**Antidepressants 12**

I**. OVERVIEW**

The symptoms of depression are intense feelings of sadness, hopeless- ness, and despair as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and sui- cidal thoughts. Mania is characterized by the opposite behavior: enthu- siasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. [Note: Depression and mania are different from schizophrenia (see p. 161), which produces disturbances in thought.]

**II. MECHANISM OF ANTIDEPRESSANT DRUGS**

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain. (See Figure 12.1 for a summary of the antidepressant agents.) This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepi- nephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neu- rotransmitters. However, the amine theory of depression and mania is overly simplistic. It fails to explain why the pharmacologic effects of any of the antidepressant and anti-mania drugs on neurotransmission occur immediately, whereas the time course for a therapeutic response occurs over several weeks. Furthermore, the potency of the antidepressant drugs in blocking neurotransmitter uptake often does not correlate with clinical- ly observed antidepressant effects. This suggests that decreased uptake of the neurot ransmitter is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects. It has been pro- posed that presynaptic inhibitory receptor densities in the brain decrease over a 2 to 4 week period with antidepressant drug use. This down-reg- ulation 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.

**III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS**

The selective serotonin reuptake inhibitors (SSRIs) are a group of chemi- cally diverse antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs, see p. 155) that nonselectively inhibit the uptake of norepinephrine and serotonin (Figure 12.2). Both of these antidepressant drug classes exhibit little ability to block the dop amine transporter. Moreover, the SSRIs have little blocking activity at mus- carinic, α-adrenergic, and histaminic H1 receptors. Therefore, common side eff ects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs. Because they have fewer adverse eff ects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. SSRIs include fl uox- etine [fl oo-OX-e-teen] (the proto typic drug), citalopram [sye-TAL-oh-pram], escitalopram [es-sye-TAL-oh-pram], fl uvoxamine [fl oo-VOX-e-meen], parox- etine [pa-ROX-e-teen], and sertraline [SER-tra-leen]. Both citalopram and fl u- oxetine are racemic mixtures, of which the respective S-enantiomers are the more potent inhibitors of the serotonin reuptake pump. Escitalopram is the pure S-enatiomer of citalopram. **A. Actions**

The SSRIs block the reuptake of serotonin, leading to increased con- centrations 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 signifi cant improve- ment in mood, and maximum benefi t may require up to 12 weeks or more (Figure 12.3). However, none of the antidepressants are uniformly eff ective. Approximately 40 percent of depressed patients treated with adequate doses for 4 to 8 weeks do not respond to the antidepres- sant agent. Patients who do not respond to one antidepressant may respond to another, and approximately 80 percent or more will respond to at least one antidepressant drug. [Note: These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.]

**B. Therapeutic uses**

The primary indication for SSRIs is depression, for which they are as eff ective as the TCAs. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disor- der, social anxiety disorder, premenstrual dysphoric disorder, and buli- mia nervosa (only fl uoxetine is approved for this last indication).

**C. Pharmacokinetics**

All of the SSRIs are well absorbed after oral administration. Peak lev- els are seen in approximately 2 to 8 hours on average. Food has little eff ect on absorption (except with sertraline, for which food increases its absorption). Only sertraline undergoes signifi cant fi rst-pass metabo- lism. The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occur extensively. [Note: These metabolites do not generally contribute to the pharma- cologic activity.] Fluoxetine diff ers from the other members of the class in two respects. First, it has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dos- ing. Second, the metabolite of the S-enantiomer, S-norfl uoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days. Fluoxetine and paroxetine are potent inhibitors of a hepatic CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs. [Note: About 7 percent of the Caucasian population lacks this P450 enzyme and, therefore, metabolize fluoxetine and other substrates of this enzyme very slowly. These individuals may be referred to in the literature as “poor metabolizers.”] Other cytochrome enzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs. Thus, they may affect the metabolism of multiple medications. Excretion of the SSRIs is primarily through the kidneys, except for paroxetine and sertraline, which also undergo fecal excretion (35 and 50 percent, respectively). Dosages of all of these drugs should be adjusted downward in patients with hepatic impairment.

**D. Adverse effects**

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without trouble- some adverse effects, such as headache, sweating, anxiety and agita- tion, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug-drug interactions (Figure 12.4).

**1. Sleep disturbances**: Paroxetine and fluvoxamine are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating antidepressants, such as fluoxetine or sertraline.

**2. Sexual dysfunction**: Loss of libido, delayed ejaculation, and anor- gasmia are underreported side effects often noted by clinicians, but these are not prominently featured in the list of standard side effects. One option for managing SSRI-induced sexual dysfunction is to replace the offending antidepressant with an antidepressant having fewer sexual side effects, such as bupropion or mirtazapine. Alternatively, the dose of the drug may be reduced. In men with erectile dysfunction and depression, treatment with sildenafil, vard- enafil, or tadalafil (see p. 363) may improve sexual function.

**3. Use in children and teenagers**: Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 chil- dren report suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and sui- cidal thinking whenever any antidepressant is started or its dose is increased or decreased. Fluoxetine, sertraline, and fluvoxamine are U.S. Food and Drug Administration (FDA)-approved for use in children to treat obsessive-compulsive disorder, and fluoxetine is approved to treat childhood depression.

4**. Overdoses:** Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs), 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 inac- tive metabolites have a higher risk for such an adverse reaction. Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome. Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and fl u-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

IV. **SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS**

Venlafaxine [VEN-la-fax-een], desvenlafaxine [dez-VEN-la-fax-een], and duloxetine (doo-LOX-e-teen) inhibit the reuptake of both serotonin and nor- epinephrine (Figure 12.5). These agents, termed selective serotonin/norepi- nephrine reuptake inhibitors (SNRIs), may be eff ective in treating depres- sion in patients in whom SSRIs are ineff ective. Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineff ective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS. Both SNRIs and TCAs, with their dual actions of inhibiting both serotonin and norepinephrine reuptake, are sometimes eff ective in relieving physi- cal symptoms of neuropathic pain such as diabetic peripheral neuropathy. However, the SNRIs, unlike the TCAs, have little activity at adrenergic, mus- carinic, or histamine receptors and, thus, have fewer of these receptor-medi- ated adverse eff ects than the TCAs (see Figure 12.2). Venlafaxine, desvenla- faxine, and duloxetine may precipitate a discontinuation syndrome if treat- ment is abruptly stopped.

1. **Venlafaxine and desvenlafaxine**

Venlafaxine is a potent inhibitor of serotonin reuptake and, at medi- um to higher doses, is an inhibitor of norepinephrine reuptake. It is also a mild inhibitor of dopamine reuptake at high doses. Venlafaxine has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. The half-life of the parent compound plus its active metabolite is approximately 11 hours. Desvenlafaxine is the active, demethylated, metabolite of the parent compound venlafaxine. The most common side eff ects of venlafaxine are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. Desvenlafaxine is not considered to have a signifi cantly diff erent clinical or adverse eff ect profi le compared to venlafaxine.

1. **Duloxetine**

Duloxetine inhibits serotonin and norepinephrine reuptake at all dos- es. It is extensively metabolized in the liver to numerous metabolites. Duloxetine should not be administered to patients with hepatic insuffi - ciency. Metabolites are excreted in the urine, and the use of duloxetine is not recommended in patients with end-stage renal disease. Food delays the absorption of the drug. The half-life is approximately 12 hours. GI side eff ects are common with duloxetine, including nausea, dry mouth, and constipation. Diarrhea and vomiting are seen less often. Insomnia, dizziness, somnolence, and sweating are also seen. Sexual dysfunction also occurs along with the possible risk for an increase in either blood pressure or heart rate. Duloxetine is a moderate inhibitor of CYP2D6 and CYP3A4 isoenzymes.