**V. ATYPICAL ANTIDEPRESSANTS**

The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes bupropion [byoo-PROE-pee- on], mirtazapine [mir-TAZ-a-peen], nefazodone [nef-AY-zoe-done], and tra- zodone [TRAZ-oh-done]. They are not any more efficacious than the TCAs or SSRIs, but their side effect profiles are different.

1. **Bupropion**

This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Its short half-life may require more than once-a-day dosing or the administration of an extended-release formulation. Bupropion also assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction, and an increased risk for seizures at high doses. Bupropion is metabolized by the CYP2B6 pathway and is considered to have a rela- tively low risk for drug-drug interactions. The daily dose of bupropion should be within the manufacturer’s recommendations to minimize the risk of seizures that may occur in above recommended doses. Its use should also be avoided in patients at risk for seizures or who have eat- ing disorders (such as bulimia).

1. **Mirtazapine**

This drug enhances serotonin and norepinephrine neurotransmission via mechanisms related to its ability to block presynaptic α2 recep- tors. Additionally, it may owe at least some of its antidepressant activ- ity to its ability to block 5-HT2 receptors. It is a sedative because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual functioning, as do the SSRIs. Increased appetite and weight gain frequently occur (Figure 12.6). Mirtazapine is markedly sedating, which may be an advantage in depressed patients having difficulty sleeping.

**C. Nefazodone and trazodone**

These drugs are weak inhibitors of serotonin reuptake. Their therapeu- tic benefit appears to be related to their ability to block postsynaptic 5-HT2A receptors. With chronic use, these agents may desensitize 5-HT1A presynaptic autoreceptors and, thereby, increase serotonin release. Both agents are sedating, probably because of their potent H1-blocking activity. Trazodone has been associated with causing priapism, and nefazodone has been associated with the risk for hepatotoxicity. Both agents also have mild to moderate α1-receptor antagonism contribut- ing to orthostasis and dizziness.

**VI. TRICYCLIC ANTIDEPRESSANTS**

The TCAs block norepinephrine and serotonin reuptake into the neuron and, thus, if discovered today, might have been referred to as SNRIs except for their differences in adverse effects relative to this newer class of antidepres- sants. The TCAs include the tertiary amines imipramine [ee-MIP-ra-meen] (the prototype drug), amitriptyline [aye-mee-TRIP-ti-leen], clomipramine [kloe-MIP-ra-meen], doxepin [DOX-e-pin], and trimipramine [trye-MIP-ra- meen]. The TCAs also include the secondary amines desipramine [dess-IP-ra- meen] and nortriptyline [nor-TRIP-ti-leen] (the respective N-demethylated metabolites of imipramine and amitriptyline) and protriptyline [proe-TRIP- ti-leen]. Maprotiline [ma-PROE-ti-leen] and amoxapine [a-MOX-a-peen] are related “tetracyclic” antidepressant agents and are commonly included in the general class of TCAs. All have similar therapeutic effi cacy, and the specifi c choice of drug may depend on such issues as patient tolerance to side eff ects, prior response, preexisting medical conditions, and duration of action. Patients who do not respond to one TCA may benefi t from a diff erent drug in this group. These drugs are a valuable alternative for patients who do not respond to SSRIs. **A. 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 concen- trations, they do not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant eff ects. Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake.

2. **Blocking of receptors**: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors (see Figure 12.3). It is not known if any of these actions produce TCAs’ therapeutic benefi t. However, actions at these receptors are likely responsible for many of the adverse eff ects of the TCAs. Amoxapine also blocks 5-HT2 and D2 receptors.

**B. Actions**

The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70 percent of indi- viduals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer (see Figure 12.3). These drugs do not com- monly produce CNS stimulation or mood elevation in normal individu- als. Physical and psychological dependence has been rarely reported, however, this necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound eff ects. These drugs, like all of the antidepressants, can be used for prolonged treatment of depression.

1. **Therapeutic uses**

The TCAs are eff ective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. 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. At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems. The TCAs, particularly ami- triptyline, have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of the pain is unclear. Low doses of TCAs, especially doxepin, can be used to treat insomnia.

1. **Pharmacokinetics**

 TCAs are well absorbed upon oral administration. Because of their lipo- philic nature, they are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have variable half- lives (for example, 4 to 17 hours for imipra mine). As a result of their variable fi rst-pass metabolism in the liver, TCAs have low and inconsis- tent bioavailability. Therefore, the patient’s response and plasma levels can be used to adjust dosage. The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerabil- ity, unless relapse occurs. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

1. **Adverse effects**

Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma (Figure 12.7). These agents also affect cardiac conduction similarly to quinidine, which may precipitate life-threatening arrhythmias should an overdose of one of these drugs be taken. The TCAs also block α-adrenergic receptors, causing orthos- tatic hypotension, dizziness, and reflex tachycardia. In clinical practice, this is the most serious problem in elderly adults. Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension. Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block hista- mine H1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs. 1. Precautions : TCAs (like all antidepressants) should be used with cau- tion in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to six- fold the maximal daily dose of imipramine can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 12.8. The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyper- plasia, epilepsy, and preexisting arrhythmias. Caution should be exer- cised with their use in very young or very old patients as well.

VII**. 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 functions as a “safety valve” to oxidatively deaminate and inactivate any excess neuro- transmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibi- tors (MAOIs) may irreversibly or reversibly inactivate the enzyme, permit- ting 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 action of these drugs. Four MAOIs are currently available for treatment of depres- sion: phenelzine [FEN-el-zeen]; tranylcypromine [tran-il-SIP-roe-meen]; iso- carboxazid [eye-soe-car-BOX-ih-zid]; and the agent that was prior-approved for 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 restrictions required of patients taking them.

1. **Mechanism of action**

Most MAOIs, such as phenelzine, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diff usion of excess neurotransmitter into the synap- tic space (Figure 12.9). These drugs inhibit not only MAO in the brain, but also MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug-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 fi rst-pass metabolism.

1. **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 amphet- amine-like stimulant eff ect that may produce agitation or insomnia.

1. **Therapeutic uses**

 The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety. Patients with low psychomotor activity may benefi t from the stimulant properties of the MAOIs. These drugs are also useful in the treatment of phobic states. A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs. Atypical depression is characterized by labile mood, rejection sensitivity, and appetite disorders. Because of their risk for drug-drug and drug-food interactions, the MAOIs are con- sidered to be last-line agents in many treatment venues.

1. **Pharmacokinetics**

 These drugs are well absorbed after oral administration, but antidepres- sant eff ects require at least 2 to 4 weeks of treatment. Enzyme regenera- tion, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepres- sant agents, a minimum of 2 weeks of delay must be allowed after termi- nation of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are metabolized and excreted rapidly in urine.

1. **Adverse eff ects**

Severe and often unpredictable side eff ects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs. For exam- ple, tyramine, which is contained in certain foods, such as aged chees- es and meats, chicken liver, pickled or smoked fi sh (such as anchovies or herring), and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from 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 head- ache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhyth- mias, seizures, and, possibly, stroke. Patients must, therefore, be edu- cated to avoid tyramine-containing foods. Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension.

[Note: Treatment with MAOIs may be dangerous in severely depressed patients with suicidal tendencies. Purposeful consumption of tyramine-containing foods is a possibility.] Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria, and constipation. MAOIs and SSRIs should not be coadministered due to the risk of the life-threatening “serotonin syndrome.” Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of fluoxetine, which should be discontinued at least 6 weeks before a MAOI is initiated. Combination of MAOIs and bupropion can produce seizures. Figure 12.10 summarizes the side effects of the anti- depressant drugs.

**VIII. TREATMENT OF MANIA AND BIPOLAR DISORDER**

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

1. **Lithium**

 Lithium salts are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes and, thus, are consid- ered “mood stabilizers.” Lithium is effective in treating 60 to 80 percent of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with lithium salts, the mode of action is unknown. [Note: Lithium is believed to attenuate signaling via recep- tors coupled to the phosphatidylinositol bisphosphate (PIP2) second- messenger system. Lithium interferes with the resynthesis (recycling) of PIP2, leading to its relative depletion in neuronal membranes of the CNS. PIP2 levels in peripheral membranes are unaffected by lithium.] Lithium is given orally, and the ion is excreted by the kidney. Lithium salts can be toxic. Their safety factor and therapeutic index are extremely low and comparable to those of digoxin. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give lithium with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Adverse effects due to higher plasma levels may include ataxia, slurred speech, coarse tremors, confusion, and con- vulsions. [Note: The diabetes insipidus that results from taking lithium can be treated with amiloride.] Thyroid function may be decreased and should be monitored. Lithium causes no noticeable effect on normal individuals. It is not a sedative, euphoriant, or depressant. B. Other drugs Several antiepileptic drugs, including, most notably, carbamazepine, valproic acid, and lamotrigine, have been identified and FDA approved as mood stabilizers, being used successfully in the treatment of bipolar disorder. Other agents that may improve manic symptoms include the older (for example, chlorpromazine and haloperidol) and newer antipsy- chotics. The atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, and quetiapine) have also received FDA approv- al for the management of mania. Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania. (See the respective chapters on these psychotropics for a more detailed description).