The Psychopharmacology of Bupropion: An Illustrated Overview

You can watch the video tutorial here

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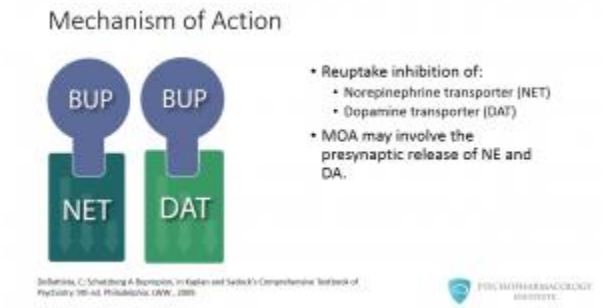
Bupropion is a norepinephrine dopamine reuptake inhibitor, or NDRI. It is approved as antidepressant as well as for smoking cessation.

Some characteristic aspects of its side effects profile include a lack of sexual side effects, compared to other antidepressants and an increased risk of seizures.

This presentation reviews the essential aspects of this medication including: mechanism of action, indications, pharmacokinetics, adverse effects profile and dosing guidelines.

Pharmacodynamics and Mechanism of Action



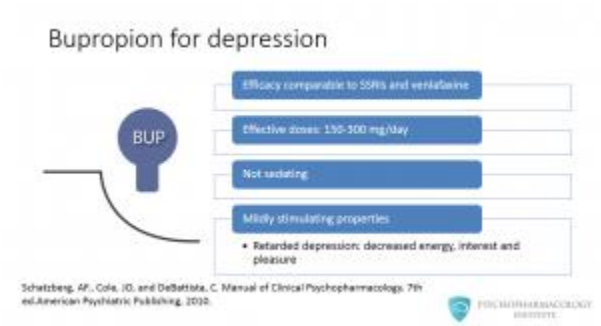
The exact mechanism of action of bupropion is not fully understood.

What is known is that bupropion enhances both noradrenergic and dopaminergic neurotransmission via reuptake inhibition of the norepinephrine transporter and the dopamine transporter. In addition, its mechanism of action may involve the presynaptic release of norepinephrine and dopamine.

In contrast to what was described in animal studies, human in vivo research suggests that bupropion effects on dopamine are relatively modest.

A more recently discovered pharmacological property of bupropion is its affinity for nicotinic receptors. Bupropion is a non competitive antagonist of nicotinic acetylcholine receptors. This is thought to contribute to its antidepressant effects, as well as to its effectiveness as smoking cessation drug.

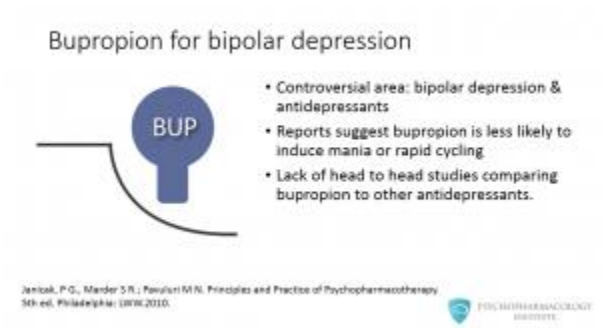
Indications



The efficacy of bupropion as antidepressant is comparable to the SSRIs and venlafaxine. In a meta-analysis conducted by Thase and colleagues, bupropion showed almost the same remission rates as SSRIs.

Effective doses are in the range of 150 to 300 mg/day. Bupropion is generally not sedating, it doesn't have antihistaminic or anticholinergic properties. In fact, because of its dopaminergic profile, it has mildly stimulating properties.

Clinicians often take this stimulating feature into consideration when selecting bupropion for patients with retarded depression: the clinical profile of these patients includes decreased energy, interest and pleasure.

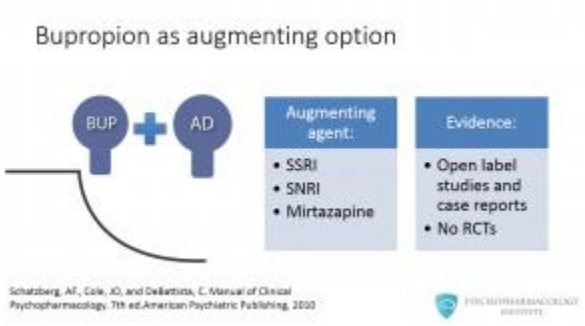


Another use is the treatment of depressive episodes in bipolar disorder. One of the most controversial aspects of the management of bipolar disorder is the treatment of depression with antidepressants.

In the case of bupropion there have been reports suggesting the drug is less likely to induce mania or rapid cycling, although manic episodes do occur.

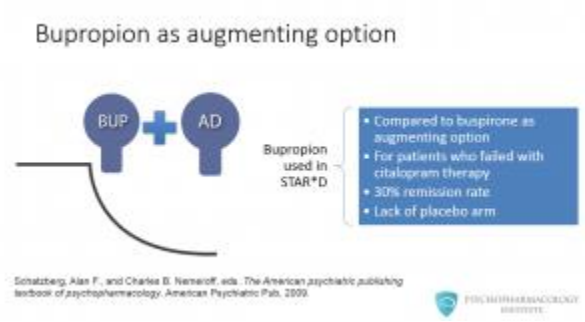
Something important to keep in mind is that there are no head to head studies comparing bupropion to other antidepressants.

It's not uncommon that patients respond insufficiently to the pharmacological treatment of depression.



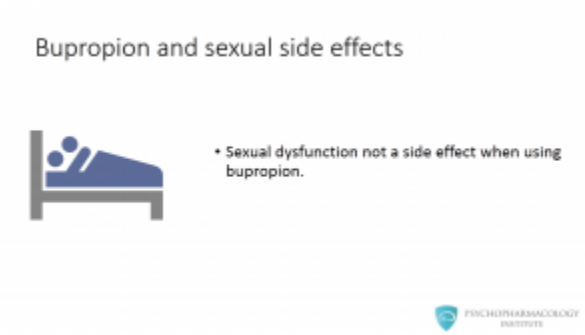
Bupropion is commonly used as an augmenting agent in combination with a different antidepressant class such as a SSRI SNRI or mirtazapine. The rationale behind these associations is that theoretically you are combining two complementary mechanisms of action.

How good is the clinical evidence for this practice? There are open label studies and case reports supporting this therapeutic option, but no controlled studies specifically designed to test this.

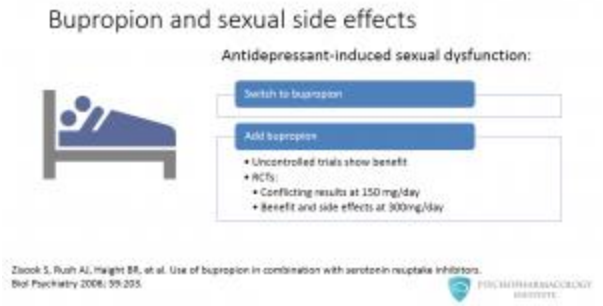


Bupropion was part of the Sequenced Treatment Alternatives to Relieve Depression trial or STAR*D. Here bupropion was compared to buspirone augmenting option after failing citalopram monotherapy.

Citalopram plus bupropion helped 30 percent of patients achieve remission, but it's not clear whether this effect is any greater than a placebo effect.



Bupropion has two distinctive clinical features regarding sexual dysfunction. The first is that sexual dysfunction does not occur significantly more frequently with bupropion than placebo.

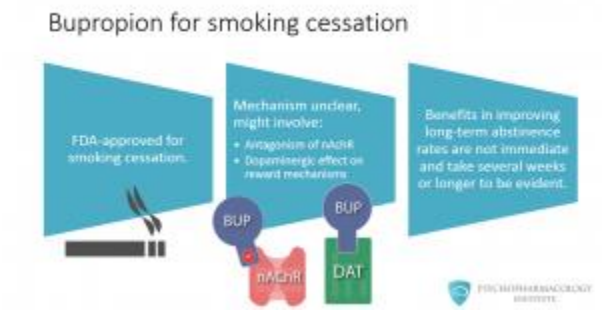


The other is that it can be used in the management of antidepressant-induced sexual dysfunction in two ways:

– By switching the antidepressant that caused sexual side effects to bupropion.

– Or, by adding bupropion as adjunctive treatment.

What is the evidence for this use? Uncontrolled trials have suggested adding bupropion is of benefit. Randomized controlled trials demonstrate conflicting results with bupropion at 150 mg a day and benefit at doses of 150 mg twice daily. This dose of 300 mg/day is associated with increased side effects.



Bupropion is one of the FDA-approved drugs for smoking cessation, it is the only antidepressant used for this indication. The mechanism of action for this indication still remains unclear.

However, one possible explanation involves the fact the drug is an antagonist at nicotinic receptors, this might prevent relapse by diminishing the reinforcing properties of nicotine.

In addition, it has been suggested that the drug's dopaminergic effect could influence reward mechanisms in addictive states.

From a clinical perspective, the benefits of bupropion in improving abstinence rates are not immediate, and take several weeks or longer to be evident.

Seasonal affective disorder (SAD) consists of recurrent major depressive episodes in the fall/winter with remissions in spring/summer. In the DSM 5 this entity is a specifier for recurrent major depressive disorder called with seasonal pattern.

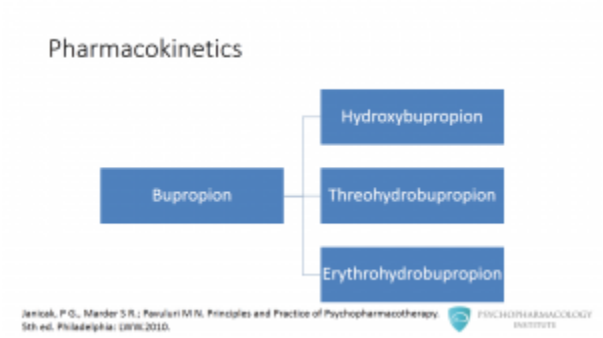
Currently bupropion is the only drug approved by the FDA for this condition.

Its efficacy has been shown in three trials that started in autumn at a time when SAD symptoms were not yet present although treatment effects were relatively small compared with placebo.

Bupropion is not currently approved by the FDA for ADHD. However, studies have demonstrated its efficacy. Currently it is considered a second-line agent with potential benefit for those patients with comorbid aggression or substance abuse.

It also has mild anorexiant effects that have been evaluated in nondepressed obese patients. Approximately 25 percent of patients in acute depression trials lost 5 lb or more while taking bupropion.

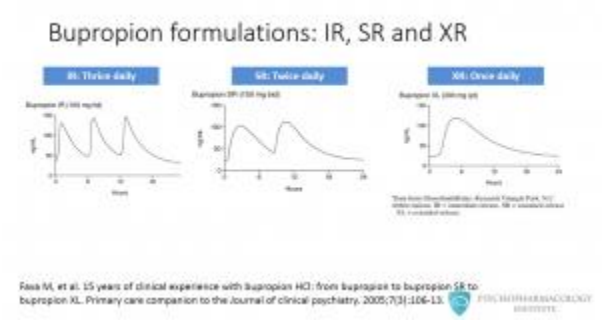
Pharmacokinetics



The parent drug has a half-life of 8 to 10 hours and is transformed to three active metabolites:

– Hydroxybupropion, which is the major metabolite
– Threohydrobupropion
– Erythrohydrobupropion

These metabolites all have half-lives of around 24 hours or more and accumulate to a greater extent than the parent drug.

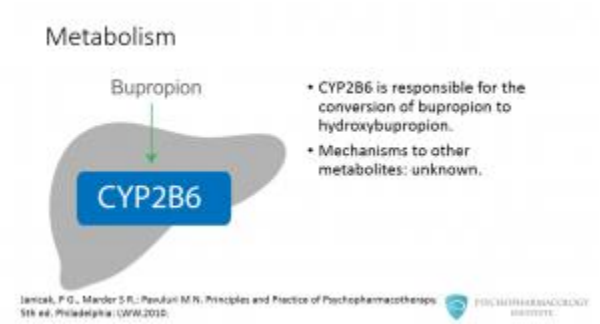


Bupropion is available in three formulations:

Immediate release, which requires three times a day dosing. Sustained release with twice a day dosing, and bupropion extended release with once a day dosing.

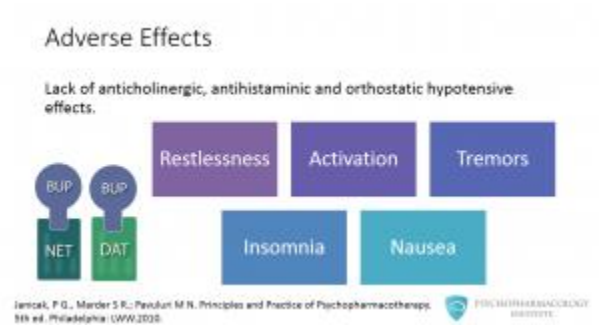
The images in this slide show that with steady-state dosing at 300 mg/day, both the SR and XL formulations, relative to the IR formulation, deliver an equivalent amount of bupropion (AUC).

The once-daily formulation, bupropion XL, was developed with the goal of improving tolerability and treatment adherence.



CYP 2B6 is responsible for the conversion of bupropion to hydroxybupropion . The mechanisms responsible for the conversion of bupropion to its other two major metabolites are not known

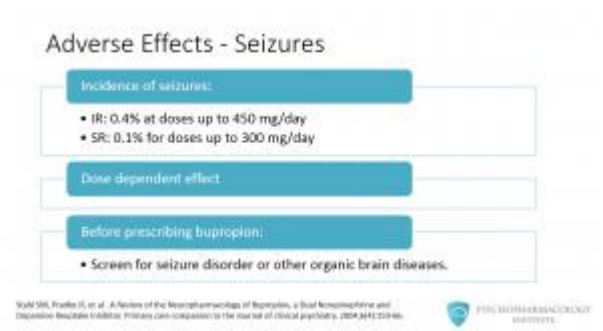
Adverse Effects



I recently mentioned that bupropion has a distinctive pharmacological profile, this is also reflected in its side effects profile.

This antidepressant is free from anticholinergic, antihistaminic and orthostatic hypotensive effects. Also, unlike the SSRIs and venlafaxine, its use is not associated with sexual dysfunction.

Its main adverse effects have been linked to increased dopaminergic and noradrenergic activity, these include: restlessness, activation, tremors, insomnia and nausea.



One of the adverse effects to keep in mind is the risk of seizures. Bupropion's release to the market was delayed after a study discovered that subjects with bulimia experienced seizures during treatment with the drug.

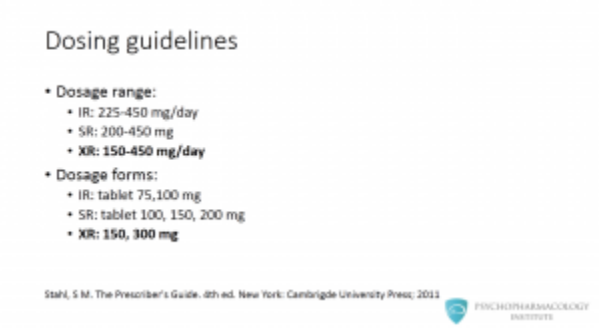
Additional research was carried out to get further details on the incidence of seizures, currently data from the manufacturer indicates that:

– For the immediate release formulation, the incidence of seizures is 0.4 at doses up to 450 mg/day.

– For the sustained release formulation, the incidence of seizures is 0.1 % for doses up to 300 mg/day

This is a dose dependent effect. Before prescribing bupropion it is advised to screen for history of seizure disorder or other organic brain diseases.

Dosing



Regarding dosing, as we previously discussed there are three formulations. You can see that what the three formulations have in common is the maximum recommended daily dose of 450 mg/day. Above this level, the seizure risk increases exponentially.

The dosage range for the immediate release formulation is 225 to 450 mg per day. Bupropion sustained release from 200 to 450 mg/ day and extended release from 150 to 450 mg/day.

The dosage forms include for immediate release tablets of 75 and 100 mg. Sustained release tablets of 100, 150, 200 mg. And extended release tablets of 150 and 300 mg.

The extended release version is the most commonly prescribed formulation. The fact that the drug is given once a day improves treatment adherence.