
  - Increases half-life of diazepam
  - Increases plasma levels of lithium
- Common adverse effects
  - Nausea
  - Vomiting
  - Diarrhea
  - Anorexia
  - Cramping
  - Flatulence
  - Fluctuations in weight
  - Sexual dysfunction
  - Seizures
- Other effects
  - Constipation
  - Poor concentration
  - Hot flashes
  - Palpitations
  - Nervousness
  - Serotonin syndrome
  - Pediatric patients – personality disorders or hyperkinesia
- Similar Drugs
  - Citalopram (Celexa)
  - Escitalopram (Lexapro)

- Fluvoxamine (Luvox)
- Paroxetine (Paxil, Pexeva)
- Sertraline (Zoloft)
- Monoamine Oxidase Inhibitors
  - Monoamine oxidase inhibitors are effective antidepressants but are seldom used due to potentially serious adverse effects.
- Prototype Drug: Phenelzine (Nardil)
  - Therapeutic classification
    - Antidepressant
  - Pharmacologic classification
    - Monoamine oxidase inhibitor
  - Pregnancy category C
  - Mechanism of Action
    - Binds irreversibly to MAO
    - Intensifies actions of endogenous epinephrine, norepinephrine, serotonin, dopamine
    - Increased concentrations result in elevated mood
  - Indications
    - Major depression
    - Off-label uses for OCD, panic disorder, social anxiety disorder, migraine prophylaxis
  - Drug interactions
    - Interacts with many other drugs
    - CNS depressants
    - Buspirone
    - Opioid analgesics
    - Insulin/oral antidiabetic medications
    - SSRIs, lithium, dextromethorphan
  - Common adverse effects
    - Dizziness
    - Orthostatic hypotension
    - Drowsiness
    - Sexual dysfunction
    - Anorexia
  - Serious adverse effects
    - Hypertensive crisis (foods with tyramine)
    - Dysrhythmias
    - Syndrome of inappropriate antidiuretic hormone-like symptoms

## Pharmacology of Anxiety Disorder

- The Problem
  - Over 40 million americans are affected by anxiety disorders
  - Can have comorbid depression, eating disorders, or substance use
- Diverse symptoms
  - Apprehension



- Worry, fear
- Palpitations
- Shortness of breath
- Heartburn
- Dry mouth
- Excess sweating
- Can be a panic attack which can lead to ER visit (palpitations)
- Accurate Diagnosis Necessary
  - Treatment differs among various types of anxiety disorders
  - Sometimes pharmacotherapy not best option
    - Can respond well to CHS such as meditation, relaxation techniques, music therapy, etc.
- Medications Associated with Anxiety (Cause anxiety)
  - Antibiotics
  - Antidepressants
  - Antihypertensives
  - Antiseizure drugs
  - Bronchodilators
  - Hallucinogens
  - Hormones
  - NSAIDs
  - Stimulants
  - Sympathomimetics
- Medical Conditions Associated with Anxiety
  - Cardiovascular
    - Angina, CVA, dysrhythmias, HF, MI, PE
  - Endocrine
    - Cushing's disease, hyperthyroidism, hypoglycemia
  - Neurologic
    - Dementia, epilepsy, Parkinson's, pain
  - Respiratory
    - Asthma, COPD, pneumonia
  - Cancer
- Five Categories
  1. Generalized anxiety disorder (GAD)
  2. Panic disorder
  3. Social anxiety disorder
  4. Obsessive-compulsive disorder (OCD)
  5. Post-traumatic stress disorder (PTSD)

#### Nonprescription Drugs

- Antihistamines
  - Diphenhydramine (Nytol, Sominex)
  - Doxylamine
  - Side effects
    - Drowsiness

- Anticholinergic
    - Dry mouth, blurred vision, urinary hesitancy, constipation
  - Tolerance in 1 to 2 weeks
- CNS depressants
  - Anxiolytic
    - Benzodiazepine and nonbenzodiazepine
      - Can promote dependence
  - Sedatives
    - Tranquilizer, relaxation, calmness, day administration
  - Hypnotic
    - Produces sleep
  - Sedative–hypnotic
    - Calming at low doses
    - Sleeping at high doses, anesthesia

#### Pharmacotherapy of Anxiety and Insomnia

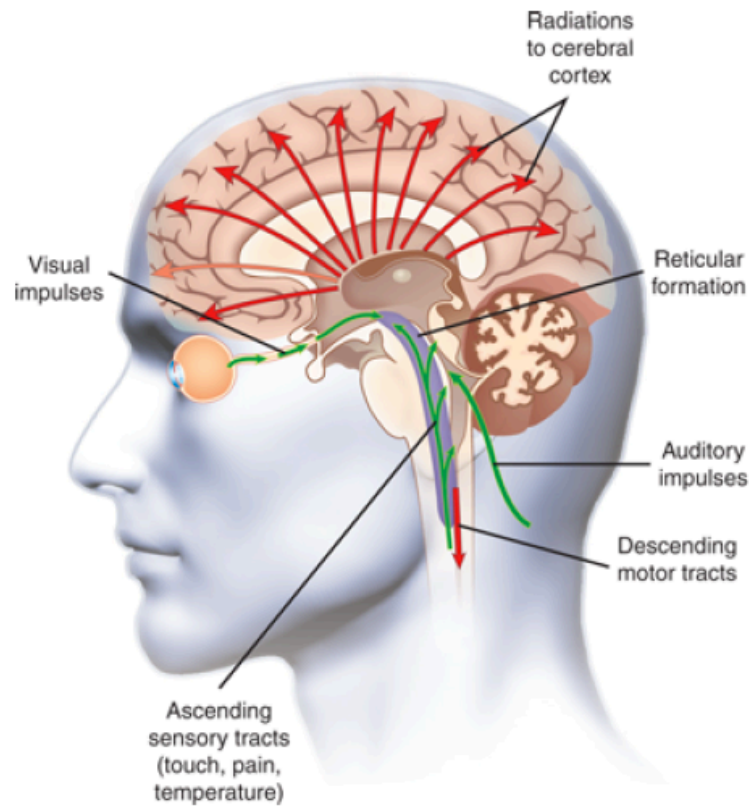
- Benzodiazepines are drugs of choice for generalized anxiety disorder and the short-term therapy of insomnia.
- Benzodiazepines
  - General characteristics
    - Schedule IV
    - Metabolized in liver, excreted in kidneys
    - Tolerance develops
    - Potential for dependence
    - OD with alcohol may be fatal
  - General uses
    - GAD, preoperative anxiety, ventilator anxiety
  - Off-label uses
    - Seizures, alcohol withdrawal, status epilepticus
  - Valium used for benzodiazepine withdrawal
- Lorazepam (Ativan)
  - Therapeutic classification
    - Antianxiety agent, sedative–hypnotic, antiseizure agent
  - Pharmacologic classification
    - Benzodiazepine, GABA receptor agonist
  - Pregnancy category D
  - Mechanism of action
    - Potentiates GABA
    - Capable of causing different levels CNS depression
      - Relaxation
      - Sleep
      - Coma
  - Indications
    - Routine management of GAD
    - Reduce anxiety prior to surgery/medical procedure

- Reduce anxiety in mechanically ventilated patients
  - Off-label use for insomnia, seizures, ethanol withdrawal, status epilepticus
- Contraindications
  - Pregnancy
  - Lactating women
  - Narrow-angle glaucoma
  - Psychosis
  - COPD
- Precautions
  - Hepatic and renal dysfunction
  - Children
- Drug interactions
  - Additive CNS depression
    - Alcohol, opiates, other sedative–hypnotics
  - Oral contraceptives
    - Increase or decrease effectiveness
- Common adverse effects
  - Dizziness
  - Ataxia
  - Drowsiness
  - Blurred vision
  - Vertigo
  - Sedation
  - Confusion
- Less common
  - Hepatotoxicity, alopecia, anaphylaxis,
  - Cardiac changes after rapid IV
  - Paradoxical CNS stimulation
  - Psych patients, elderly, ADHD
- Antidepressants
  - Frequently used to treat anxiety
  - Alter norepinephrine and serotonin
    - Serotonin reuptake inhibitors (SSRIs)
    - Tricyclic antidepressants (TCAs)
    - Monoamine oxidase inhibitors (MAOIs)
      - Avoid cheese and chocolate

The reticular activation system

responsible for sleeping and wakefulness and performs an alerting function for the cerebral cortex. Acts as a filter allowing us to ignore weak repetitive and unimportant sensory stimuli.

It is important in pharmacology because many drugs work by decreasing neuronal activity in this system and cause drowsiness or sleep.



#### Functions of Neurotransmitters: Serotonin


Serotonin is a neurotransmitter, and some also consider it a hormone. The body uses it to send messages between nerve cells. It appears to play a role in mood, emotions, appetite, and digestion. As the precursor for melatonin, it helps regulate sleep-wake cycles and the body clock.

#### The Limbic area of Brain

The limbic system, also known as the paleomammalian cortex, is a set of brain structures located on both sides of the thalamus, immediately beneath the medial temporal lobe of the cerebrum primarily in the forebrain. It supports a variety of functions including emotion, behavior, long-term memory, and olfaction.


## Side effects of Antipsychotics

### Side effects of atypical antipsychotic drugs




#### Weight Gain

Mean weight gain in patients receiving standard doses of antipsychotics over a 10-week period:  
4.45 kg with clozapine,  
4.15 kg with olanzapine,  
2.92 kg with sertindole,  
2.10 kg with risperidone,  
and 0.04 kg with ziprasidone.




#### Cataracts

Some drugs may be associated with an increased risk of ocular lens opacities. Also, patients with schizophrenia often have risk factors for lens opacities, such as Diabetes, hypertension and poor nutrition.



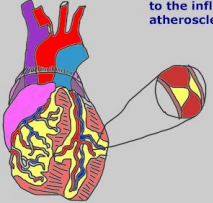
#### Sexual side effects

Antipsychotic-induced sexual dysfunction is related to the effects of the drugs on alpha-1 and alpha-2 adrenergic, H1 histamine and dopaminergic receptors, in particular to the blockade of D2 receptors in pituitary lactotroph cells, which leads to an excess of prolactin secretion




#### Diabetes Mellitus

The prevalence of type-2 DM in people with schizophrenia is more than twice higher than in the general population. Most of these studies indicate that drugs associated with greater weight gain.



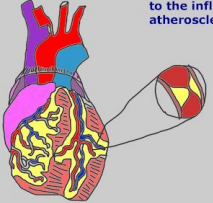
#### Hyperlipidemia

A high concentration of lipid in the blood, an increased risk for cardiovascular disease due to the influence on atherosclerosis



#### Extrapyramidal symptoms

Move-ments disorders, kinesi-a (inability to initiate move-ment) and akathisia (inability to remain motionless)



#### Myocarditis

Inflammation of heart muscle. It can cause a mild disease without any symptoms that resolves itself, or it may cause chest pain, heart failure, or sudden

#### Prolongation QTC Interval

An increase in the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QTC interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death