ANTIPSYCHOTICS
- Block dopamine receptors
- May be divided into three groups:
  - Typicals
  - Atypicals
  - Aripiprazole

TYPICAL ANTIPSYCHOTICS
- Two major subtypes:
  - High potency/low dose—have high affinity for the postsynaptic dopamine receptor (e.g., haloperidol)
  - Low potency/high dose—have low affinity for the postsynaptic dopamine receptor (e.g., chlorpromazine)
- Preferentially block D2 receptors

ATYPICAL ANTIPSYCHOTICS
- Preferentially block D4 receptors, but also 5HT2
- More effective than typicals in reducing negative symptoms of psychosis
- Examples:
  - Respridone (Risperdal)
  - Olanzapine (Zyprexa)
  - Clozapine (Clozaril)
  - Quetiapine (Seroquel)

ARIPIPRAZOLE
- Is a combined dopamine agonist and antagonist
- The unique properties of the drug make it very effective in treatment of positive and negative symptoms
- Patients respond if they fall into the “right bucket”

INDICATIONS
- Positive symptoms of psychosis
  - Hallucinations
  - Delusions
  - Thought disorder
  - Movement disorder
- Negative symptoms of psychosis
  - Avolition
  - Asociality
  - Flat affect
INDICATIONS
- Nonpsychotic behavioral control:
  - Dementia
  - Delirium
  - Mental retardation
  - Tourette’s syndrome
  - Transient psychotic symptoms in patients with some personality disorders

MECHANISM OF ACTION
- All block the post-synaptic receptor for dopamine, but different dopamine receptors
- The atypicals also block 5HT2 receptors
- Aripiprazole blocks dopamine receptors in some parts of the brain and stimulates dopamine receptors in other parts of the brain

THERAPEUTIC MONITORING—MOVEMENT DISORDERS
- The most common is akathisia
- Extrapyramidal side effects
  - Pseudoparkinsonism
  - Involves the dynamic equilibrium between dopamine and acetylcholine in the corpus striatum

PATHWAYS FOR DOPAMINE
- Nigrostriatal
  - Mesocortical-mesolimbic
  - Tubero-infundibular
  - Chemoreceptor trigger zone

NIGROSTRIATAL PATHWAY
- Begins in the substantia nigra and terminates in the corpus striatum
- Involves the extrapyramidal motor system
- High concentrations of D2 receptors, so more likely to be impacted by traditional antipsychotics

MESOCORTICAL-MESOLIMBIC PATHWAYS
- Preferential site of activity of antipsychotic medications
- May cause cognitive impairments, particularly in children
**TUBEROINFUNDIBULAR PATHWAY**
- Begins in the hypothalamus and terminates in the anterior lobe of the pituitary gland
- Dopamine inhibits the release of prolactin
- Dopamine antagonists allow for the release of prolactin
  - Breast enlargement
  - Milk letdown

**CHEMORECEPTOR TRIGGER ZONE**
- Located in the brainstem
- Site of activity of dopamine antagonists that inhibit nausea and vomiting
- Must be cautious in the use of these agents as may affect other dopamine pathways

**TARDIVE DYSKINESIA**
- Associated with long term use of antipsychotics, increasing age, female gender and presence of a mood disorder
- More common in the typical agents, particularly high potency/low dose
- Constant, involuntary, stereotyped, choreoathetoid movements usually starting in the head and neck
- Tends to be permanent

**TARDIVE DYSKINESIA**
- Dopamine antagonists block post synaptic receptors
- New receptors develop
- New receptors are supersensitive to dopamine causing the movement disorder
- Increasing the dose of medication temporarily halts the movements
- Decreasing the dose of medication worsens the movements
- No effective treatments

**NEUROLEPTIC MALIGNANT SYNDROME**
- Idiosyncratic and potentially life threatening
- Develops over hours to days
- Characterized by autonomic instability and motor abnormalities
- Tachycardia, cardiac arrhythmias, hypertension, hypotension, diaphoresis and fever progressing to hyperthermia
- Rigidity/dystonia, akinesia, mutism and dysphagia

**NEUROLEPTIC MALIGNANT SYNDROME**
- Agitation, incontinence, delirium, seizures and coma
- Increased creatine kinase, increased WBC and abnormal liver function tests
- Risk factors:
  - High dose antipsychotics
  - Rapid dose escalation
  - IM antipsychotics
  - Dehydration
  - Prior history of NMS
NEUROLEPTIC MALIGNANT SYNDROME

- Treatment
  - Discontinue antipsychotic
  - Dantrolene (a muscle relaxant)
  - Bromocriptine (a dopamine agonist)
  - Cardiac monitoring and intubation if necessary

SIDE EFFECTS OF ANTIPSYCHOTICS

- Anticholinergic—Occur most often in low potency antipsychotics:
  - Blurred vision
  - Dry mouth
  - Constipation
  - Urinary retention
- Hypotension—Orthostatic due to peripheral blockade of alpha receptors

SIDE EFFECTS OF ANTIPSYCHOTICS

- Agranulocytosis—Potentially irreversible, associated with use of clozapine
- Cardiac—Low potency antipsychotics and risperidone cause QT prolongation
- Specific side effects:
  - Increased photosensitivity causing skin and ocular pigmentation
  - Thioridazine causes pigmentary retinopathy at high doses

THERAPEUTIC MONITORING

- Abnormal involuntary movement scale—AIMS
- Seizure threshold
- Blood levels of little use
- Duration of treatment depends on underlying disorder

ANTIDEPRESSANTS

- Common characteristics:
  - Increase the availability of the catecholamine neurotransmitters at the synapse
  - All used to treat major depressive illness
  - Take 2-4 weeks to exert effect

TERMINATION OF NEUROTRANSMITTER EFFECTS

- Passive diffusion
- Enzymatic degradation by MAO or COMT
- Energy dependent reuptake process
DELAY IN RESPONSE
- Maximum increase in neurotransmitter usually within 24 hours
- Chronic bombardment of the post-synaptic receptors occurs over 2-4 weeks causing down regulation of the receptors

CLASSES OF ANTIDEPRESSANTS
- Tricyclic antidepressants (imipramine, amitriptyline, desimpramine, nortriptyline)
- Selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, citalopram)
- Monoamine oxidase inhibitors (tranylcypromine)
- Others (bupropion, venlafaxine, trazodone)

INDICATIONS
- Moods disorders—Depressive disorders, depressed phase of bipolar illness, and mood disorders due to a general medical condition
- Anxiety disorders—Panic Disorder, Obsessive Compulsive Disorder, Separation Anxiety Disorder
- Other disorders—Bulimia (SSRI), neuropathic pain (TCA), enuresis (imipramine), ADHD (bupropion), smoking cessation (bupropion)

MECHANISMS OF ACTION
- Tricylic antidepressants—block reuptake of norepinephrine and serotonin
- Selective serotonin reuptake inhibitors—block reuptake of serotonin
- Monoamine oxidase inhibitors—decreased enzyme activity
- Others:
  - Bupropion—blocks reuptake of dopamine and norepinephrine

CHOICE OF MEDICATION
- All of equal efficacy
- Symptom profile
- Diagnosis
- Prior patient or family response
- Side effects
- Co-morbid conditions (e.g., obesity, chronic pain, GERD)

CHOICE OF MEDICATION
- SSRIs, bupropion and venlafaxine are the best tolerated due to side effects profiles
- Nortriptyline if therapeutic blood monitoring is desired
- High-dose SSRI and clomipramine (a TCA) for Obsessive-Compulsive Disorder
THERAPEUTIC MONITORING
- Therapeutic trial—six weeks at adequate dosages
- Inadequate dosages and trial length most common reasons for failure
- Six months of treatment for first episode of major depression
- Longer period for chronic depression
- Augment with lithium, T3, a psychostimulant or adding a second antidepressant if no response

SIDES EFFECTS OF SSRI
- Most common:
  - Nausea
  - Headache
  - Akathisia
  - Insomnia/sedation
  - Delayed ejaculation/anorgasmia
  - Serotonin syndrome

SEROTONIN SYNDROME
- Occurs most often when SSRI and MAOI used concomitantly
- Autonomic symptoms:
  - Tachycardia
  - Hypertension
  - Diaphoresis
  - Fever progressing to hyperthermia

SEROTONIN SYNDROME
- Motor symptoms:
  - Shivering
  - Myoclonus
  - Tremor
  - Hyperreflexia
  - Oculomotor abnormalities

SEROTONIN SYNDROME
- Behavioral symptoms:
  - Restlessness
  - Agitation
  - Delirium
  - Coma
- Treatment:
  - Discontinue offending agents
  - Supportive

SIDES EFFECTS OF TCAs
- Orthostatic hypotension due to peripheral alpha blockade
- Anticholinergic toxicity
- Cardiac toxicity—quinidine like side effects:
  - Sinus and supraventricular tachycardias
  - Ventricular tachycardias and fibrillation
  - Prolongation of the PR, QRS, QT interval
  - Bundle branch block, first-, second- and third-degree heart block
  - Sudden death
SIDE EFFECTS OF MAOIs
- Inhibit MAO activity in the brain and gut
- Ingestion of sympathomimetic agents such as tyramine causes hyperadrenergic crisis
- Must be on a tyramine restricted diet and avoid over-the-counter cold and pain remedies
- Treatment of hyperadrenergic crisis involves IV phentolamine (an alpha blocker) or continuous nitroprusside infusion

SIDE EFFECTS OF OTHER AGENTS
- Trazodone—Often given for insomnia; may cause priapism
- Bupropion—Higher than average risk of seizures and precipitation of mania or psychosis

PHOTOTHERAPY
- Used in the treatment of seasonal affective disorder or delayed sleep phase syndrome
- Administer light intensity of 2,500 to 10,000 lux
- May induce mania in a susceptible individual

ELECTROCONVULSIVE THERAPY
- Indications:
  - Refractory mania
  - Psychosis with prominent mood components
  - Catatonia
  - Depression where rapid improvement is medically indicated
  - Pregnancy
- Mechanism of action:
  - Induction of an electrical seizure lasting 25-60 seconds
  - Electrical current through the brain
  - Five treatments over a two-three week period
**ELECTROCONVULSIVE THERAPY**
- Pre-work up
- Remove foreign objects from mouth
- Anticholinergics to reduce oral secretions
- Paralytics to reduce risk of injury from tonic-clonic muscle activity
- Short-acting anesthetics
- 100% oxygen

**ELECTROCONVULSIVE THERAPY**
- Bilateral more effective than unilateral
- Side effects:
  - Headache
  - Brief delirium
  - Memory loss
- Relative contraindications:
  - Space occupying mass in the brain
  - Recent myocardial infarction

**MOOD STABLIZERS**
- Indications:
  - Acute treatment of mania
  - Prophylaxis against depression and mania
  - Seizure related mood disorders
  - Impulsive behavior not associated with bipolar disorder
  - Adjunctive to antidepressants (lithium)

**MOOD STABLIZERS**
- Most commonly used:
  - Lithium
  - Valproate
  - Carbamazepine
- Other agents:
  - Calcium channel blockers
  - Benzodiazepines
  - Atypical antipsychotics

**LITHIUM**
- Mechanism of action:
  - Alters the two intracellular second messenger systems
  - As an ion, directly alters ion channel function
  - Alters GABA metabolism

**LITHIUM**
- First line of treatment (?) for regular cycling bipolar disorder in patients with normal renal functioning
- Augments effects of antidepressants
- Is cleared renally, unchanged, and may reach toxic levels in altered renal function
- Less effective in rapid cycling bipolar illness
- Effective for depression and mania
**LITHIUM**

- **Therapeutic monitoring:**
  - Prior to starting lithium:
    - Renal function (BUN/creatinine and UA)
    - Thyroid status (TSH)
    - Cardiac functioning (EKG)
  - During treatment:
    - Lithium levels (0.8-1.2 mEq/liter in acute mania)
    - TSH and renal functioning

- **Side effects:**
  - Minor, but troublesome:
    - Tremor
    - Polyuria
    - Polydipsia
    - Gastrointestinal distress
    - Minor memory problems
    - Acne exacerbation
    - Weight gain
  - Toxic levels:
    - Ataxia
    - Coarse tremor
    - Confusion
    - Coma
    - Sinus arrest
    - Death

**ANTICONVULSANTS**

Rationale for use is the notion of “kindling.” This suggests that limbic structures in the temporal lobe are responsible for manic episodes. If overly active electrically, as occurs in seizures, mania develops. Prevention and treatment of condition involves resolution of kindling.

**VALPROATE**

- **Mechanism of action:**
  - Augments GABA
  - Increases GABA synthesis
  - Decreases GABA breakdown
  - Enhances postsynaptic efficacy of GABA

- **Indications:**
  - Often now considered first line of treatment in bipolar illness
  - Indicated in acute mania and prophylaxis against mania
  - More effective than lithium in rapid cycling
  - Mixed bipolar disorder
  - Impulse dyscontrol
  - Not effective in the depressive phase of bipolar illness
**VALPROATE**

- **Side effects:**
  - Therapeutic levels:
    - Sedation
    - Mild tremor
    - Mild ataxia
    - Gastrointestinal distress
  - Toxic levels:
    - Confusion
    - Coma
    - Cardiac arrest and death

**VALPROATE**

- **Side effects:**
  - Thrombocytopenia and impaired platelet functioning
  - Idiosyncratic side effects:
    - Fatal hepatotoxicity
    - Fulminate pancreatitis
    - Agranulocytosis

**VALPROATE**

- **Therapeutic monitoring:**
  - Liver function tests and CBC at baseline and throughout treatment
  - Serum valproic acid levels until stable blood level and dosing regimen obtained

**CARBAMAZEPINE**

- **Mechanism of action:**
  - Unclear in bipolar illness—kindling
  - Blocks sodium channels
  - Decreased neurotransmitter release at presynaptic terminals
  - Indirectly alters central GABA receptors

**CARBAZEPINE**

- **Indications:**
  - Second line treatment of mania
  - Acute mania
  - Prophylaxis
  - More effective than lithium in rapid cycling
  - Mixed bipolar disorder
  - Impulse dyscontrol

**CARBAZEPINE**

- **Side effects:**
  - Therapeutic levels:
    - CNS effects similar to lithium and valproate
    - Nausea
    - Rash
    - Mide leukopenia
  - Toxic levels:
    - Autonomic instability
    - Atrioventricular block
    - Respiratory depression
    - Coma
CARBAZEPINE

Idiosyncratic side effects:
- Agranulocytosis
- Pancytopenia
- Aplastic anemia

Therapeutic monitoring:
- At baseline, CBC and liver function tests
- Monitor drug levels and CBC regularly

LAMOTRIGINE (Lamictal)

Mechanism of action in mania unknown
- Inhibits voltage-sensitive sodium channels
- Has antidepressant and mood stabilizing properties
- Used in treatment failure or side-effects from first line drugs

LAMOTRIGINE

Side effects:
- Common:
  - Ataxia
  - Blurred vision
  - Diplopia
  - Dizziness
  - Nausea and vomiting
  - Severe, life-threatening allergic rash—simple rash to Stevens–Johnson syndrome

GABAPENTIN (Neurontin)

Mechanism of action in mania and seizures unclear
- Lacks sufficient efficacy as monotherapy, so used as an adjunct
- Is excreted unchanged by the kidneys
- Minimal side effects

TOPIRAMATE (Topamax)

Mechanism of action unknown. Evidence suggests:
- Blocks voltage-dependent sodium channels
- Augments GABA receptor
- Antagonizes glutamate receptor
- Causes weight loss, so may be an effective alternative to mood stabilizers that cause weight gain