**Dr. H.M.AlkuraishyAntipsychotic** Lec.10-11

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states.

**SCHIZOPHRENIA**

Schizophrenia is a particular type of psychosis it is characterized by delusions, hallucinations, and thinking or speech disturbances. Schizophrenia has a strong dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways( increase in dopaminergic neurotransmission).

**ANTIPSYCHOTIC DRUGS**

**A. First-generation antipsychotics:**The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors of D2 dopamine receptors. First-generation antipsychoticsare more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine.

**B. Second-generation antipsychotic drugs:** The second generation antipsychotic drugs (also referred to as “atypical "antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine receptors.

**Mechanism of action**

**1. Dopamine receptor–blocking activity in the brain:** All of the first generation and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery .The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D2 receptors in the mesolimbic system of the brain.

**2. Serotonin receptor–blocking activity in the brain:** Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly5-HT2A receptors.

**Actions:**The antipsychotic actions reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors. It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis.

**1. Antipsychotic actions:** All of the antipsychotic drugs can reducethe hallucinations and delusions associated with schizophrenia (theso-called “positive” symptoms) by blocking dopamine receptors in the mesolimbic system of the brain. The “negative” symptoms, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generationagents, such as clozapine, ameliorate the negative symptoms to some extent. All of the drugs also have a calming effect and reducespontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the antipsychotics do not depress the intellectual functioning of the patient as much, and motor coordination difficulties are minimal. The antipsychotic effects usually take several days to weeks to occur, suggesting thatthe therapeutic effects are related to secondary changes in the cortico-striatal pathways.

**2. Extra-pyramidal effects:** Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second-generation antipsychotics exhibit a lowerincidence of these symptoms.

**3. Antiemetic effects:** With the exception of aripiprazole, most of the antipsychotic drugs have antiemetic effects that are mediated byblocking D2-dopaminergic receptors of the chemoreceptor triggerzone of the medulla.

**4. Anticholinergic effects:** Some of the antipsychotics, particularly thioridazine, chlorpromazine, clozapine, and olanzapine, produce anticholinergi ceffects, including blurred vision; dry mouth (the exceptionis clozapine, which increases salivation); confusion; and inhibitionof gastrointestinal and urinary tract smooth muscle, leading toconstipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

**5. Other effects:** Blockade of α-adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics alsoalter temperature-regulating mechanisms and can produce poikilothermia(condition in which body temperature varies with the environment).In the pituitary, antipsychotics block D2 receptors, leadingto an increase in prolactin release. Second-generation antipsychotics are less likely to produce prolactin elevations. Sedation occurs with those drugs that are potent antagonists of the H1-histaminereceptor, including chlorpromazine, olanzapine, quetiapine, and clozapine. Sexual dysfunction may also occur with the antipsychoticsdue to various receptor-binding characteristics.

**Therapeutic uses**

**1. Treatment of schizophrenia**

**2. Prevention of severe nausea and vomiting:**

**3. Other uses:** tranquilizers, chronic pain with severe anxiety, intractable hiccups, pruritus and autism.

**Absorption and metabolism**

After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for ziprasidone and paliperidone the absorption of which is increased with food). These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances, usually by the cytochrome P450 system

**Adverse effects**

**1. Extrapyramidal side effects:**

**2. Tardive dyskinesia:** Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements,including bilateral and facial jaw movements and “fly-catching”motions of the tongue. A prolonged holiday from antipsychoticsmay causes the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesiais postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade. This makes the neuron supersensitiveto the actions of dopamine, and it allows the dopaminergic inputto this structure to overpower the cholinergic input, causing excessmovement in the patient. Traditional anti-EPS medications do notgenerally improve tardive dyskinesia and may actually worsen thiscondition.

**3. Antipsychotic malignant syndrome:** This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychoticagent and supportive therapy. Administration of dantrolene or bromocriptine may be helpful.

**4. Other effects:** orthostatic hypotension, amenorrhea, galactorrhea, gynecomastia, infertility, and impotence,weight gain and exacerbation of preexisting diabetes mellitus or hyperlipidemia.

* Metabolic adverse effects appears to be mediated by the following mechanisms:

- Blocking the [M3 muscarinic acetylcholine receptor](http://en.wikipedia.org/wiki/Muscarinic_acetylcholine_receptor_M3) which is responsible for regulating the release of [insulin](http://en.wikipedia.org/wiki/Insulin)

- Inappropriately changing the body's energy source from carbohydrates to lipids.

- Causing weight gain by antagonising the [histamine H1](http://en.wikipedia.org/wiki/Histamine_H1_receptor) and serotonin [5-HT2C](http://en.wikipedia.org/wiki/5-HT2C) receptors and perhaps by interacting with other neurochemical pathways in the [central nervous system](http://en.wikipedia.org/wiki/Central_nervous_system)

* **Maintenance treatment**

Patients who have had two or more psychotic episodes, secondary toschizophrenia, should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy.

**Antidepressants**

The symptoms of depression are intense feelings of sadness, hopelessness, and inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

**MECHANISM OF ANTIDEPRESSANT DRUGS**

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain. This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. It has been proposed that pre-synaptic inhibitory receptor densities in the brain decrease over a 2 to 4 week period with antidepressant drug use. This down-regulation of inhibitory receptors permits greater synthesis and release of neurotransmitters into the synaptic cleft and enhanced signaling in the postsynaptic neurons, presumably leading to a therapeutic response.

**TRICYCLIC ANTIDEPRESSANTS**

The TCAs block norepinephrine and serotonin reuptake into the neuron, TCAs include the tertiary amines imipramine (the prototype drug), amitriptyline, clomipramine doxepin , and trimipramine.

**Mechanism of action**

**1. Inhibition of neurotransmitter reuptake:** TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters.

**2. Blocking of receptors:** blockα -adrenergic, serotonergic, histaminic, and muscarinic receptors.

**Therapeutic uses:**

* Moderate to severe depression.
* Imipramine has been used to control bed-wetting in children (older than age 6 years) by causing contraction of the internal sphincter of the bladder.
* The TCAs, particularly amitriptyline, have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain).
* TCAs, especially doxepin, can be used to treat insomnia.

**Adverse effects**: Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma . These agents also affect cardiac conduction similarly to quinidine, which may precipitate life-threatening arrhythmias should an overdose of one of these drugs be α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. In clinical practice, this is the most serious problem in elderly adults.

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

The selective serotonin reuptake inhibitors (SSRIs) inhibit serotonin reuptake leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

**Therapeutic uses**:depression, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa .

**Pharmacokinetics:** All of the SSRIs are well absorbed after oral administration. Food has little effect on absorption (except with sertraline, for which food increases its absorption). Only sertraline undergoes significant first-pass metabolism. The majority of SSRIs have plasma half-lives that range between16 and 36 hours.

**Adverse effects:**

**1. Sleep disturbances: Paroxetine and fluvoxamine** are sedating while **fluoxetine or sertraline** are stimulating.

**2. Sexual dysfunction:** but fewer sexual side effects, such as **bupropion or mirtazapine**.

**3. Overdoses:** Large intakes of SSRIs do not usually cause cardiac arrhythmias, but seizures are a possibility because all antidepressants may lower the seizure threshold. All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a MAOI or other highly serotonergic drug. Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs.

**5. Discontinuation syndrome:** Whereas all of the SSRIs have the potential for causing a discontinuation syndrome after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction. Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome.

**SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS**

**Venlafaxine, desvenlafaxine, and duloxetine** inhibit the reuptake of both serotonin and norepinephrine

**A. Venlafaxine and desvenlafaxine**

Venlafaxine is a potent inhibitor of serotonin reuptake and, at mediumto higher doses, is an inhibitor of norepinephrine reuptake.

**B. Duloxetine:** inhibits serotonin and norepinephrine reuptake at all doses.It is extensively metabolized in the liver to numerous metabolites.

**ATYPICAL ANTIDEPRESSANTS**

**A. Bupropion:** dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Bupropion also assists in decreasingthe craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking. Side effects may include drymouth, sweating, nervousness, tremor, a very low incidence of sexualdysfunction, and an increased risk for seizures at high doses.

**B. Mirtazapine:** This drug enhances serotonin and norepinephrine neurotransmissionvia mechanisms related to its ability to block presynaptic α2 receptors.Additionally; it may owe at least some of its antidepressant activityto its ability to block 5-HT2 receptors. It is a sedative because of itspotent antihistaminic activity, but it does not cause the antimuscarinic side effects.

**C. Nefazodone and trazodone:** These drugs are weak inhibitors of serotonin reuptake. Their therapeutic benefit appears to be related to their ability to block postsynaptic5-HT2A receptors. With chronic use, these agents may desensitize 5-HT1A presynaptic autoreceptors and, thereby, increase serotonin release. Trazodonehas been associated with causing priapism, and nefazodonehas been associated with the risk for hepatotoxicity.

**NOREPINEPHRINE REUPTAKE INHIBITORS**

[Selective norepinephrine reuptake inhibitors](http://en.wikipedia.org/wiki/Selective_norepinephrine_reuptake_inhibitor) (NRIs) inhibit the reuptake of norepinephrine. The NRIs include: [Atomoxetine](http://en.wikipedia.org/wiki/Atomoxetine)  indicated in treatment for [Attention deficit hyperactivity disorder](http://en.wikipedia.org/wiki/Attention_deficit_hyperactivity_disorder).

**NOREPINEPHRINE-DOPAMINE DISINHIBITORS/MELATONIN AGONISTS** (agomelatine ) act by antagonizing the serotonin [5-HT2C receptor](http://en.wikipedia.org/wiki/5-HT2C_receptor), which normally acts to inhibit norepinephrine and dopamine release and melatonin receptor agonist.

**MONOAMINE OXIDASE INHIBITORS**

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO inactivates any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors(MAOIs) may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and leak into the synaptic space. This is believed to cause activation of norepinephrine and serotonin receptors, and it may be responsible for the indirect antidepressant actionof these drugs. Four MAOIs are currently available for treatment of depression: phenelzine; tranylcypromine;isocarboxazid; and the agent that was prior-approvedfor Parkinson disease, but is now also approved for depression, selegiline, which is the first antidepressant available in a transdermal delivery system.Use of MAOIs is now limited due to the complicated dietary restrictionsrequired of patients taking them.

**Mechanism of action:** Most MAOIs, such as phenelzine, causing irreversible inactivation. These results in increased stores of norepinephrine, serotonin, and dopamine within the neuronand subsequent diffusion of excess neurotransmitter into the synaptic space .These drugs inhibit not only MAO in the brain, but also MAO in the liver and gut that catalyze oxidative deaminationof drugs and potentially toxic substances, such as tyramine, which isfound in certain foods. The MAOIs, therefore, show a high incidence ofdrug-drug and drug-food interactions. Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

**Actions:** Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs and TCAs, is delayed several weeks. Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia.

**Therapeutic uses**: The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety.

**Pharmacokinetics:** These drugs are well absorbed after oral administration, but antidepressanteffects require at least 2 to 4 weeks of treatment.

**Adverse effects:** Severe and often unpredictable side effects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs. For example,tyramine, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut.Individuals receiving a MAOI are unable to degrade tyramine obtainedfrom the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in what is termed a“hypertensive crisis,” with signs and symptoms such as occipital headache,stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias,seizures, and, possibly, stroke.

**OTHERS**

### Nicotine: Nicotine is believed to act as an antidepressant, by stimulating the release of dopamine and norepinephrine; in addition, nicotine is believed to exert an antidepressant effect due to the desensitization of nicotinic receptors, which occurs as a result of tolerance treatment-resistant depression.  [Varenicline](http://en.wikipedia.org/wiki/Varenicline), a nicotinic receptor-acting drug used to wean people off of nicotine dependence has also demonstrated antidepressant properties.

### CaffeineIndividuals using [caffeine](http://en.wikipedia.org/wiki/Caffeine), at moderate doses have a reduced incidence of depressive symptoms and an overall reduced risk of [suicide](http://en.wikipedia.org/wiki/Suicide).

[**Psychostimulants**](http://en.wikipedia.org/wiki/Psychostimulants)**:**such as [amphetamine](http://en.wikipedia.org/wiki/Amphetamine) , [methylphenidate](http://en.wikipedia.org/wiki/Methylphenidate) , [modafinil](http://en.wikipedia.org/wiki/Modafinil)  these effective in treatment-resistant depression with concomitant antidepressant therapy.

#### Ketamine:effective in treatment-resistant depression, it produces a rapid antidepressant effect, acting within two hours as opposed to the several weeks taken by typical antidepressants to work

#### Nutrition:[Omega 3 fatty acids](http://en.wikipedia.org/wiki/Omega_3_fatty_acids" \o "Omega 3 fatty acids) have been proposed as a treatment for depression, alone or in combination with other treatments. One small pilot study of childhood depression (age's six to 12) suggested omega 3 fatty acids may have therapeutic benefits for treating childhood depression.

**TREATMENT OF MANIA AND BIPOLAR DISORDER**

Mania is characterized by the opposite behavior: enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

The treatment of bipolar disorder has increased in recent years, partly dueto the increased recognition of the disorder and also due to the increase inthe number of medications FDA-approved for the treatment of mania.

**A. Lithium**:Lithium salts are used prophylactically for treating manic-depressivepatients and in the treatment of manic episodes and, thus, are considered“mood stabilizers.” Lithium is believed to attenuate signaling via receptors coupled to the phosphatidylinositol bisphosphate (PIP2) second messenger system. Lithium interferes with the resynthesis (recycling) ofPIP2, leading to its relative depletion in neuronal membranes of the CNS. Lithiumis given orally and the ion is excreted by the kidney. Lithium salts can be toxic. Their safety factor and therapeutic index are extremely low andcomparable to those of digoxin. Common adverse effects may includeheadache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give lithium with food), fine hand tremor, dizziness, fatigue, dermatologicreactions, and sedation. Adverse effects due to higher plasma levelsmay include ataxia, slurred speech, coarse tremors, confusion, and convulsions. Thyroid function may be decreased andshould be monitored. Lithium causes no noticeable effect on normalindividuals. It is not a sedative, euphoriant, or depressant.

**B. Other drugs**: carbamazepine, valproic acid, and lamotrigine,the atypical antipsychotics (risperidone, olanzapine, ziprasidone,aripiprazole, asenapine, and quetiapine) have also received FDA approval for the management of mania. Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania.