Bupropion, commonly known by the brand name Wellbutrin, is an antidepressant and smoking cessation aid. In treating depression, presumptively bupropion’s action is facilitated by enhancing neurotransmission of the neurotransmitters dopamine and norepinephrine in the brain, but its exact mechanism of action is unclear. The hypothesis for bupropion’s mechanism of action is by inhibition of both dopamine and norepinephrine reuptake. After release of these neurotransmitters from their neurons, dopamine and norepinephrine are transported back into their nerve cells. The inhibition of the transport mechanism by bupropion on these neurotransmitters hence increases their levels in surrounding neurons, thus facilitating neurotransmission. Bupropion has little or no action on reuptake of serotonin like the selective serotonin reuptake inhibitor, such as fluoxetine.

It is postulated that depression and other neuropsychiatric disorders (e.g., anxiety) may be caused by low levels of the neurotransmitters serotonin, norepinephrine, or dopamine in the brain. These neurotransmitters are also known as monoamines because they share a common group (an amine group) in their chemical structures. The theory posits that deficiency in one or another of these monoamine neu-
Antidepressants is involved in the etiology of depression. This theory—that depression is due to deficiency of monoamine neurotransmitters—is known as the **monoamine hypothesis**.

The theory, however, is ineffective in explaining the cause of depression because studies have failed to consistently correlate depression with deficiency of neurotransmitters. The cause of depression is not simply deficiency of monoamine neurotransmitters, but it may be found in other areas of biology, such as genetics.

Most antidepressants increase the levels of one or more neurotransmitters by their varied mechanisms of action. The action of antidepressants in neurotransmission is almost immediate, but clinical response is usually more gradual. Patients may see clinical improvement within the first 2 weeks of therapy, with further improvements in their symptoms over the course of several weeks.

Bupropion is also an effective smoking cessation aid. Nicotine from tobacco products stimulates receptors (sites on the surface of neurons where chemical messengers couple with the cell to produce a signal) on nerve cells in the brain called acetylcholine neurons. By blocking these receptors, bupropion blunts the stimulation of nicotine, decreasing the craving for smoking.

Bupropion comes in various formulations and brands. It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder and smoking cessation. However, bupropion is used for different types of treatments, some of which have not received FDA approval. The use of a medication for its FDA-approved indications is called its **labeled use**. In clinical practice, however, practitioners may prescribe medications for **unapproved indications** (off-label uses) when published clinical studies indicate the efficacy, and the standards of medical practice support the safety, of those treatments. Bupropion’s off-label uses, for example, include treatment of adults and children with attention-deficit/hyperactivity disorder, nerve pain (neuropathy), and premenstrual dysphoric disorder.

**Dosing Information**

Bupropion is available in three formulations: immediate-release (Wellbutrin), sustained-release (Wellbutrin SR), and 24-hour extended-release (Wellbutrin XL, Forfivo XL, and Aplenzin) tablets. All three contain the same active ingredient but differ in the rate of absorption and duration of action. The immediate-release tablet requires dosing two or three times daily, whereas the sustained-release and the extended-release tablets can be dosed twice a day and once a day, respectively. Bupropion for smoking cessation comes in 12-hour extended-release tablets and is marketed under the brand name Zyban.

For treatment of depression, the maximum recommended dosage is 450 mg/day with immediate-release bupropion and 400 mg/day and 300 mg/day with sustained-release and extended-release bupropion, respectively. Aplenzin is formulated with hydrobromide salt, as opposed to bupropion HCl for other brands and generics, but the active drug is bupropion. Aplenzin’s maximum recommended dosage is 522 mg/day. For smoking cessation, the maximum recommended dosage for Zyban is 300 mg/day.

**Common Side Effects**

Bupropion has a favorable side-effect profile and is generally well tolerated. It neither affects appetite nor induces weight gain. Bupropion is not known to cause sexual dysfunction, and it is an alternative antidepressant available for practitioners when patients experience sexual side effects from other antidepressants. The most common side effects associated with bupropion are dry mouth, nervousness, tremors, and insomnia. Patients usually develop tolerance to these side effects after 1–2 weeks of therapy.

**Adverse Reactions and Precautions**

There is a risk of seizures with bupropion at high doses. The risk of seizures is dose related with immediate-release bupropion, and the rate increases tenfold when the total daily dosage is greater than 450 mg/day.
Also, to minimize risk of seizures, when immediate-release bupropion is administered three times a day, each single dose should not exceed 150 mg. The rate of seizures is lower with sustained- and extended-release bupropion, but nevertheless, seizures may still occur with higher dosages. To minimize the risk of seizures, the maximum recommended dosage should not be exceeded (see “Dosing Information”).

The concurrent use of stimulants, alcohol, and cocaine with bupropion may also increase the risk of seizures. Patients with a history of seizures, head injury, bulimia nervosa, or anorexia nervosa should not take bupropion because these conditions may enhance the risk of seizures, even at recommended dosages.

Bupropion may cause weight loss, which may be desirable for some patients, but in patients for whom weight loss is not desirable, such as a frail elderly patient or a small pediatric patient, their weight should be monitored while taking bupropion.

Patients should not discontinue bupropion without first consulting their practitioner. It should be discontinued gradually by tapering the dose. Stopping the medication abruptly, especially after taking it regularly for long periods, may trigger discontinuation (withdrawal) symptoms, including headaches, nausea, vomiting, diarrhea, insomnia, tremors, tingling of hands and/or legs (paresthesia), and possibly other unpleasant symptoms.

With antidepressant therapy, there may be risks of suicidal thinking and behavior in children and adolescents with depressive disorders and other neuropsychiatric disorders. The risk with antidepressants is age related, associated with patients younger than age 24 years, and higher during the early course of treatment. The FDA advises practitioners to exercise caution when treating pediatric patients and added warnings of suicidal risk to the labeling for all antidepressants.

**RISK DURING PREGNANCY AND BREAST-FEEDING**

Bupropion crosses the placenta from maternal circulation. On the basis of outcome studies of more than 1,000 women who were exposed to bupropion during pregnancy, including the first trimester, it was concluded that bupropion did not increase risk of teratogenicity (congenital malformations). When looking specifically at congenital heart defects, study findings of babies with bupropion exposure during the first trimester suggest they may be more likely to have some heart problems when compared with babies who were not exposed. However, the studies were limited by the small number of cases, and the evidence is inconclusive in associating any risk from bupropion.

It is not recommended that women take bupropion during pregnancy if possible. Use of bupropion during pregnancy may be justified if discontinuing the antidepressant poses greater known risk to the mother than the potential risk to the fetus. Some women may experience a relapse of depression if they stop their antidepressant, and relapse may pose a greater risk to the baby. Women of childbearing age should be cautioned of the potential hazards to the fetus if they become pregnant while taking this drug.

Nursing mothers should not take bupropion because both the drug and its metabolite pass into breast milk and can be ingested by the baby. If stopping the drug is not an alternative, breast-feeding should not be started or should be discontinued.

**POTENTIAL DRUG INTERACTIONS**

Bupropion, like most drugs, is broken down (metabolized) in the liver, and some drugs may interfere with bupropion’s metabolism. However, bupropion may play a larger role in inhibiting the metabolism of other medications, including certain antidepressants (e.g., paroxetine, fluoxetine, desipramine, nortriptyline), antipsychotics (e.g., haloperidol, thioridazine, aripiprazole), and certain antiarrhythmic medications (e.g., propafenone, flecainide). When any of these medications are taken concomitantly with bupropion, the inhibition of their metabolism by bupropion may significantly elevate their blood levels and increase the risk of toxicity.

Antidepressants known as **monoamine oxidase inhibitors** (MAOIs; e.g., phenelzine, selegiline, isocarboxazid, and tranylcypromine) are contraindicated with bupropion. A washout period of 14 days
should be allowed when stopping an MAOI before starting bupropion and similarly when stopping bupropion before introducing an MAOI. The combination of an MAOI with bupropion may precipitate dangerously elevated blood pressure known as a **hypertensive crisis**.

Drugs that lower the seizure threshold can enhance the risk of seizure when combined with bupropion. Drugs such as clozapine, clomipramine, and theophylline can lower the seizure threshold and should be used cautiously with bupropion. Alcohol in excessive amounts (e.g., binge drinking) may also lower the seizure threshold, and patients should minimize or avoid alcohol use while taking bupropion. Moreover, bupropion may lower alcohol tolerance in some patients, who were reported have adverse neuropsychiatric episodes as a result of drinking while taking bupropion.

**OVERDOSE**

Relative to some other antidepressants, such as tricyclic antidepressants (e.g., amitriptyline), bupropion is safer in overdose. In most cases of bupropion overdose, the most serious reactions were seizures, and patients generally recovered without significant aftereffects. When other drugs are involved with bupropion, overdose may present much more serious complications and is often fatal.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought along as well because the information on the prescription label can be helpful to the treating practitioner in determining the number of pills ingested.

The American Association of Poison Control Centers (www.aapcc.org) can also be contacted via their helpline at 1-800-222-1222, and they can provide the location of the local poison center.

**TREATMENT SUMMARY**

The risk of suicide is inherent in depression and may persist until the individual responds to treatment. After starting or changing antidepressant therapy, the person, especially a child or adolescent, should be closely observed for signs of worsening depression, and the family or caregiver should communicate any concerns to the practitioner.

- **Warning:** Always let your practitioner or a family member know if you have suicidal thoughts. Notify your practitioner whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.
- Do not discontinue bupropion without consulting your practitioner. Bupropion should be discontinued gradually by tapering the dose. Stopping the medication abruptly may trigger discontinuation (withdrawal) symptoms.
- If you are taking bupropion in divided doses, do not take your last dose close to bedtime. If you have difficulty with insomnia, take your evening dose earlier in the afternoon.
- If you miss a dose, take it as soon as possible. If it is close to the next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.
- Do not crush or cut the sustained-release or extended-release tablets; swallow them whole.
- Bupropion may be taken with or without food.
- Avoid alcohol while taking bupropion because alcohol can enhance central nervous system side effects.
- Be aware that bupropion is also prescribed for smoking cessation under the brand name Zyban. Be sure your practitioner is aware of your other medications, so that bupropion is not duplicated by two different practitioners.
- Keep in mind that the benefits of bupropion may not be noticeable right away. It may take weeks before the benefits from bupropion are fully achieved.
• Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
• Keep your medication out of the reach of children.

If you have any questions about your medication, consult your medical practitioner or pharmacist.