



# Bupropion

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**Bupropion** is a medication primarily used as an antidepressant and smoking cessation aid.<sup>[6][7][8]</sup> It is marketed as **Wellbutrin** and **Zyban** among other trade names. It is one of the most frequently prescribed antidepressants in the United States and Canada,<sup>[9]</sup> although in many countries this is an off-label use.<sup>[10]</sup> It is an effective antidepressant on its own, but is also popular as an add-on medication in cases of incomplete response to first-line SSRI antidepressants.<sup>[11]</sup> Bupropion is taken in tablet form and is available only by prescription in most countries.<sup>[9]</sup>

The most important side effect is an increase in risk for epileptic seizures, which caused the drug to be withdrawn from the market for some time and then caused the recommended dosage to be reduced.<sup>[11]</sup> In comparison to many other antidepressants, it does not cause as much weight gain or sexual dysfunction.<sup>[11]</sup> Bupropion acts as a norepinephrine-dopamine reuptake inhibitor (NDRI). It is an atypical antidepressant, different from most commonly prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs).<sup>[10]</sup>

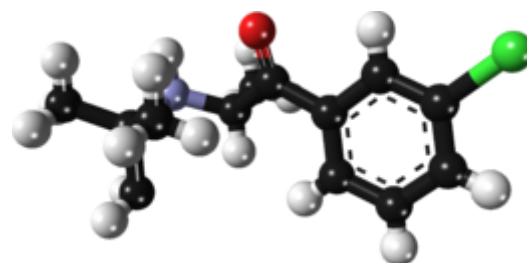
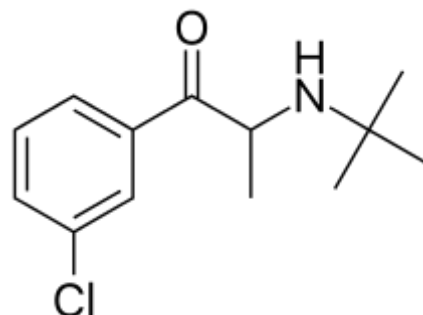
Bupropion is known to affect several different biological targets.<sup>[11][12]</sup> It often is described as a norepinephrine-dopamine reuptake inhibitor (NDRI), and is also a nicotinic antagonist.<sup>[12][13]</sup> However, bupropion does not appear to have significant dopaminergic actions in humans under normal clinical circumstances.<sup>[12][14]</sup> Chemically, bupropion belongs to the class of aminoketones and is similar in structure to stimulants such as cathinone and amfepramone, and to phenethylamines in general.<sup>[11]</sup>

Bupropion was first made by Nariman Mehta and patented by Burroughs Wellcome in 1969, which later became part of what is now GlaxoSmithKline. It was first approved for medical use in the United States in 1989. It was originally called by the generic name amfebutamone, before being renamed in 2000.<sup>[15]</sup>

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## Bupropion



1 : 1 mixture (racemate)

### Clinical data

<b>Pronunciation</b>	<span><span>/<span><span>ˈ</span><span>b</span><span>j</span><span>uː</span><span>ˈ</span><span>p</span><span>r</span><span>oʊ</span><span>.</span><span>p</span><span>i</span><span>.</span><span>ɒ</span><span>n</span></span>/</span></span> <i>bew-<b>PROH</b>-pee-on</i>
<b>Trade names</b>	Wellbutrin, Elontril, Zyban
<b>AHFS/Drugs.com</b>	Monograph ( <a href="https://www.drugs.com/monograph/bupropion-hydrochloride.html">https://www.drugs.com/monograph/bupropion-hydrochloride.html</a> )
<b>MedlinePlus</b>	a695033 ( <a href="https://medlineplus.gov/druginfo/meds/a695033.html">https://medlineplus.gov/druginfo/meds/a695033.html</a> )
<b>License data</b>	US FDA: Bupropion ( <a href="http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&amp;SearchTerm=Bupropion&amp;SearchType=BasicSearch">http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&amp;SearchTerm=Bupropion&amp;SearchType=BasicSearch</a> )
<b>Pregnancy category</b>	AU: B2 US: C (Risk not ruled out)
<b>Dependence liability</b>	none to very low
<b>Addiction liability</b>	none to very low
<b>Routes of</b>	Medical: oral

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## Medical uses

### Depression

Bupropion is one of the most widely prescribed antidepressants, and the available evidence indicates that it is effective in clinical depression<sup>[16]</sup> — as effective as several other widely prescribed drugs, including fluoxetine (Prozac) and paroxetine (Paxil),<sup>[17]</sup> although trends favoring the efficacy of escitalopram (Lexapro), sertraline (Zoloft) and venlafaxine (Effexor) over bupropion have been observed.<sup>[17]</sup> Mirtazapine (Remeron), on the other hand is significantly more effective than bupropion.<sup>[17]</sup> Bupropion has several features that distinguish it from other antidepressants: for instance, unlike the majority of antidepressants, it does not usually cause sexual dysfunction.<sup>[18]</sup> Bupropion treatment also is not associated with the sleepiness or weight gain that may be produced by other antidepressants.<sup>[19]</sup>

In depressed people who experience symptoms of sleepiness and fatigue, bupropion has been found to be more effective than selective serotonin reuptake inhibitors (SSRIs) in alleviating these symptoms.<sup>[20]</sup> There appears to be a modest advantage for the SSRIs over bupropion in the treatment of anxious depression.<sup>[21]</sup>

<b>administration</b>	Recreational: insufflation, intravenous
<b>ATC code</b>	N06AX12 (WHO ( <a href="http://www.who.no/atc_ddd_index/?code=N06AX12">http://www.who.no/atc_ddd_index/?code=N06AX12</a> ))
<b>Legal status</b>	
<b>Legal status</b>	AU: S4 (Prescription only) CA: R-only UK: POM (Prescription only) US: R-only
<b>Pharmacokinetic data</b>	
<b>Protein binding</b>	84% (bupropion), 77% (hydroxybupropion metabolite), 42% (threohydrobupropion metabolite) <sup>[1]</sup>
<b>Metabolism</b>	Hepatic (mostly CYP2B6-mediated hydroxylation, but with some contributions from CYP1A2, CYP2A6, CYP2C9, CYP3A4, CYP2E1 and CYP2C19) <sup>[1][2][3][4]</sup>
<b>Biological half-life</b>	12–30 hours <sup>[3][5]</sup>
<b>Excretion</b>	Renal (87%; 0.5% unchanged), Faecal (10%) <sup>[1][2][3]</sup>
<b>Identifiers</b>	
<b>IUPAC name</b>	
<b>Synonyms</b>	3-Chloro- <i>N-tert</i> -butyl-β-keto-α-methylphenethylamine; 3-Chloro- <i>N-tert</i> -butylcathinone; bupropion hydrochloride; amfebutamone
<b>CAS Number</b>	34911-55-2 ( <a href="http://www.commonchemistry.org/ChemicalDetail.aspx?ref=34911-55-2">http://www.commonchemistry.org/ChemicalDetail.aspx?ref=34911-55-2</a> ) <span>✗</span>
<b>PubChem (CID)</b>	444 ( <a href="https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=444">https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=444</a> )
<b>IUPHAR/BPS</b>	7135 ( <a href="http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7135">http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7135</a> )

According to surveys, the addition to a prescribed SSRI is a common strategy when people do not respond to the SSRI, even though this is not an officially approved indication.<sup>[22]</sup> The addition of bupropion to an SSRI (most commonly fluoxetine or sertraline) may result in an improvement in some people who have an incomplete response to the first-line antidepressant.<sup>[22]</sup>

Bupropion was approved by the U.S. Food and Drug Administration (FDA), in 2006, for the prevention of seasonal affective disorder.<sup>[23]</sup> In some countries (including Australia, New Zealand and the UK) this is an off-label use.<sup>[24][25]</sup>

## Smoking cessation

The next most common use is as an aid for smoking cessation.<sup>[26][27]</sup> Bupropion reduces the severity of nicotine cravings and withdrawal symptoms.<sup>[28]</sup> Bupropion is helpful for smoking cessation in smokers with no history of depression; thus, the effectiveness of bupropion is not due to its antidepressant effect. A typical bupropion treatment course lasts up to twelve weeks, with the people halting the use of tobacco about ten days into the course. Bupropion approximately doubles the chance of quitting smoking successfully.<sup>[28]</sup> The effectiveness of bupropion is comparable to nicotine replacement therapy, but less effective than varenicline.<sup>[28]</sup>

In Australia and the UK smoking cessation is the only licensed use of bupropion.<sup>[24][25]</sup>

## Attention deficit hyperactivity disorder

Bupropion has been used as a treatment for attention deficit hyperactivity disorder (ADHD) since at least 2004,<sup>[29]</sup> with reports of positive results in both minors and adults.<sup>[30]</sup> In a double-blind study of children, while aggression and hyperactivity as rated by the children's teachers were significantly improved in comparison to placebo, parents and clinicians could not distinguish between the effects of bupropion and placebo.<sup>[30]</sup> The 2007 guideline on the ADHD treatment from American Academy of Child and Adolescent Psychiatry notes that the evidence for bupropion is "far weaker" than for the FDA-approved treatments. Its effect may also be "considerably less than of the approved agents ... Thus it may be prudent for the clinician to recommend a trial of behavior therapy at this point, before moving to these second-line agents."<sup>[31]</sup> Similarly, the Texas Department of State Health Services guideline recommends considering bupropion or a tricyclic antidepressant as a fourth-line treatment after trying two different stimulants and atomoxetine.<sup>[32]</sup>

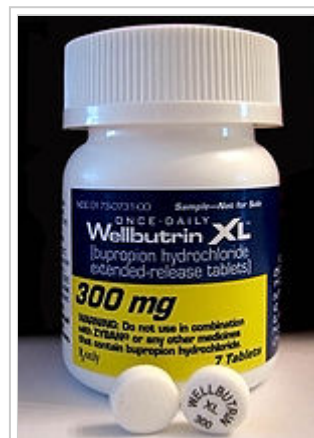
## Sexual dysfunction

<b>DrugBank</b>	DB01156 ( <a href="https://www.drugbank.ca/drugs/DB01156">https://www.drugbank.ca/drugs/DB01156</a> ) ✓
<b>ChemSpider</b>	431 ( <a href="http://www.chemspider.com/Chemical-Structure.431.html">http://www.chemspider.com/Chemical-Structure.431.html</a> ) ✓
<b>UNII</b>	01ZG3TPX31 ( <a href="http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=01ZG3TPX31">http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=01ZG3TPX31</a> ) ✓
<b>KEGG</b>	D07591 ( <a href="http://www.kegg.jp/entry/D07591">http://www.kegg.jp/entry/D07591</a> ) ✓
<b>ChEBI</b>	CHEBI:3219 ( <a href="https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:3219">https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:3219</a> ) ✓
<b>ChEMBL</b>	CHEMBL894 ( <a href="https://www.ebi.ac.uk/chembl/index.php/compound/inspect/CHEMBL894">https://www.ebi.ac.uk/chembl/index.php/compound/inspect/CHEMBL894</a> ) ✓

### Chemical and physical data

<b>Formula</b>	C <sub>13</sub> H <sub>18</sub> ClNO
<b>Molar mass</b>	239.74 g/mol
<b>3D model (Jmol)</b>	Interactive image ( <a href="http://chemapps.stolaf.edu/jmol/jmol.php?model=O%3DC%28C%28C%29NC%28C%29%28C%29C%29C1%3DCCC%3DCCC%28Cl%29%3DC1">http://chemapps.stolaf.edu/jmol/jmol.php?model=O%3DC%28C%28C%29NC%28C%29%28C%29C%29C1%3DCCC%3DCCC%28Cl%29%3DC1</a> )
<b>SMILES</b>	
<b>InChI</b>	

✗✓ (what is this?) (verify)



Wellbutrin XL

Bupropion is one of few antidepressants that do not cause sexual dysfunction.<sup>[33]</sup> A range of studies demonstrate that bupropion not only produces fewer sexual side effects than other antidepressants, but can actually help to alleviate sexual dysfunction.<sup>[34]</sup> According to a survey of psychiatrists, it is the drug of choice for the treatment of SSRI-induced sexual dysfunction, although this is not an indication approved by the U.S. Food and Drug Administration. There have also been a few studies suggesting that bupropion can improve sexual function in women who are not depressed, if they have hypoactive sexual desire disorder (HSDD).<sup>[35]</sup>

## Obesity

Bupropion, when used for treating obesity over a period of 6 to 12 months, may result in weight loss of 2.7 kg over placebo.<sup>[36]</sup> This is not much different from the weight loss produced by several other medications, such as sibutramine or orlistat.<sup>[36]</sup>

It has been studied in combination with naltrexone.<sup>[37]</sup> Concerns from bupropion include an increase in blood pressure and heart rate.<sup>[37]</sup> In September 2014, a combination (bupropion/naltrexone) was approved by the US FDA for the treatment of obesity.<sup>[38]</sup>

## Other uses

There has been controversy about whether it is useful to add an antidepressant such as bupropion to a mood stabilizer in patients with bipolar depression, but recent reviews have concluded that bupropion in this situation does no significant harm and may sometimes give significant benefit.<sup>[39][40]</sup>

Bupropion has shown no effectiveness in the treatment of cocaine dependence, but there is weak evidence that it may be useful in treating methamphetamine dependence.<sup>[41]</sup>

Based on studies indicating that bupropion lowers the level of the inflammatory mediator TNF-alpha, there have been suggestions that it might be useful in treating inflammatory bowel disease or other autoimmune conditions, but very little clinical evidence is available.<sup>[42]</sup>

Bupropion—like other antidepressants, with the exception of duloxetine (Cymbalta)<sup>[43]</sup>—is not effective in treating chronic low back pain.<sup>[44]</sup> It does, however, show some promise in the treatment of neuropathic pain.<sup>[45]</sup>

## Contraindications

The drug label advises that bupropion should not be prescribed to individuals with epilepsy or other conditions that lower the seizure threshold, such as anorexia nervosa, bulimia nervosa, active brain tumors, or concurrent alcohol and/or benzodiazepine use and/or withdrawal. It should be avoided in individuals who are also taking monoamine oxidase inhibitors (MAOIs). When switching from MAOIs to bupropion, it is important to include a washout period of about two weeks between the medications.<sup>[3]</sup> The label recommends that caution should be exercised when treating patients with liver damage, severe kidney disease, and severe hypertension, and in pediatric patients, adolescents and young adults due to the increased risk of suicidal ideation.<sup>[3]</sup>

## Side effects

Epileptic seizures are the most important adverse effect of bupropion. A high incidence of seizures was responsible for the temporary withdrawal of the drug from the market between 1986 and 1989. The risk of seizure is strongly dose-dependent, but also dependent on the preparation. The sustained-release preparation is associated with a seizure incidence of 0.1% at daily dosages of less than 300 mg of bupropion and 0.4% at 300–400 mg.<sup>[46]</sup> The immediate release preparation is associated with a seizure incidence of 0.4% for dosages below 450 mg; the incidence climbs to 5% for dosages between 450–600 mg per day.<sup>[46]</sup> For comparison, the incidence of unprovoked seizure in the general population is 0.07 to 0.09%, and the risk of seizure for a variety of other antidepressants is generally between 0 and 0.6% at recommended dosage levels.<sup>[47]</sup> Clinical depression itself has been reported to increase the occurrence of seizures, and a study examining FDA clinical trial data has suggested that in most cases, low to moderate doses of antidepressants may not actually increase seizure risk at all.<sup>[48]</sup> However, this study also found that bupropion and clomipramine were unique among antidepressants in that they were associated with increased incidence of seizures.<sup>[48]</sup>

The prescribing information notes that hypertension, sometimes severe, was observed in some patients, both with and without pre-existing hypertension. The frequency of this adverse effect was under 1% and not significantly higher than found with placebo.<sup>[3]</sup> A review of the available data carried out in 2008 indicated that bupropion is safe to use in patients with a variety of serious cardiac conditions.<sup>[49]</sup>

In the UK, more than 7,600 reports of suspected adverse reactions were collected in the first two years after bupropion's approval by the Medicines and Healthcare Products Regulatory Agency as part of the Yellow Card Scheme, which monitored side effects. Approximately 540,000 people were treated with bupropion for smoking cessation during that period. The MHRA received 60 reports of "*suspected* [emphasis MHRA's] adverse reactions to Zyban which had a fatal outcome". The agency concluded that "in the majority of cases the individual's underlying condition may provide an alternative explanation."<sup>[50]</sup> This is consistent with a large, 9,300-patient safety study that showed that the mortality of smokers taking bupropion is not higher than the natural mortality of smokers of the same age.<sup>[51]</sup>

## Psychiatric

Suicidal thoughts and behaviors are rare in clinical trials, and the FDA requires all antidepressants, including bupropion, to carry a boxed warning stating that antidepressants may increase the risk of suicide in persons younger than 25. This warning is based on a statistical analysis conducted by the FDA which found a 2-fold increase in suicidal thought and behavior in children and adolescents, and 1.5-fold increase in the 18–24 age group.<sup>[52]</sup> For this analysis the FDA combined the results of 295 trials of 11 antidepressants in order to obtain statistically significant results. Considered in isolation, bupropion was not statistically different from placebo.<sup>[52]</sup>

Suicidal behavior is less of a concern when bupropion is prescribed for smoking cessation. According to a 2014 Cochrane review, while there is an association with suicide it is unclear if bupropion was the cause.<sup>[53]</sup> In 2016 the FDA removed the black box warning about psychiatric problems when used for stopping smoking.<sup>[54]</sup>

In 2009 the FDA issued a health advisory warning that the prescription of bupropion for smoking cessation has been associated with reports about unusual behavior changes, agitation and hostility. Some patients, according to the advisory, have become depressed or have had their depression worsen, have had thoughts about suicide or dying, or have attempted suicide.<sup>[55]</sup> This advisory was based on a review of anti-smoking products that identified 75 reports of "suicidal adverse events" for bupropion over ten years.<sup>[56]</sup>

Bupropion-induced psychosis may develop in select patient populations, or worsen a pre-existing psychotic syndrome.<sup>[57]</sup> Symptoms may include delusions, hallucinations, paranoia, and confusion. In most cases these symptoms can be reduced or eliminated by reducing the dose, ceasing treatment or adding antipsychotic medication.<sup>[3][57]</sup> However, adding a benzodiazepine to treat psychosis, instead of an antipsychotic, may become a valid alternative according to the model of amphetamine-induced psychosis.<sup>[58]</sup> Psychotic symptoms are associated with factors such as higher doses of bupropion, a history of bipolar disorder or psychosis, concomitant medications, for example, lithium or benzodiazepines, old age, or substance abuse.<sup>[57][59]</sup>

In a large-scale study of programs where bupropion was used for smoking cessation or treatment of depression, no withdrawal symptoms were observed.<sup>[60]</sup> As of 2002 there were two case reports of people experiencing withdrawal symptoms when discontinuing bupropion taken to aid smoking cessation;<sup>[61]</sup> the prescribing information states that dose tapering is not required when discontinuing treatment for smoking cessation.<sup>[1]</sup>

## Overdose

Bupropion is considered moderately dangerous in overdose.<sup>[62][63]</sup> For significant overdoses, seizures have been reported in about a third of all cases; other serious effects include hallucinations, loss of consciousness, and arrhythmias when bupropion was one of several kinds of pills taken in an overdose, fever, muscle rigidity, muscle damage, hypertension or hypotension, stupor, coma, and respiratory failure have been reported. While most people recover, some people have died, and before they died suffered multiple uncontrolled seizures and heart attacks.<sup>[3]</sup>

In the majority of childhood exploratory ingestions involving one or two tablets, children show no apparent symptoms.<sup>[64]</sup>

## Interactions

Since bupropion is metabolized to hydroxybupropion by the CYP2B6 enzyme, drug interactions with CYP2B6 inhibitors are possible: this includes medications like paroxetine, sertraline, fluoxetine, diazepam, clopidogrel, and orphenadrine. The expected result is the increase of bupropion and decrease of hydroxybupropion blood concentration. The reverse effect (decrease of bupropion and increase of hydroxybupropion) can be expected with CYP2B6 inducers, such as carbamazepine, clotrimazole, rifampicin, ritonavir, St John's wort, phenobarbital, phenytoin and others.<sup>[65]</sup> Conversely, because bupropion is itself an inhibitor of CYP2D6 ( $K_i = 21 \mu\text{M}$ ),<sup>[1][66]</sup> as is its active metabolite, hydroxybupropion ( $K_i = 13.3 \mu\text{M}$ ), it can slow the clearance of other drugs metabolized by this enzyme.<sup>[1][2][3][65]</sup>

Bupropion lowers the threshold for epileptic seizures,<sup>[67]</sup> and therefore can potentially interact with other medications that also lower it, such as carbapenems, cholinergic agents, fluoroquinolones, interferons, chloroquine, mefloquine, lindane, theophylline, systemic corticosteroids (e.g., prednisone), and some tricyclic antidepressants (e.g., clomipramine).<sup>[3]</sup> The prescribing information recommends minimizing the use of alcohol, since in rare cases bupropion reduces alcohol tolerance, and because the excessive use of alcohol may lower the seizure threshold.<sup>[3]</sup> Also, bupropion should not be taken by individuals undergoing abrupt cessation of alcohol or benzodiazepine use.

Caution should be observed when combining bupropion with a monoamine oxidase inhibitor (MAOI).<sup>[68]</sup>

## Pharmacology

Pharmacodynamics

Based on preclinical research with animal and human proteins, bupropion has been characterized as a weak norepinephrine-dopamine reuptake inhibitor (NDRI).<sup>[12]</sup> It has also been found to act as a releasing agent of dopamine and norepinephrine (NDRA), similarly to other cathinones.<sup>[14][74][75]</sup> However, when ingested orally by humans, bupropion is extensively converted in the body into several active metabolites with differing activities and influences on the effects of the drug during first-pass metabolism.<sup>[12][14]</sup> These metabolites are present in much higher concentrations in the body compared to bupropion

itself.<sup>[12][14][76]</sup> The most important example is the major metabolite of bupropion, hydroxybupropion, a selective norepinephrine reuptake inhibitor (and likely releasing agent) and nicotinic acetylcholine receptor (nAChR) antagonist that lacks significant dopaminergic actions, and which, with oral bupropion treatment, can reach area under the curve (AUC) plasma concentrations that are as much as 16–20 times greater than those of bupropion itself.<sup>[12]</sup> Hence, the effects of bupropion cannot be understood unless its metabolism is also considered.<sup>[12][14][77]</sup>

Dopaminergic activity

The occupancy of dopamine transporter (DAT) sites by bupropion and its metabolites in the human brain as measured by positron emission tomography was 26% according to GlaxoSmithKline researchers and 14% in an independent study.<sup>[12][78][79]</sup> Despite this weak DAT occupancy however, a subsequent study looked at the actual extracellular concentrations of dopamine in the human brain after an acute oral treatment of bupropion and failed to observe any increase, concluding that the weak DAT occupancy was not sufficient to increase dopamine levels.<sup>[12][13]</sup> In contrast, the same study also looked at dopamine levels in the *rat* brain after administration of bupropion via intraperitoneal injection and *did* see an increase, which could have been related to species differences.<sup>[12]</sup> However, an alternative explanation is that the difference had to do with the different routes of administration employed (i.e., oral vs. i.p.) and the associated differences in pharmacokinetics and metabolism, namely, the bypassing of first-past metabolism with the latter route, that resulted.<sup>[12]</sup> Although oral bupropion at clinical doses does not appear to have a significant potential for abuse, there are many isolated case reports of bupropion abuse and "cocaine-like" effects in humans who ingested the drug via a non-oral route (e.g., injection, insufflation, etc.).<sup>[80]</sup> Notably, awareness of the abuse potential of bupropion via non-conventional routes appears to be especially prominent in correctional facilities.<sup>[81]</sup>

Antinicotinic and other activities

Human pharmacology<sup>[69][70][71][72][73]</sup>

Exposure (concentration over time; bupropion exposure = 100%) and half-life					
	Bupropion	<i>R,R</i> -Hydroxy bupropion	<i>S,S</i> -Hydroxy bupropion	<i>Threo</i> -hydro bupropion	<i>Erythro</i> -hydro bupropion
Exposure	100%	800%	160%	310%	90%
Half-life	10 h (IR) 17 h (SR)	21 h	25 h	26 h	26 h
Inhibition potency (potency of DA uptake inhibition by bupropion = 100%)					
DA uptake	100%	ND	ND	ND	ND
NE uptake	27%	ND	ND	ND	ND
5-HT uptake	2%	ND	ND	ND	ND
α <sub>3</sub> β <sub>4</sub> nicotinic	53%	15%	10%	ND	ND
α <sub>4</sub> β <sub>2</sub> nicotinic	8%	3%	29%	ND	ND
α <sub>1</sub> * nicotinic	12%	13%	13%	ND	ND
DA = dopamine; NE = norepinephrine; 5-HT = serotonin; ND = no data					

Bupropion is also known to act as a non-competitive antagonist of the  $\alpha_3\beta_2$ ,  $\alpha_3\beta_4$ ,  $\alpha_4\beta_2$ , and, very weakly,  $\alpha_7$  nACh receptors,<sup>[14][82]</sup> and these actions appear to be importantly involved in its beneficial properties not only in smoking cessation, but in depression as well.<sup>[12][14][76][83]</sup> The metabolites of bupropion also act as non-competitive antagonists of these nACh receptors, and hydroxybupropion is even more potent in comparison.<sup>[12][84][85][86][87]</sup> At therapeutically-relevant concentrations bupropion and hydroxybupropion act as negative allosteric modulators of serotonin 3A receptors.<sup>[88]</sup> Pharmacological data on bupropion and its metabolites are shown in the table. Bupropion is known to weakly inhibit the  $\alpha_1$  adrenergic receptor, with a 14% potency of its dopamine uptake inhibition, and the H<sub>1</sub> receptor, with a 9% potency.<sup>[69]</sup>

## Pharmacokinetics

Bupropion is metabolized in the liver by the cytochrome P450 isoenzyme CYP2B6.<sup>[46]</sup> It has several active metabolites: *R,R*-hydroxybupropion, *S,S*-hydroxybupropion, *threo*-hydrobupropion and *erythro*-hydrobupropion, which are further metabolized to inactive metabolites and eliminated through excretion into the urine. Both bupropion and its primary metabolite hydroxybupropion act in the liver as potent inhibitors of the enzyme CYP2D6, which metabolizes not only bupropion itself but also a variety of other drugs and biologically active substances.<sup>[66]</sup> This mechanism creates the potential for a variety of drug interactions.

The biological activity of bupropion can be attributed to a significant degree to its active metabolites, in particular to *S,S*-hydroxybupropion. GlaxoSmithKline developed this metabolite as a separate drug called radafaxine,<sup>[89]</sup> but discontinued development in 2006 due to "an unfavourable risk/benefit assessment".<sup>[90]</sup>

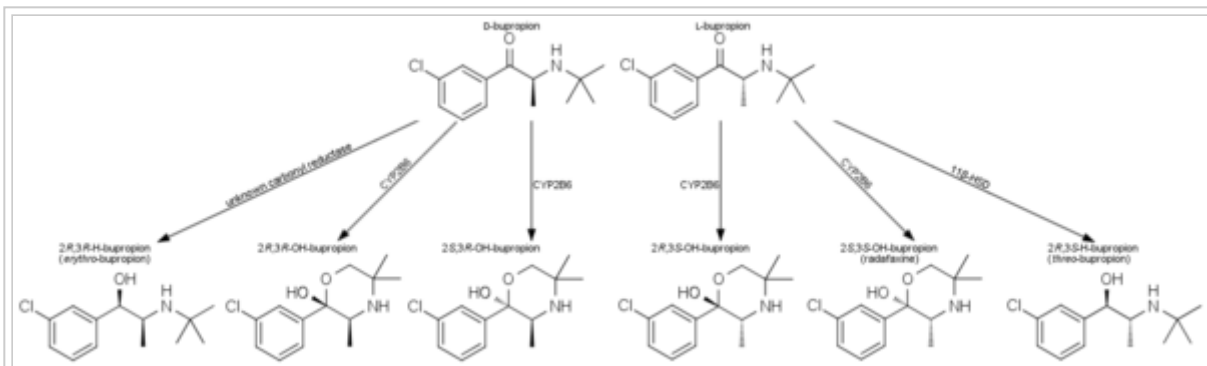
Bupropion is metabolized to hydroxybupropion by CYP2B6, an isozyme of the cytochrome P450 system. Alcohol causes an increase of CYP2B6 in the liver, and persons with a history of alcohol use metabolize bupropion faster. Bupropion is metabolized to *threo*-hydrobupropion via cortisone reductase.<sup>[91]</sup> The metabolic pathway responsible for the creation of *erythro*-hydrobupropion remains elusive.

The metabolism of bupropion is highly variable: the effective doses of bupropion received by persons who ingest the same amount of the drug may differ by as much as 5.5 times (with a half-life of 12–30 hours), while the effective doses of hydroxybupropion may differ by as much as 7.5 times (with a half-life of 15–25 hours).<sup>[3][5][92]</sup> Based on this, some researchers have advocated monitoring of the blood level of bupropion and hydroxybupropion.<sup>[93]</sup> The half-lives of *erythro*hydrobupropion and *threo*hydrobupropion are roughly 23–43 hours and 24–50 hours respectively.<sup>[1][3]</sup>

There have been reported cases of false-positive urine amphetamine tests in persons taking bupropion.<sup>[94][95][96]</sup>

In 2016, three new major metabolites of bupropion, all formed exclusively by CYP2C19, were identified.<sup>[97]</sup> These include 4'-OH-bupropion, *erythro*-4'-OH-hydrobupropion and *threo*-4'-OH-hydrobupropion, and represent 24% of a dose of bupropion excreted in urine.<sup>[97]</sup> For comparison, bupropion and its three previously known primary metabolites, hydroxybupropion, *threo*hydrobupropion, and *erythro*hydrobupropion represent 23% of a dose of bupropion excreted in urine.<sup>[97]</sup>



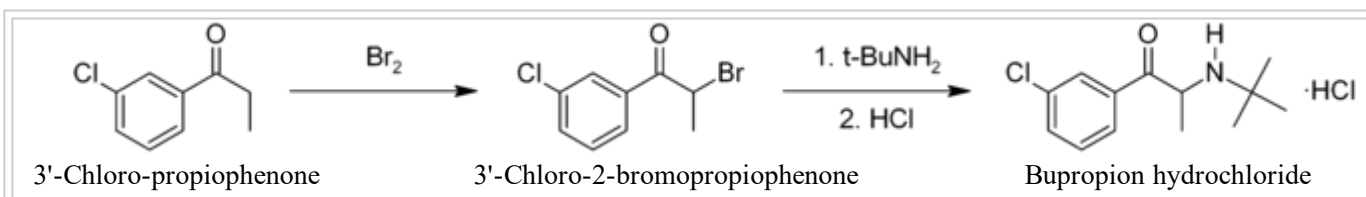


Metabolism of racemic bupropion. The carbonyl reductase enzyme that is responsible for producing *erythro*-bupropion is unknown as of March 2015.

## Chemistry

### Synthesis

Bupropion is a substituted cathinone. It is synthesized in two chemical steps starting from 3'-chloro-propiophenone. The alpha position adjacent to the ketone is first brominated followed by nucleophilic displacement of the resulting alpha-bromoketone with *t*-butylamine and treated with hydrochloric acid to give bupropion as the hydrochloride salt in 75–85% overall yield.<sup>[98][99]</sup>

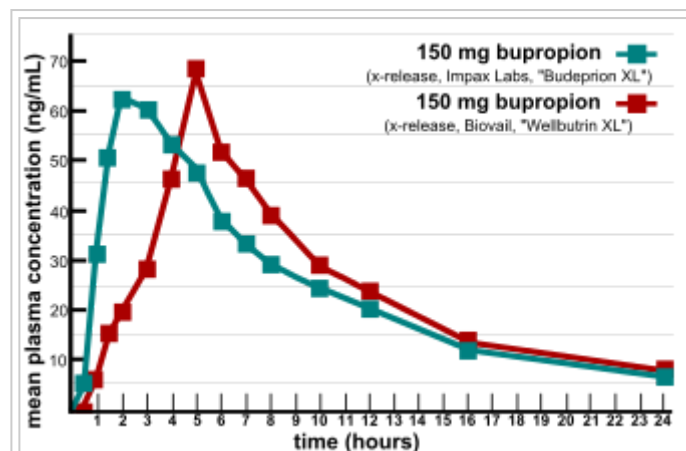


This diagram shows the synthesis of bupropion via 3'-chloro-propiophenone.

## History

Bupropion was invented by Nariman Mehta of Burroughs Wellcome (now GlaxoSmithKline) in 1969, and the US patent for it was granted in 1974.<sup>[98]</sup> It was approved by the United States Food and Drug Administration (FDA) as an antidepressant on 30 December 1985, and marketed under the name Wellbutrin.<sup>[100]</sup> However, a significant incidence of epileptic seizures at the originally recommended dosage caused the withdrawal of the drug in 1986. Subsequently, the risk of seizures was found to be highly dose-dependent, and bupropion was re-introduced to the market in 1989 with a lower maximum recommended daily dose.<sup>[101]</sup>

In 1996, the FDA approved a sustained-release formulation of bupropion called Wellbutrin SR, intended to be taken twice a day (as compared with three times a day for immediate-release Wellbutrin).<sup>[102]</sup> In 2003, the FDA approved another sustained-release formulation



A bioequivalency profile comparison of 150 mg extended-release bupropion as produced by Impax Laboratories for Teva and Biovail for GlaxoSmithKline.

called Wellbutrin XL, intended for once-daily dosing. Wellbutrin SR and XL are available in generic form in the United States and Canada. In Canada, generic XR bupropion is distributed by Mylan. In 1997, bupropion was approved by the FDA for use as a smoking cessation aid under the name Zyban.<sup>[102]</sup> In 2006, Wellbutrin XL was similarly approved as a treatment for seasonal affective disorder.<sup>[103]</sup>

In April 2008, the FDA approved a formulation of bupropion as a hydrobromide salt instead of a hydrochloride salt, to be sold under the name Aplenzin by Sanofi-Aventis.<sup>[104]</sup>

## Issue with generic bioequivalence

On 11 October 2007, two providers of consumer information on nutritional products and supplements, ConsumerLab.com and The People's Pharmacy, released the results of comparative tests of different brands of bupropion.<sup>[105]</sup> The People's Pharmacy received multiple reports of increased side effects and decreased efficacy of generic bupropion, which prompted it to ask ConsumerLab.com to test the products in question. The tests showed that "one of a few generic versions of Wellbutrin XL 300 mg, sold as Budeprion XL 300 mg, didn't perform the same as the brand-name pill in the lab."<sup>[106]</sup> The FDA investigated these complaints and concluded that Budeprion XL is equivalent to Wellbutrin XL in regard to bioavailability of bupropion and its main active metabolite hydroxybupropion. The FDA also said that coincidental natural mood variation is the most likely explanation for the apparent worsening of depression after the switch from Wellbutrin XL to Budeprion XL.<sup>[107]</sup> On 3 October 2012, however, the FDA reversed this opinion, announcing that "Budeprion XL 300 mg fails to demonstrate therapeutic equivalence to Wellbutrin XL 300 mg."<sup>[108]</sup> The FDA did not test the bioequivalence of any of the other generic versions of Wellbutrin XL 300 mg, but requested that the four manufacturers submit data on this question to the FDA by March 2013.<sup>[108]</sup> As of October 2013 the FDA has made determinations on the formulations from some manufacturers not being bioequivalent.<sup>[109]</sup>

In 2012, the U.S. Justice Department announced that GlaxoSmithKline had agreed to plead guilty and pay a \$3-billion fine, in part for promoting the unapproved use of Wellbutrin for weight loss and sexual dysfunction.<sup>[110]</sup>

In France, marketing authorization was granted for Zyban on 3 August 2001, with a maximum daily dose of 300 mg;<sup>[111]</sup> only sustained-release bupropion is available, and only as a smoking cessation aid. Bupropion was granted a licence for use in adults with major depression in the Netherlands in early 2007, with GlaxoSmithKline expecting subsequent approval in other European countries.<sup>[112]</sup>

## Society and culture

### Names

Bupropion is the International Nonproprietary Name (INN) and British Approved Name (BAN) while bupropion hydrochloride is the United States Adopted Name (USAN). Amfebutamone was the former INN.

Bupropion is marketed under many brand names including Aplenzin (United States), Budeprion (United States), Elontril (Central Europe), Wellbutrin (Americas), Quomem (Thailand), Prexaton (Australia), Voxra (Nordic countries), and Zyban (various regions), among others.

### Recreational use

According to the US government classification of psychiatric medications, bupropion is "non-abusable".<sup>[113]</sup> However, in animal studies, squirrel monkeys and rats could be induced to self-administer bupropion intravenously, which is often taken as a sign of addiction potential.<sup>[66]</sup> There have been a number of anecdotal and case-study reports of bupropion abuse, but the bulk of evidence indicates that the subjective effects of bupropion *via the oral route* are markedly different from those of addictive stimulants such as cocaine or amphetamine.<sup>[114]</sup> That said, bupropion, via non-conventional routes of administration (e.g., injection, insufflation), is reported to be abused in the United States and Canada, notably in prisons.<sup>[115][116][117]</sup>

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## External links

- Bupropion ([https://www.dmoz.org/Health/Pharmacy/Drugs\\_and\\_Medications/B/Bupropion/](https://www.dmoz.org/Health/Pharmacy/Drugs_and_Medications/B/Bupropion/)) at DMOZ
- Official Wellbutrin website (<http://www.wellbutrin-xl.com/>)
- List of international brand names for bupropion (<http://www.merck.com/mmpe/lexicomp/bupropion.html>)



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