### Bupropion

#### Therapeutics

**Brands**
- Wellbutrin, Wellbutrin SR, Wellbutrin XL
- Zyban
- Aplenzin

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine reuptake inhibitor and releaser (D-RIRe)
- NDRI (norepinephrine dopamine reuptake inhibitor); antidepressant; smoking cessation treatment

**Commonly Prescribed for**
- Major depressive disorder (bupropion, bupropion SR, and bupropion XL)
- Seasonal affective disorder (bupropion XL)
- Nicotine addiction (bupropion SR)
- Bipolar depression
- Attention deficit /hyperactivity disorder (ADHD)
- Sexual dysfunction

#### How the Drug Works

- Boosts neurotransmitters norepinephrine/noradrenaline and dopamine
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing norepinephrine neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, bupropion can increase dopamine neurotransmission in this part of the brain
- Blocks dopamine reuptake pump (dopamine transporter), presumably increasing dopaminergic neurotransmission

#### How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

#### If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Treatment for nicotine addiction should consist of a single treatment for 6 weeks

#### If It Doesn’t Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer, although this may be a less frequent problem with bupropion than with other antidepressants

#### Best Augmenting Combos

<table>
<thead>
<tr>
<th>For Partial Response or Treatment Resistance</th>
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<tbody>
<tr>
<td>Trazodone for residual insomnia</td>
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<tr>
<td>Benzodiazepines for residual anxiety</td>
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<tr>
<td>Can be added to SSRIs to reverse SSRI-induced sexual dysfunction, SSRI-induced apathy (use combinations of antidepressants with caution as this may...</td>
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activate bipolar disorder and suicidal ideation)

- Can be added to SSRIs to treat partial responders
- Often used as an augmenting agent to mood stabilizers and/or atypical antipsychotics in bipolar depression
- Mood stabilizers or atypical antipsychotics can also be added to bupropion for psychotic depression or treatment-resistant depression
- Hypnotics for insomnia
- Mirtazapine, modafinil, atomoxetine (add with caution and at lower doses since bupropion could theoretically raise atomoxetine levels) both for residual symptoms of depression and attention deficit disorder

Tests
- Recommended to assess blood pressure at baseline and periodically during treatment

SIDE EFFECTS

How Drug Causes Side Effects
- Side effects are probably caused in part by actions of norepinephrine and dopamine in brain areas with undesired effects (e.g., insomnia, tremor, agitation, headache, dizziness)
- Side effects are probably also caused in part by actions of norepinephrine in the periphery with undesired effects (e.g., sympathetic and parasympathetic effects such as dry mouth, constipation, nausea, anorexia, sweating)
- Most side effects are immediate but often go away with time

Notable Side Effects
- Dry mouth, constipation, nausea, weight loss, anorexia, myalgia
- Insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus
- Sweating, rash
- Hypertension

Life-Threatening or Dangerous Side Effects
- Rare seizures (higher incidence for immediate-release than for sustained-release; risk increases with doses above the recommended maximums; risk increases for patients with predisposing factors)
- Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported
- Hypomania (more likely in bipolar patients but perhaps less common than with some other antidepressants)
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain
- Reported but not expected

Sedation
- Patients may experience weight loss

What to Do About Side Effects
- Wait
- Wait
- Keep dose as low as possible
- Take no later than mid-afternoon to avoid insomnia
- Switch to another drug

Best Augmenting Agents for Side Effects
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for drug-induced insomnia
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines or buspirone for drug-induced anxiety, agitation
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially
a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of bupropion

Dosing Tips
- XL formulation has replaced immediate release and SR formulations as the preferred option
- XL is best dosed once a day, whereas SR is best dosed twice daily, and immediate release is best dosed 3 times daily
- Dosing higher than 450 mg/day (400 mg/day SR) increases seizure risk
- Patients who do not respond to 450 mg/day should discontinue use or get blood levels of bupropion and its major active metabolite 6-hydroxy-bupropion
- If levels of parent drug and active metabolite are low despite dosing at 450 mg/day, experts can prudently increase dosing beyond the therapeutic range while monitoring closely, informing the patient of the potential risk of seizures and weighing risk/benefit ratios in difficult-to-treat patients
- When used for bipolar depression, it is usually as an augmenting agent to mood stabilizers, lithium, and/or atypical antipsychotics
- For smoking cessation, may be used in conjunction with nicotine replacement therapy
- Do not break or chew SR or XL tablets as this will alter controlled-release properties
- The more anxious and agitated the patient, the lower the starting dose, the slower the titration, and the more likely the need for a concomitant agent such as trazodone or a benzodiazepine
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose
- Rarely lethal; seizures, cardiac disturbances, hallucinations, loss of consciousness

Long-Term Use
- For smoking cessation, treatment for up to 6 months has been found effective
- For depression, treatment up to 1 year has been found to decrease rate of relapse

### Usual Dosage Range
- Bupropion: 225–450 mg in 3 divided doses (maximum single dose 150 mg)
- Bupropion SR: 200–450 mg in 2 divided doses (maximum single dose 200 mg)
- Bupropion XL: 150–450 mg once daily (maximum single dose 450 mg)
- Bupropion hydrobromide: 174–522 mg once daily (maximum single dose 522 mg)

### Dosage Forms
- Bupropion: tablet 75 mg, 100 mg
- Bupropion SR (sustained-release): tablet 100 mg, 150 mg, 200 mg
- Bupropion XL (extended-release): tablet 150 mg, 300 mg, 450 mg
- Bupropion hydrobromide (extended-release): tablet 174 mg, 378 mg, 522 mg

### How to Dose
- Depression: for bupropion immediate-release, dosing should be in divided doses, starting at 75 mg twice daily, increasing to 100 mg twice daily, then to 100 mg 3 times daily; maximum dose 450 mg per day
- Depression: for bupropion SR, initial dose 100 mg twice a day, increase to 150 mg twice a day after at least 3 days; wait 4 weeks or longer to ensure drug effects before increasing dose; maximum dose 400 mg total per day
- Depression: for bupropion XL, initial dose 150 mg once daily in the morning; can increase to 300 mg once daily after 4 days; maximum single dose 450 mg once daily
- Depression: for bupropion hydrobromide, initial dose 174 mg once daily in the morning; can increase to 522 mg administered as a single dose
- Nicotine addiction [for bupropion SR]: initial dose 150 mg/day once a day, increase to 150 mg twice a day after at least 3 days; maximum dose 300 mg/day; bupropion treatment should begin 1–2 weeks before smoking is discontinued

### Overdose
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### Long-Term Use
- For smoking cessation, treatment for up to 6 months has been found effective
- For depression, treatment up to 1 year has been found to decrease rate of relapse
Habit Forming
- No
- Can be abused by individuals who crush and then snort or inject it

How to Stop
- Tapering is prudent to avoid withdrawal effects, but no well-documented tolerance, dependence, or withdrawal reactions

Pharmacokinetics
- Inhibits CYP450 2D6
- Parent half-life 10–14 hours
- Metabolite half-life 20–27 hours
- Food does not affect absorption

Drug Interactions
- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to bupropion
- Use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert)
- There is increased risk of hypertensive reaction if bupropion is used in conjunction with MAOIs or other drugs that increase norepinephrine
- There may be an increased risk of hypertension if bupropion is combined with nicotine replacement therapy
- Via CYP450 2D6 inhibition, bupropion could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, bupropion could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

Other Warnings/Precautions
- Use cautiously with other drugs that increase seizure risk (TCAs, lithium, phenothiazines, thioxanthenes, some antipsychotics)
- Bupropion should be used with caution in patients taking levodopa or amantadine, as these agents can potentially enhance dopamine neurotransmission and be activating
- Do not use if patient has severe insomnia
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Discontinuing smoking may lead to pharmacokinetic or pharmacodynamic changes in other drugs the patient is taking, which could potentially require dose adjustment

Do Not Use
- Zyban or Aplenzin in combination with each other or with any formulation of Wellbutrin
- If patient has history of seizures
- If patient is anorexic or bulimic, either currently or in the past, but see Pearls
- If patient is abruptly discontinuing alcohol, sedative use, or anticonvulsant medication
- If patient has had recent head injury
- If patient has a nervous system tumor
- If patient is taking an MAOI (except as noted under Drug Interactions)
- If patient is taking thioridazine
- If there is a proven allergy to bupropion

Renal Impairment
- Lower initial dose, perhaps give less frequently
- Drug concentration may be increased
- Patient should be monitored closely

Hepatic Impairment
- Lower initial dose, perhaps give less frequently
- Patient should be monitored closely
• In severe hepatic cirrhosis, bupropion XL should be administered at no more than 150 mg every other day

**Cardiac Impairment**
- Limited available data
- Evidence of rise in supine blood pressure
- Use with caution

**Elderly**
- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established
- May be used for ADHD in children or adolescents
- May be used for smoking cessation in adolescents
- Preliminary research suggests efficacy in comorbid depression and ADHD
- Dosage may follow adult pattern for adolescents
- Children may require lower doses initially, with a maximum dose of 300 mg/day

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Epidemiological studies do not indicate increased risk of congenital malformations overall or of cardiovascular malformations
- In animal studies, no clear evidence of teratogenicity has been observed; however, slightly increased incidences of fetal malformations and skeletal variations were observed in rabbit studies at doses approximately equal to and greater than the maximum recommended human doses, and greater and decreased fetal weights were observed in rat studies at doses greater than the maximum recommended human doses
- Pregnant women wishing to stop smoking may consider behavioral therapy before pharmacotherapy
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

**Breast Feeding**
- Some drug is found in mother’s breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

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THE ART OF PSYCHOPHARMACOLOGY

**Potential Advantages**
- Retarded depression
- Atypical depression
- Bipolar depression
- Patients concerned about sexual dysfunction
- Patients concerned about weight gain

**Potential Disadvantages**
- Patients experiencing weight loss associated with their depression
- Patients who are excessively activated

**Primary Target Symptoms**
- Depressed mood
- Sleep disturbance, especially hypersomnia
- Cravings associated with nicotine withdrawal
- Cognitive functioning

**Pearls**
- ✽ May be effective if SSRIs have failed or for SSRI “poop-out”
- ✽ Less likely to produce hypomania than some other antidepressants
- ✽ May improve cognitive slowing/pseudodementia
- ✽ Reduces hypersomnia and fatigue
- Approved to help reduce craving during smoking cessation
- Anecdotal use in attention deficit disorder
- May cause sexual dysfunction only infrequently
- May exacerbate tics
- Bupropion may not be as effective in anxiety disorders as many other antidepressants
- Prohibition for use in eating disorders due to increased risk of seizures is related to past observations when bupropion immediate-release was dosed at especially high levels to low body weight patients with active anorexia nervosa
- Current practice suggests that patients of normal BMI without additional risk factors for seizures can benefit from bupropion, especially if given prudent doses of the XL formulation; such treatment should be administered by experts, and patients should be monitored closely and informed of the potential risks
- Recently approved hydrobromide salt formulation of bupropion may facilitate high dosing for difficult-to-treat patients, as it allows administration of single-pill doses up to 450 mg equivalency to bupropion hydrochloride salt (522 mg tablet), unlike bupropion hydrochloride controlled-release formulations for which the biggest dose in a single pill is 300 mg
- As bromide salts have anticonvulsant properties, hydrobromide salts of bupropion could theoretically reduce risk of seizures, but this has not been proven
- The active enantiomer of the principal active metabolite [(+)-6-hydroxy-bupropion] is in clinical development as a novel antidepressant
- The combination of bupropion and naltrexone has demonstrated efficacy as a treatment for obesity and is currently being evaluated in a long-term study to assess the cardiovascular health outcomes of this treatment
- Phase II trials of the combination of bupropion and zonisamide for the treatment of obesity have been completed

**Suggested Reading**


