

# Bupropion

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## Bupropion

**Primary Disciplinary Field(s):** Pharmacology, Psychiatry, Neuropharmacology

### 1. Core Definition

Bupropion is classified as an **atypical antidepressant** medication, belonging to the aminoketone class of drugs, and is pharmacologically distinct from conventional agents such as selective serotonin reuptake inhibitors (SSRIs). It is widely utilized in clinical practice under brand names like Wellbutrin for the treatment of major depressive disorder (MDD) and is equally prominent as a dedicated smoking cessation aid, marketed as Zyban. Its unique mechanism of action establishes it as a critical alternative in various complex clinical contexts.

The foundational mechanism of bupropion is its function as a **norepinephrine-dopamine reuptake inhibitor (NDRI)**. This action involves blocking the reuptake mechanisms for norepinephrine and dopamine, thereby increasing the synaptic concentrations of these two key neurotransmitters in the brain. Since these neurotransmitters are crucial for regulating mood, motivation, reward, and energy levels, this augmentation underpins its efficacy in combating core depressive symptoms, such as anhedonia and low energy, as well as diminishing nicotine cravings.

Beyond its primary indications for MDD and nicotine dependence, bupropion is frequently prescribed off-label for several other conditions. These include the management of attention deficit hyperactivity disorder (ADHD), particularly when traditional stimulant treatments are contraindicated or poorly tolerated. Furthermore, its profile is advantageous in treating depressive episodes associated with **bipolar disorder**, often favored due to its comparatively lower documented risk of inducing a manic switch compared to other classes of antidepressants.

### 2. Etymology and Historical Development

Bupropion was first synthesized in 1974 by Burroughs Wellcome, a pharmaceutical research entity that is now part of GlaxoSmithKline. Initially identified as Amfebutamone, its chemical structure, an aminoketone, immediately distinguished it from the prevailing antidepressant classes of the era, such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). The drug received its initial approval from the U.S. Food and Drug Administration (FDA) in 1985 for the treatment of major depressive disorder, marketed as Wellbutrin .

Despite its initial promise, bupropion faced a significant setback shortly after its launch. Concerns over a dose-dependent increase in the risk of seizures led to its temporary withdrawal from the market in 1986. This crisis mandated rigorous reformulation and the establishment of safer, lower dosing guidelines. A pivotal moment in its history occurred with its successful reintroduction in

1989, featuring new sustained-release (SR) and extended-release (XL) formulations. These novel delivery systems effectively lowered the peak plasma concentration of the drug, which significantly mitigated the risk of seizures and enhanced its overall tolerability and clinical utility .

The drug's therapeutic scope expanded critically in the 1990s following clinical trials that confirmed its effectiveness in assisting individuals to quit smoking. Based on these findings, bupropion received a secondary FDA approval in 1997 specifically for smoking cessation, marketed under the brand name Zyban . This established bupropion as a cornerstone non-nicotine pharmacological intervention for nicotine dependence, significantly broadening its public health impact.

### 3. Key Characteristics and Mechanism of Action

The primary mechanism underlying bupropion's therapeutic effects is the selective inhibition of neuronal reuptake of norepinephrine and dopamine in the central nervous system. This is achieved by blocking the respective transporters--the **Norepinephrine Transporter (NET)** and the **Dopamine Transporter (DAT)**. By preventing the rapid clearance of these neurotransmitters from the synaptic cleft, bupropion effectively amplifies noradrenergic and dopaminergic neurotransmission. This enhanced signaling is considered the biological basis for both its antidepressant properties and its ability to alleviate withdrawal symptoms associated with nicotine dependence .

A distinctive characteristic of bupropion is its minimal interaction with the serotonin system. Unlike most conventional antidepressants, it has negligible effects on serotonin reuptake, as well as minimal affinity for histaminergic, cholinergic, or adrenergic receptors. Consequently, it avoids many of the common side effects associated with serotonergic drugs, such as sexual dysfunction, unwanted weight gain, and general sedation. This unique profile positions bupropion as an activating antidepressant, making it particularly valuable for patients suffering from fatigue or psychomotor slowing.

Bupropion is typically administered orally and undergoes extensive hepatic metabolism, primarily facilitated by the cytochrome P450 2B6 (CYP2B6) enzyme. This process generates several active metabolites that contribute to the drug's overall pharmacological effects. Clinical dosing flexibility is ensured by the availability of various formulations, including immediate-release (IR), sustained-release (SR), and extended-release (XL). The XL formulation is particularly significant, as it allows for convenient, once-daily administration, which often promotes better patient adherence compared to the multiple daily dosing required by the IR formulation.

### 4. Therapeutic Significance and Impact

The introduction of bupropion significantly diversified the treatment landscape for mood disorders, providing a crucial option for patients who fail to respond to, or cannot tolerate, serotonergic

antidepressant agents. Its unique dopaminergic activity is highly effective in treating depressive symptoms specifically linked to dopamine dysregulation, such as marked anhedonia (loss of pleasure), motivational deficits, and poor concentration. This targeted action allows clinicians to tailor treatment more precisely to the patient's symptom profile .

In the domain of public health, bupropion has had a profound impact through its use in **smoking cessation programs**. As a non-nicotine pharmacological aid, it effectively targets the neurobiological pathways involved in addiction. It works to reduce both the psychological urge to smoke and the severity of physical nicotine withdrawal symptoms, including anxiety, irritability, and difficulties in concentration. By serving as a cornerstone treatment in comprehensive smoking cessation strategies, bupropion has contributed substantially to improved rates of quitting and overall reduction in tobacco-related morbidity and mortality.

Moreover, bupropion offers significant benefits in managing patients with comorbid conditions. Because it typically does not cause the weight gain or sexual dysfunction often seen with other antidepressants, it is an optimal choice for patients dealing with coexisting obesity or metabolic syndrome, or for those for whom maintaining sexual function is a high priority. Its acknowledged efficacy in addressing attentional deficits also supports its off-label use in individuals suffering from both depression and ADHD, demonstrating its versatility in complex neuropsychiatric care.

## 5. Adverse Effects and Contraindications

While generally well-tolerated, bupropion treatment requires careful patient selection and monitoring due to potential adverse effects. The most frequently reported adverse effects include insomnia, which can often be mitigated by administering the final daily dose early in the afternoon, along with dry mouth, headache, dizziness, nausea, and constipation. Some patients may also experience increased agitation, anxiety, or confusion, particularly early in the treatment course.

The most serious risk associated with bupropion is a dose-dependent increase in the incidence of **seizures**. To minimize this risk, strict adherence to maximum daily dosing guidelines and careful dose titration are mandatory. The seizure threshold is significantly lowered in certain groups, making bupropion strictly contraindicated in patients with a history of seizure disorders, those with a current or prior diagnosis of **anorexia nervosa or bulimia nervosa**, or individuals undergoing abrupt discontinuation of alcohol or sedating benzodiazepines.

Furthermore, consistent with all classes of antidepressant medications, bupropion carries a mandatory FDA **black box warning** regarding an elevated risk of suicidal thoughts and behaviors in children, adolescents, and young adults, especially during initial therapy or dose adjustments . Bupropion must also not be administered concurrently with Monoamine Oxidase Inhibitors (MAOIs) or used within 14 days of discontinuing an MAOI, due to the critical and potentially life-threatening risk of causing a hypertensive crisis.

## Further Reading

Wellbutrin SR (bupropion hydrochloride extended-release tablets) Prescribing Information. U.S. Food and Drug Administration.

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