ANTIPSYCHOTICS

1. Have in common that they block dopamine receptors.
2. May be roughly divided into two groups.
   a. Typical Antipsychotics: also called “neuroleptics” because of their tendency to cause movement disorders. Two major subtypes:
      i. High potency/low dose: low anticholinergic properties so many extrapyramidal side effects secondary to dopamine blockade in the nigrostriatal pathway. Examples include haloperidol (Haldol), thiothixene (Navane) and fluphenazine (Prolixin). Haldol and Prolixin are available in an injectable, depot preparation.
      ii. Low potency/high dose: high anticholinergic properties so few extrapyramidal side effects secondary to dopamine blockade in the nigrostriatal pathway. Very sedating. Examples include chlorpromazine (Thorazine) and thioridazine (Mellaril).
   b. Atypical Antipsychotics: fewer extrapyramidal side effects due to lack of blockade of the D_2 receptors. More effective than the typical antipsychotics in treating the refractory and negative symptoms of psychotic illness.

Indications:

1. Generally effective in treating the positive psychotic symptoms (e.g., hallucinations, bizarre behavior, delusions) associated with psychotic and mood disorders. Atypicals more effective for negative symptoms.
2. Also used for nonpsychotic behavioral control in dementia, delirium, mental retardation, Tourette’s syndrome, and transient psychotic symptoms in some personality disorders.

Mechanism of Action:

1. Dopamine hypothesis (Dopamine Antagonists): purports that dopamine hyperactivity leads to psychosis. Evidence is as follows: antipsychotic potency in traditional antipsychotics correlates highly with their potency of dopamine receptor blockade, individuals with schizophrenia have an increased number of brain dopamine receptors, and dopamine agonists drugs (e.g., amphetamines) can induce or exacerbate existing psychosis.
2. Contrary to the dopamine hypothesis is that newer drugs such as clozapine and the atypical agents have prominent serotonin (5HT_2) receptor blockade.
3. Typical Antipsychotics: Have an affinity for the blocking the D_2 receptor in all dopamine pathways. Blockade in the mesolimbic pathway alleviates psychotic symptoms. Blockade of dopamine in the nigrostriatal pathway causes extrapyramidal side effects. Blockade of dopamine in the tuberoinfundibular pathway causes the release of prolactin.
4. Atypical Antipsychotics (Serotonin/Dopamine Antagonists): Include clozapine (Clozaril), quetiapine (Seroquel), olanzapine (Zyprexa) and risperidone (Risperdal). Selectively block D_4 and 5HT_2 receptors, causing less movement disorder side effects.

Therapeutic Monitoring:

1. Patients must be monitored for neurologic sides effects such as akathisia (restlessness), neuroleptic malignant syndrome (NMS), and extrapyramidal symptoms (EPS).
2. Antipsychotics may lower the seizure threshold.
3. Patients taking clozapine much have weekly white blood counts to monitor for agranulocytosis.
4. Bloods levels are generally of little use.
5. Noncompliance is the most common reason for treatment failure.
6. The duration of treatment depends on the disorder, and chronic maintenance may be needed in patients who have schizophrenia.

**Side Effects and Adverse Drug Reactions** (Refer to Fadem, page 147):

1. *Anticholinergic Side Effects:* Occurs most frequently in low-potency antipsychotics and includes dry mouth, constipation, urinary retention, and blurred vision. May cause an anticholinergic delirium.
2. *Reduced Seizure Threshold:* Low-potency typical antipsychotics and clozapine are associated with lowering the seizure threshold. If seizures occur, may lower the dose, change medications or add an antiseizure medication.
3. *Hypotension:* Orthostatic hypotension is common in low-potency agents and risperidone due to alpha-receptor blockade.
5. *Cardiac Side Effects:* Low-potency antipsychotics and risperidone may cause QT prolongation increasing the risk for torsades de pointes.
7. *Other Side Effects:* Skin and ocular pigmentation may occur due to increased photosensitivity. Thioridazine may cause pigmentary retinopathy at high doses. Quetiapine (Seroquel) increases the risk for cataracts.

**ANTIDEPRESSANTS, ECT, AND PHOTOTHERAPY**

1. As a class, antidepressants have in common their ability to treat major depressive illness.
2. Antidepressants act on serotonergic, noradrenergic and dopaminergic systems.
3. Choice of medication depends on diagnosis, history of response in the patient or a relative, and the side effects profile.
4. Effects are not typically seen for 2 to 4 weeks in depression, with neurovegetative symptoms responding before improvement in the mood disturbance.
5. Antidepressants are divided into groups based on structure or prominent functional activities (Refer to Fadem, pages 148-149):
   a. *Selective serotonin reuptake inhibitors (SSRIs)*
   b. *Tricyclic antidepressants (TCAs)*
   c. *Monoamine oxidase inhibitors (MAOIs)*
   d. *Others*

**Indications:**

1. *Mood disorders:* depressive disorders, depressed phase of bipolar illness, and mood disorder due to a general medical condition.
2. *Anxiety disorders:* panic disorder, obsessive-compulsive disorder, school phobia and separation anxiety disorder (SSRIs, TCAs, and MAOIs).
3. *Other disorders:* bulimia, neuropathic pain, enuresis (imipramine), ADHD, cataplexy due to narcolepsy and smoking cessation (buproprion or Zyban).

**Mechanism of Action:**

1. *SSRIs:* bind to presynaptic serotonin reuptake proteins, thereby inhibiting reuptake and increasing the levels of serotonin in the synaptic cleft.
2. *TCAs:* block the reuptake of both serotonin and norepinephrine.
3. *MAOIs:* inhibit the presynaptic enzyme, monoamine oxidase that catalyzes norepinephrine, dopamine, and serotonin, thereby increasing levels of these neurotransmitters.
4. The immediate mechanism of action does not explain the delayed antidepressant effects. It is believed that chronic bombardment of the postsynaptic receptors causes downregulation of the post-synaptic neuron and its receptors leading to clinical efficacy.
Choice of Medication:

1. All antidepressants have equal efficacy, therefore symptom profile, diagnosis, prior patient or family member response and side effects dictate the best medication.
2. SSRIs, bupropion and venlafaxine are the best tolerated and are usually considered first-line agents for major depression. These medications have very low sedation, anticholinergic, and orthostatic hypotensive side effects. They are especially useful in patients with cardiac conduction problems, constipation, glaucoma, or prostatic hypertrophy.
3. Nortriptyline and desipramine have the least sedative, anticholinergic, and orthostatic hypotensive effects of the TCAs.
4. MAOIs (phenelzine and tramcypramine) require a tyramine-restricted diet and are used when patients have failed on other medications, in patients with seizure disorders, or for atypical depression or social phobia.
5. High-dose SSRIs and clomipramine (a TCA) are the treatments of choice for OCD.

Therapeutic Monitoring:

1. A therapeutic trial is considered to be six-weeks at adequate dosages.
2. The most common reasons for failed trials are inadequate dose and trial length.
3. In a first episode of unipolar depression, treatment should continue for at least six months.
4. Recurrent or chronic depression may require longer treatment.
5. Increasing the dose, augmentation with lithium or T3, switching antidepressants, or addition of a second antidepressant or psychostimulant is helpful in refractory depression.
6. Serum levels may be helpful with TCAs.

Side Effects and Adverse Drug Reactions:

1. **SSRIs:** The main side effects are:
   a. Nausea, headache, neuromuscular restlessness (resembling akathisia), insomnia, sedation, or delayed ejaculation/anorgasmia.
   b. When combined with MAOIs, may result in a fatal serotonin syndrome.
2. **TCAs:** The main side effects are:
   a. Orthostatic hypotension due to alpha blockade.
   b. Anticholinergic toxicity: dry mouth, constipation, blurred near vision, urinary hesitancy, or anticholinergic delirium.
   c. Cardiac toxicity: TCAs have quinidine-like side effects on the heart leading to sinus tachycardia, supraventricular tachyarrhythmias, ventricular tachycardia, ventricular fibrillation, prolongation of the PR, QRS, QT intervals, bundle branch block, first-, second-, and third-degree heart block, or ST and T-wave changes.
   d. Sexual dysfunction: impotence in men and decreased sexual arousal in women.
3. **MAOIs:** The main side effects are:
   a. Hyperadrenergic crisis: Occurs with the ingestion of sympathomimetic amines (such as tyramine) that fail to be detoxified due to inhibition of gastrointestinal MAO. Treatment involves IV phentolamine (an alpha blocker) or continuous IV nitroprusside infusion.
   b. Must be on a tyramine restricted diet: no cured meats or fish, beer, red wine, all cheese except cottage and cream cheeses, and overripe fruits. Must also avoid over-the-counter cold and pain remedies.
   c. MAOIs cause dose-related orthostatic hypotension; tranylcypromine can cause insomnia and agitation; phenelzine can cause daytime somnolence.
4. **Other Antidepressants:**
   a. Nefazodone (Serzone) and trazodone (Desyrel) are serotonin-modulating antidepressants. Nefazodone may cause irreversible liver failure. Trazodone may cause priapism.
   b. Buproprion (Wellbutrin, Zyban) inhibits the uptake of dopamine and norepinephrine, and may be useful in ADHD or smoking cessation. They have a low incidence of sexual side effects.
effects. Bupropion has a higher than average risk of seizures. Blocking dopamine reuptake may precipitate a manic episode or psychosis.

**Phototherapy:** Consists of administering light intensity of 2,500 to 10,000 lux for seasonal affective disorder or delayed sleep phase syndrome. It may induce mania in a susceptible individual.

**Electroconvulsive Therapy:**

1. ECT is used primarily for refractory mania, psychoses with prominent mood components, catatonia or depression where rapid improvement is medically indicated or the use of medication may be contraindicated (e.g., pregnancy).
2. ECT involves the induction of a generalized seizure lasting 25-60 second via electrical current across the brain. Five-to-ten treatments over a two-three week period are given.
3. Anticholinergics are given to decrease oral secretions, paralytics are given to reduce risk of injury from tonic-clonic muscle activity, and short-acting anesthetics (e.g., methohexital) are administered.
4. Bilateral ECT is more effective than unilateral ECT, but produces more memory problems.
5. The most common side effects are a brief delirium and memory loss. The mortality rate is the same as that associated with the use of general anesthesia.
6. There are no absolute contraindications to ECT. Relative contraindications include a space occupying mass in the brain or a recent myocardial infarction.

**MOOD STABILIZERS**

1. Mood stabilizers are used in the treatment of mania, and lithium is effective as prophylaxis against bipolar depression.
2. The mood stabilizers are also used for nonbipolar impulse control (e.g., uncontrollable aggressive outbursts).
3. The most common mood stabilizers are lithium, valproate, and carbamazepine, although almost all antiseizure medications are being used now.
4. Other medications used as mood stabilizers include calcium channel blockers, benzodiazepines and antipsychotics (e.g., olanzapine has been approved as monotherapy in the treatment of bipolar disorder).

**Indications:**

1. Acute treatment of mania and prophylaxis against depression and mania.
2. Seizure related mood instability.
3. Impulsive behavior not associated with bipolar disorder.
4. Adjunct to antidepressants in the treatment of major depression (lithium).
5. Overall mechanism of action is unknown.

**Lithium:**

**Mechanism of action:**

1. Alters the two intracellular second messenger systems.
2. As an ion, can directly alter ion channel function.
3. Alters GABA metabolism.

**Choice of Medication:**

1. Lithium is indicated as a first-line treatment for regular cycling bipolar disorder in patients with normal renal functioning.
2. Lithium is used to augment antidepressants in the treatment of major depression.
3. Lithium is cleared renally, unchanged and may reach toxic levels in altered renal function.
Lithium is less effective in rapid cycling bipolar illness.

**Therapeutic Monitoring:**

1. Prior to starting lithium, assess renal function (BUN/creatinine and urinalysis), thyroid status (TSH) and cardiac functioning (EKG).
2. Lithium levels should be monitored regularly until a stable dosing regimen has been obtained.
3. TSH and renal function should be monitored at regular intervals.

**Side Effects:**

1. Minor but troublesome side effects: tremor, polyuria, gastrointestinal distress, minor memory problems, acne exacerbation, and weight gain.
2. At toxic levels, ataxia, coarse tremor, confusion, coma, sinus arrest, and death can occur.
3. Lithium has a narrow therapeutic window.

**Valproate:**

**Mechanism of Action:** Augments GABA, increases GABA synthesis, decreases GABA breakdown and enhances its postsynaptic efficacy.

**Choice of Medication:** Indicated in acute mania and prophylaxis against mania in bipolar illness. Is more effective than lithium for rapid cycling and mixed bipolar disorders. Is also used in impulse dyscontrol.

**Therapeutic Monitoring:**

1. Liver function tests and a CBC should be checked at baseline and regularly after treatment is started due to possible fatal hepatotoxicity and possible agranulocytosis and thrombocytopenia.
2. Valproate blood levels should be monitored regularly until a stable blood level and dosing regimen have been obtained.

**Side Effects:**

1. At therapeutic levels may cause sedation, mild tremor, mild ataxia, and gastrointestinal distress.
2. Thrombocytopenia and impaired platelet functioning may occur.
3. At toxic levels, confusion, coma, cardiac arrest, and death can occur.
4. Idiosyncratic side effects include fatal hepatotoxicity, fulminate pancreatitis, and agranulocytosis.

**Carbamazepine:**

**Mechanism of Action:** Is unknown in bipolar disorder. Carbamazepine blocks sodium channels and decreases neurotransmitter release at presynaptic terminals. It also indirectly alters central GABA receptors.

**Choice of Medication:** Is generally considered a second-line drug for mania. It may be used for acute mania, prophylaxis, and is more effective than lithium in rapid cycling or mixed bipolar disorder. It may also be used in impulse dyscontrol.

**Side Effects:**

1. At therapeutic levels may produce similar CNS side effects as lithium and valproate.
2. Nausea, rash, and mild leukopenia are common.
3. At toxic levels, autonomic instability, atrioventricular block, respiratory depression and coma may occur.
4. Idiosyncratic side effects include agranulocytosis, pancytopenia, and aplastic anemia.
Therapeutic Monitoring:

1. At baseline, obtain CBC and hepatic function panel to assure adequate liver functioning as the liver metabolizes the drug.
2. Monitor drug levels and CBC regularly.

**Lamotrigine:**

**Mechanism of Action:** Unknown in bipolar disorder. Inhibits voltage-sensitive sodium channels.

**Choice of Medication:** Has antidepressant and mood stabilizing properties. Used in treatment failure or if patients have side effects to first-line drugs.

**Side Effects:**

1. Most common are ataxia, blurred vision, diplopia, dizziness, nausea and vomiting.
2. Severe, life-threatening allergic rashes can occur. May be a simple rash and lead to Stevens-Johnson syndrome.

**Therapeutic Monitoring:** Has complex drug interactions with valproate. No assays for serum levels are available. Watch for rash.

**Gabapentin:**

**Mechanism of Action:** Unknown in bipolar and seizure disorders.

**Choice of Medication:** Lacks sufficient efficacy as monotherapy for bipolar disorder, but may be a useful adjunct.

**Therapeutic Monitoring:** Is excreted unchanged by the kidneys. Minimal side effects.

**ANXIOLYTICS**

1. Have anxiolysis in common.
2. Include the benzodiazepines and buspirone.

**Indications:**

1. Anxiety disorders: panic disorder, generalized anxiety disorder, adjustment disorder, or anxiety associated with depression.
2. Insomnia.
3. Alcohol withdrawal.
4. Agitation of mania, dementia, and psychotic disorders.
5. Buspirone is used primarily for generalized anxiety disorder.

**Mechanism of Action:**

1. **Benzodiazepines:** Are CNS agonists for GABA_A. Augment the functioning of GABA in the limbic system. Because they are direct agonists, their mechanism of action is virtually instantaneous with arrival in the CNS.
2. **Buspirone:** Agonists at the serotonergic 5HT_{1A} receptor. Buspirone has some D_{3} antagonist effects. Does not work rapidly and requires several weeks of sustained dosage.
**Choice of Medication** (Refer to *Fadem*, page 152):

1. The selection of a benzodiazepine depends on potency, rate of onset, route of metabolism, half-life, and clinically proven effectiveness.
2. The high potency drugs, alprazolam and clonazepam are used to treat panic disorder.
3. Fast-onset benzodiazepines, such as diazepam, may produce a “high feeling” increasing chances of addiction. Flurazepam and triazolam are commonly used for insomnia.
4. Alprazolam, chlordiazepoxide, clonazepam, diazepam, triazolam and flurazepam require oxidation for metabolism. Lorazepam, oxazepam and temazepam require conjugation. Those requiring oxidation are more likely to accumulate to toxic levels in patients with impaired liver function.
5. Medications with long half-lives can easily result in toxicity with repeated dosages (e.g., chlordiazepoxide, diazepam and flurazepam).
6. Medications with active metabolites have a longer elimination half-life. Includes alprazolam, chlordiazepoxide, diazepam, flurazepam and triazolam.
7. Buspirone is indicated for generalized anxiety disorder and in patients with a history of benzodiazepine abuse. It is not as efficacious as the benzodiazepines in controlling anxiety.

**Therapeutic Monitoring:** No routine monitoring is required for any of these medications.

**Side Effects and Adverse Drug Reactions:**

1. **Benzodiazepines:** Primary side effects are sleepiness or a general groggy feeling. May produce disinhibition. Can cause fatal carbon dioxide retention in patients with COPD. Used alone, rarely causes a fatally in an overdose.
2. **Buspirone:** Major side effects are dizziness, nervousness and nausea.

**MISCELLANEOUS MEDICATIONS**

**Psychostimulants**

1. Used in the treatment of ADHD, narcolepsy, and some forms of depression.
2. Most commonly used are dextroamphetamine (Dexedrine), methylphenidate (Ritalin) and pemoline (Cylert).
3. Facilitate endogenous neurotransmitter release.
4. May induce tolerance, psychological dependence and abuse.
5. Side effects primarily due to sympathomimetic actions including tachycardia, insomnia, anxiety, hypertension, and diaphoresis. Weight loss may or may not be a desirable side effect.

**Anticholinergics**

1. Used primarily to treat or prevent neuroleptic-induced movement disorders (e.g., dystonia, EPS).
2. Most commonly used are benztropine and trihexyphenidyl. Diphenhydramine, an antihistamine, also possess anticholinergic properties and me be used.
3. Drugs are CNS muscarinic antagonists.
4. Side effects, due to peripheral anticholinergic action, include blurry vision, constipation and urinary retention.
5. CNS side effects are delirium and sedation.

**Beta Blockers**

1. Alter central and peripheral catecholamine function.
2. Used to diminish central arousal.
3. Used to control tachycardia, tremor, sweating and hyperventilation.
4. Most common side effects are bradycardia, hypotension, asthma exacerbation, and masked hypoglycemia in patients with diabetes.
5. May induce depression.

**Disulfiram (Antabuse)**

1. Blocks the oxidation of acetaldehyde, a step in the metabolism of alcohol.
2. Build up of acetaldehyde produces a toxic, and at times, fatal reaction.
3. Used to prevent alcohol ingestion.
4. Side effects are hepatitis, optic neuritis, and impotence.

**Clonidine**

1. Is a central alpha-2 receptor agonist.
2. The alpha-2 receptor is presynaptic and inhibits the release of norepinephrine.
3. Used for opiate withdrawal, Tourette’s syndrome, ADHD and hyperarousal syndromes such as PTSD.
4. Side effects are sedation, dizziness and hypotension.

**Cognitive Enhancers**

1. Include donepezil (Aricept) and tacrine (Cognex).
2. Are reversible inhibitors of acetylcholinesterase, decreasing the metabolism of acetylcholine.
3. Used in Alzheimer’s dementia due to loss of cholinergic neurons in the basal forebrain that project to the cerebral cortex and hippocampus.
4. Effects in dementia are short lived.
5. Common side effects are GI upset, bradycardia, and urinary retention. Tacrine may elevate serum transaminases.

**MAJOR ADVERSE DRUG REACTIONS**

**Dystonia**

1. Characterized by severe muscle spasms.
2. Usually involves muscles of the head and neck, but may include extremities and larynx. Common forms include occulogyric crisis and torticollis.
3. Risk factors include high-potency antipsychotics and young men.
5. Treated with anticholinergic agents.

**Akathisia**

1. A side effect of antipsychotic medication and SSRIs.
2. A subjective sense of inner restlessness or a strong desire to move one’s body.
3. Appear anxious and agitated; may pace or move about.
4. Can produce severe dysphoria and anxiety.
5. Risk factors are recent onset or increase in medication. Most occur in first month of treatment.
6. Treatment includes reducing the offending agent, beta-blockers, or benzodiazepines.
7. Anticholinergics usually ineffective.

**Extrapyramidal Symptoms**

1. Also known as neuroleptic-induced Parkinsonism.
2. Most common symptoms are rigidity and akinesia, resting tremor, drooling, cogwheeling or “lead pipe” rigidity.
3. Risk factors are high-potency neuroleptics, increasing age, and a prior history of EPS.
5. Treatment includes reducing the offending agent and anticholinergics.

**Neuroleptic Malignant Syndrome**

1. An idiosyncratic and potentially life-threatening complication of antipsychotic drug use.
2. Develops gradually over a period of hours to days.
3. The diagnosis of NMS may be complicated by the patient’s underlying psychopathology.
4. Characterized by autonomic instability and motor abnormalities.
5. Autonomic symptoms include tachycardia, cardiac arrhythmias, hypertension, hypotension, diaphoresis and fever progressing to hyperthermia.
6. Motor symptoms include rigidity/dystonia, akinesia, mutism and dysphagia.
7. Behavioral symptoms include agitation, incontinence, delirium, seizures and coma.
8. Laboratory findings include increased creatine kinase, increased WBC and abnormal liver function tests.
9. Risk factors include high-dose antipsychotics, rapid dose escalation, IM antipsychotics, dehydration or a prior history of NMS.
10. Treatment includes discontinuation of the antipsychotic, dantrolene (a muscle relaxant) and bromocriptine (a dopamine agonist). Intensive care with cardiac monitoring and intubation may be necessary.

**Tardive Dyskinesia**

1. A movement disorder that occurs with long-term neuroleptic use.
2. Consists of constant, involuntary, stereotyped choreoathetoid movements usually in the head and neck muscles.
3. Risk factors include long-term use of neuroleptics, increasing age, female sex, and presence of a mood disorder.
4. Tends to be permanent.
5. Treatment includes changing antipsychotic, lowering the dose, or switching to clozapine.

**Serotonin Syndrome**

1. Usually occurs when serotonin-altering medications are used with MAOIs.
2. Symptoms are autonomic, motor and behavioral.
3. Autonomic symptoms include tachycardia, hypertension, diaphoresis and fever progressing to hyperthermia.
4. Motor symptoms include shivering, myoclonus, tremor, hyperreflexia, and oculomotor abnormalities.
5. Behavioral symptoms include restlessness, agitation, delirium and coma.
6. Risk factor is only the combination of medications.
7. Treatment is supportive. The offending agent is discontinued.