Antidepressants & Mood Stabilizing Agents

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Reference: Basic & Clinical Pharmacology: Bertrum G. Katzung and Anthony J. Treveror, 13th edition, 2015, chapter 30: p.510-530; chapter 29: p.503-507

Learning Objectives:

At the end of session, the student should be able to:

1. Classify antidepressant drugs.
2. Explain the effect of each class of antidepressants on neurotransmitter systems.
3. Identify the drugs belonging to each class of antidepressants.
4. List side effects of tricyclic antidepressants.
5. State clinically important drug interactions of tricyclic antidepressants.
6. Specify side effects of selective serotonin reuptake inhibitors (SSRIs).
7. State clinically important drug interactions of SSRIs.
8. Describe side effects of MAOIs.
9. Explain clinically important drug interactions of MAOIs.
10. Identify mood-stabilizing agents.
11. Explain side effects of lithium.
12. Identify important pharmacokinetic drug interactions of lithium

Antidepressants & Mood Stabilizing Agents

Antidepressant and mood-stabilizing agents are used in the treatment of mood disorders known as major affective disorders. Two major affective disorders include major depressive disorder and bipolar affective disorder.

Major depressive disorder (MDD) represents one of the most common causes of disability in the developed world. It is characterized by depressed mood most of the time for at least 2 weeks or loss of interest or pleasure in most activities, or both. In addition, depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy. Thoughts of guilt, worthlessness, and suicide are common.

Antidepressants have a broad spectrum of use in medical practice. For example, antidepressants have received FDA approvals for the treatment of panic disorder, generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), andobsessive-compulsive disorder (OCD). In addition, antidepressants are commonly used to treat pain disorders such as neuropathic pain and the pain associated with fibromyalgia. Some antidepressants are used for treating premenstrual dysphoric disorder (PMDD), mitigating the vasomotor symptoms of menopause, and treating stress urinary incontinence. However, the primary indication of antidepressant agents remains the treatment of MDD.

Antidepressants are classified into four major groups as follows:

1. Tricyclic antidepressants (TCAs)

2. Monoamino oxidase (MAO) inhibitors

3. Selective serotonin reuptake inhibitors (SSRIs)

4. Selective norepinephrine serotonin reuptake inhibitors (SNRIs)

In the treatment of MDD, it is difficult to demonstrate that one antidepressant is consistently more effective than another. Thus, the choice of an antidepressant for the treatment of depression rests primarily on practical considerations such as cost, availability, adverse effects, potential drug interactions, the patient's history of response or lack thereof, and patient preference

Pharmacodynamics

All currently available antidepressants enhance monoamine neurotransmission by one of several mechanisms. The most common mechanism is inhibition of the activity of serotonin transporter (SERT), norepinephrine transporter (NET), or both monoamine transporters. SSRIs inhibit SERT; and SNRIs and the TCAs inhibit both SERT and NET. The SNRIs differ from the TCAs in that they lack the potent antihistamine, α-adrenergic blocking, and anticholinergic effects of the TCAs. As a result, the SNRIs tend to be favored over the TCAs in the treatment of MDD because of their better tolerability. Another mechanism for increasing the availability of monoamines is inhibition of their enzymatic degradation (by the MAOIs). Additional strategies for enhancing monoamine tone include binding presynaptic autoreceptors (mirtazapine) or specific postsynaptic receptors (5-HT2 antagonists and mirtazapine). However, there is a time delay between the effect of antidepressants on monoamine neurotransmission and their onset of clinical therapeutic effects. It appears that the increased availability of monoamines for binding in the synaptic cleft results in a cascade of events that enhance the transcription of some proteins and the inhibition of others, ultimately leading to their clinical benefits.

Tricyclic Antidepressants

This class includes **imipramine, desipramine, clomipramine, amitriptyline, nortriptyline and doxepine.** The TCAs were the dominant class of antidepressants until the introduction of SSRIs in the 1980s and 1990s. At the present time, the TCAs are used primarily in depression that is

unresponsive to more commonly used antidepressants such as the SSRIs or SNRIs. Their loss of popularity stems in large part from relatively poorer tolerability compared with newer agents, difficulty of use, and lethality in overdose.

Adverse effects of TCAs:

Anticholinergic effects: including dry mouth, constipation, urinary retention, blurred vision, and confusion are common adverse effects of the TCAs.

Antihistaminic effects: The TCAs also tend to be potent antagonists of the histamine H1 receptor causing sedation and weight gain.

Blockade of α1- adrenoceptors: can result in substantial orthostatic hypotension, particularly in older patients.

Cardiac effects: The TCAs are class 1A antiarrhythmic agents and are arrhythmogenic at higher doses.

Sexual dysfunction: are common, particularly with highly serotonergic TCAs such as clomipramine.

Precipitating manic episodes: the use of antidepressants in depressed phase of bipolar depression is sometimes associated with switches into mania or more rapid cycling.

Toxicity: Overdose of TCAs can induce lethal arrhythmias, including ventricular tachycardia and fibrillation. In addition, blood pressure changes and anticholinergic effects including altered mental status and seizures are sometimes seen in TCA overdoses. TCAs are the most common method used in suicide attempts by depressed patients.

Drug interactions: The use of TCA with MAOIs or sympathomimetics may lead to hypertensive crisis. There may also be additive anticholinergic or antihistamine effects when TCAs are combined with other agents that share these properties such as benztropine or

diphenhydramine. Similarly, antihypertensive drugs may exacerbate the orthostatic hypotension induced by TCAs.

Selective serotonin reuptake Inhibitors

There are currently six available SSRIs, and they are the most common antidepressants in clinical use. This class includes **fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine and escitalopram (**the (*S*) enantiomer of citalopram**)**. The popularity of SSRIs stems largely from their ease of use, safety in overdose, relative tolerability, cost, and broad spectrum of uses.

Adverse effects of the SSRIs:

Gastrointestinal effects: The use of SSRIs is commonly associated with nausea, gastrointestinal upset, diarrhea, and other gastrointestinal symptoms which usually emerge early in the course of treatment and tend to improve after the first week.

Headache and increased anxiety may develop early during treatment and resolve with time.

Diminished sexual function and interest: at least 30–40% of patients treated with SSRIs report loss of libido, delayed orgasm, or diminished arousal. The sexual effects often persist as long as the patient remains on the antidepressant but may diminish with time.

Drug interactions: The most common interactions with SSRIs are pharmacokinetic interactions. For example, paroxetine and fluoxetine are potent CYP2D6 inhibitors. Thus, administration with 2D6 substrates such as TCAs can lead to dramatic and sometimes unpredictable elevations in the tricyclic drug concentration. The result may be toxicity from the TCA.

The most serious interaction with the SSRIs is pharmacodynamic interactions with MAOIs that produce a serotonin syndrome.

Monoamino Oxidase Inhibitors (MAOIs)

Monoamino oxidase has two subtypes A and B. MAO-A is responsible for degradation of serotonin and norepinephrine, while MAO-B is mainly responsible for degradation of dopamine. Current MAOIs include the **phenelzine, isocarboxazid** and **tranylcypromine** which bind irreversibly and non-selectively with MAO-A and –B. MAOIs were introduced in the 1950s but are now rarely used in clinical practice because of toxicity and potentially lethal food and drug interactions. Their primary use now is in the treatment of depression unresponsive to other antidepressants.

Adverse effects of MAOIs include insomnia, postural hypotension, sexual dysfunction, precipitating manic episodes in bipolar patients, and weight gain. An overdose with an MAOI can produce a variety of effects including autonomic instability, hyperadrenergic symptoms, psychotic symptoms, confusion, delirium, fever, and seizures.

Drug interactions: MAOIs are associated with two classes of serious drug interactions. The first of these is the pharmacodynamic interaction of MAOIs with serotonergic agents including SSRIs, SNRIs, and most TCAs along with some analgesic agents such as meperidine. These combinations of an MAOI with a serotonergic agent may result in a life-threatening **serotonin syndrome.** Symptoms range from mild to lethal and include a triad of cognitive (delirium, coma), autonomic (hypertension, tachycardia, diaphoreses), and somatic (myoclonus, hyperreflexia, tremor) effects.

The second serious interaction with MAOIs occurs when an MAOI is combined with tyramine in the diet or with sympathomimetic substrates of MAO. An MAOI prevents the breakdown of tyramine in the gut, and this result in high serum levels that enhance peripheral noradrenergic effects, including raising blood pressure dramatically. Patients on an MAOI who ingest large

amounts of dietary tyramine may experience malignant hypertension and subsequently a stroke or myocardial infarction. Thus, patients taking MAOIs require a low-tyramine diet and should avoid foods such as aged cheeses, tap beer, soy products, and dried sausages, which contain high amounts of tyramine. Similar sympathomimetics also may cause significant hypertension when combined with MAOIs. Thus, over-the-counter cold preparations that contain pseudoephedrine and phenylpropanolamine are contraindicated in patients taking MAOIs.

Selective norepinephrine serotonin reuptake inhibitors

The SNRIs include **venlafaxine,** its metabolite **desvenlafaxine and duloxetine**.

SNRIs have many of the serotonergic adverse effects associated with SSRIs. In addition, SNRIs may also have noradrenergic effects, including increased blood pressure and heart rate, and CNS activation, such as insomnia, anxiety, and agitation. The hemodynamic effects of SNRIs tend not to be problematic in most patients. A dose-related increase in blood pressure has been seen more commonly with the immediate-release form of venlafaxine than with other SNRIs. Likewise, there are more reports of cardiac toxicity with venlafaxine overdose than with either the other SNRIs or SSRIs. Duloxetine is rarely associated with hepatic toxicity in patients with a history of liver damage.

Mood-stabilizing agents for Bipolar Disorder

Bipolar disorder, once known as **manic-depressive** illness, has two phases that is manic and depressed phases. The key symptoms of bipolar disorder in the manic phase are expansive or irritable mood, grandiosity, hyperactivity, impulsivity, disinhibition, diminished need for sleep, racing thoughts, psychotic symptoms in some (but not all) patients, and cognitive impairment. Depression in bipolar patients is phenomenologically similar to that of major depression, with

the key features being depressed mood, diurnal variation, sleep disturbance, anxiety, and sometimes, psychotic symptoms. Patients with bipolar disorder are at high risk for suicide.

Lithium was the first agent shown to be useful in the treatment of the manic phase of bipolar disorder. Lithium continues to be used for acute-phase illness as well as for prevention of recurrent manic and depressive episodes. Lithium has a slow onset of action and has often been supplemented with concurrent use of antipsychotic drugs or potent benzodiazepines in severely manic patients. After mania is controlled, the antipsychotic drug may be stopped and benzodiazepines and lithium continued as maintenance therapy.

A group of mood-stabilizing drugs that are also anticonvulsant agents has become more widely used than lithium. It includes **carbamazepine** and **valproic acid** for the treatment of acute mania and for prevention of its recurrence. **Lamotrigine** is approved for prevention of recurrence.

Antipsychotics including **aripiprazole, chlorpromazine, olanzapine, quetiapine, risperidone,** and **ziprasidone** are approved by the FDA for treatment of the manic phase of bipolar disorder.

The depressive phase of manic-depressive disorder often requires concurrent use of other agents including antipsychotics such as quetiapine or lurasidone. Antidepressants have not shown consistent utility and may be destabilizing. Tricyclic antidepressant agents have been linked to precipitation of mania, with more rapid cycling of mood swings, although most patients do not show this effect. Similarly, SNRI agents have been associated with higher rates of switching to mania than some antidepressants. Selective serotonin reuptake inhibitors are less likely to induce mania but may have limited efficacy. Bupropion has shown some promise but—like tricyclic antidepressants—may induce mania at higher doses. As shown in recent controlled trials, the anticonvulsant lamotrigine is effective for some patients with bipolar depression, but results have been inconsistent. For some patients, however, one of the older monoamine oxidase inhibitors

may be the antidepressant of choice. Quetiapine and the combination of olanzapine and fluoxetine haves been approved for use in bipolar depression.

Lithium

Lithium is used for treating acute phase of mania and as a prophylactic agent to prevent both mania and depression. Clinicians rely on measurements of serum lithium concentrations for assessing both the dosage required for treatment of acute mania and for prophylactic maintenance. Therapeutic serum concentration of lithium is 0.6-1.4mM. Lithium has a low therapeutic index that is any value over 2 mM must be considered as indicating likely toxicity. Therapeutic overdoses of lithium are more common than those due to deliberate or accidental ingestion of the drug. Therapeutic overdoses are usually due to accumulation of lithium resulting from some change in the patient's status, such as diminished serum sodium, use of diuretics (e.g. thiazides), or fluctuating renal function. Patients receiving lithium should avoid dehydration to prevent decreased renal clearance of lithium. A reduction in lithium clearance has been noted with several of the newer nonsteroidal anti-inflammatory drugs that block synthesis of prostaglandins. This interaction has not been reported for either aspirin or acetaminophen. In situations with decreased renal clearance of lithium, doses of lithium may need to be reduced to prevent toxicity.

Adverse Effects & Complications of Lithium

Unlike antipsychotic or antidepressant drugs, which exert several actions on the central or autonomic nervous system, lithium ion at therapeutic concentrations is devoid of autonomic blocking effects and of activating or sedating effects. Lithium can produce many adverse effects at varying times after treatment is started. Some are harmless, but it is important to be alert to adverse effects that may signify impending serious toxic reactions.

A. Tremor is one of the most common adverse effects of lithium treatment, and it occurs with therapeutic doses.

B. Decreased Thyroid Function: Lithium probably decreases thyroid function in most patients exposed to the drug, but the effect is reversible or nonprogressive.

C. Nephrogenic Diabetes Insipidus: Polydipsia and polyuria are common but reversible concomitants of lithium treatment, occurring at therapeutic serum concentrations. The principal physiologic lesion involved is loss of responsiveness to antidiuretic. Lithium-induced diabetes insipidus is resistant to vasopressin but responds to amiloride.

D. Edema: Edema is a common adverse effect of lithium treatment and may be related to some effect of lithium on sodium retention.

E. Cardiac Adverse Effects: The bradycardia-tachycardia ("sick sinus") syndrome is a definite contraindication to the use of lithium because the ion further depresses the sinus node. T-wave flattening is often observed on the electrocardiogram but is of questionable significance.

F. Use in Pregnancy: Renal clearance of lithium increases during pregnancy and reverts to lower levels immediately after delivery. The issue of lithium-induced dysmorphogenesis is not settled. An earlier report suggested an increase in cardiac anomalies—especially Ebstein's anomaly—in lithium babies. However, more recent data suggest that lithium carries a relatively low risk of teratogenic effects. Further research is needed in this important area.

G. Leukocytosis is always present during lithium treatment, probably reflecting a direct effect on leukopoiesis rather than mobilization from the marginal pool. This adverse effect has now become a therapeutic effect in patients with low leukocyte counts.

Valproic Acid

Valproic acid (valproate), an antiepileptic drug, has been demonstrated to have antimanic effects and is now being widely used for this indication in the USA. Overall, valproic acid shows efficacy equivalent to that of lithium during the early weeks of treatment. It is significant that valproic acid has been effective in some patients who have failed to respond to lithium. Moreover, its side-effect profile is such that one can rapidly increase the dosage over a few days to produce blood levels in the apparent therapeutic range, with nausea being the only limiting factor in some patients. Combinations of valproic acid with other psychotropic medications likely to be used in the management of either phase of bipolar illness are generally well tolerated. Valproic acid is an appropriate first-line treatment for mania, although it is not clear that it will be as effective as lithium as a maintenance treatment in all subsets of patients. Many clinicians advocate combining valproic acid and lithium in patients who do not fully respond to either agent alone.

Carbamazepine

Carbamazepine has been considered to be a reasonable alternative to lithium when the latter is less than optimally efficacious. However, the pharmacokinetic interactions of carbamazepine and its tendency to induce the metabolism of CYP3A4 substrates make it a more difficult drug to use with other standard treatments for bipolar disorder. Carbamazepine may be used to treat acute mania and also for prophylactic therapy. Carbamazepine may be used alone or, in refractory patients, in combination with lithium or, rarely, valproate. The use of carbamazepine as a mood stabilizer is similar to its use as an anticonvulsant. Blood dyscrasias have figured prominently in the adverse effects of carbamazepine when it is used as an anticonvulsant, but they have not been a major problem with its use as a mood stabilizer.