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Continuing Education Activity

Bupropion is an antidepressant medication that has received FDA approval for the treatment of depression and seasonal affective disorder and as an aid for smoking cessation. Since its approval in 1985, bupropion has been utilized off-label for various conditions, including antidepressant-induced sexual dysfunction, depression associated with bipolar disorder, obesity, and ADHD in pediatric patients. This activity reviews bupropion's clinical applications, including indications, dosing, mechanism of action, adverse event profile, and toxicity. By understanding bupropion's pharmacological properties, healthcare professionals can optimize treatment regimens and reduce the risk of adverse effects, thereby improving patient outcomes. The activity also emphasizes the essential role of the interprofessional healthcare team in managing bupropion therapy, underlining the significance of collaboration and well-defined roles in patient care.

Objectives:

- Identify the FDA-approved and off-label indications of bupropion.
- Assess the mechanism of action of bupropion.
- Screen patients for contraindications and potential risks associated with bupropion therapy.
- Implement effective collaboration and communication among interprofessional team members to improve outcomes and treatment efficacy for patients who might benefit from bupropion therapy.

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Indications

Bupropion is an antidepressant that can also help patients stop smoking. This medication was first patented by Burroughs Wellcome (now part of GlaxoSmithKline) in 1974 and approved by the FDA in 1985. Under the brand name, Wellbutrin, the sustained-release (SR) formula was introduced in 1996, and the extended-release (XL) formulation was introduced in 2003.[1] In 1997, bupropion was introduced for the smoking cessation indication. Until the year 2000, the drug was sometimes referred to as amfebutamone.

FDA-Approved Indications

- Adult depression
- Seasonal affective disorder
- Smoking cessation [4][5][6][7]

Off-Label Uses

- Antidepressant-induced sexual dysfunction
- Attention-deficit/hyperactivity disorder (ADHD)
- Depression associated with bipolar disorder
- Obesity [8][9]
- ADHD in pediatric patients [10]

The American Gastroenterological Association (AGA) advises incorporating naltrexone-bupropion extended-release (ER) alongside lifestyle changes for adults with obesity instead of relying solely on lifestyle changes.

The American Thoracic Society (ATS) guidelines suggest that bupropion can be used for tobacco dependence; however, varenicline is preferred over bupropion. The ATS acknowledges that future studies should assess the relative clinical effects of varenicline and bupropion in specific at-risk groups, including pregnant women, adolescents, and patients with a history of treatment resistance.

The American Society of Addiction Medicine and the American Academy of Addiction Psychiatry Clinical Practice Guidelines for stimulant use disorder suggest that for patients with cocaine use disorder, clinicians may consider prescribing bupropion to support cocaine abstinence. Bupropion may also be considered for patients with co-occurring tobacco use disorder, as it can help reduce nicotine or tobacco use, and for those with co-occurring depression. For patients with amphetamine-type stimulant use disorder who use stimulants with low to moderate frequency (fewer than 18 days per month), clinicians may consider prescribing bupropion to reduce stimulant use. Additionally, bupropion may be considered for patients with co-occurring tobacco use disorder or depressive disorders for the same reasons mentioned above.

Mechanism of Action

Depression

Bupropion is an aminoketone antidepressant, and its mechanism of action is not fully understood. Bupropion inhibits dopamine and norepinephrine transporters (DAT and NET), reducing the reuptake of these neurotransmitters. The drug reduces noradrenergic neuron activity in the locus coeruleus and increases dopaminergic activity in the nucleus accumbens. Bupropion

has minimal effects on serotonin activity. The exact therapeutic mechanism in major depressive disorder is not fully defined but involves the selective inhibition of norepinephrine and dopamine reuptake.

Smoking Cessation

Nicotine activates cholinergic receptors in the brain and body, releasing neurotransmitters such as acetylcholine, dopamine, norepinephrine, and serotonin. The addictive properties of nicotine are primarily the result of dopamine release in reward-related brain areas such as the ventral tegmental area and nucleus accumbens. Bupropion supports smoking cessation by targeting these circuits, providing anti-craving and anti-withdrawal benefits. The drug inhibits the reuptake of dopamine and norepinephrine, disrupting the reward pathways linked to nicotine addiction. Additionally, bupropion may act on nicotinic cholinergic receptors, improving its effectiveness in smoking cessation.

Pharmacokinetics

Absorption: Bupropion is rapidly absorbed from the gastrointestinal tract. Peak serum concentrations are achieved at 2 hours for immediate release, 3 hours for sustained-release, and 5 hours for extended-release. The duration of action is 1 to 2 days. The onset of bupropion's therapeutic effect usually occurs during the second week of therapy.

Distribution: The volume of distribution of bupropion ranges from 20 L/kg to 47 L/kg. The plasma protein binding is approximately 85%.

Metabolism: Bupropion is metabolized to hydroxybupropion by hepatic CYP2B6.[19] Non-CYP metabolism follows to form erythro-hydrobupropion and threo-hydrobupropion. These metabolites demonstrate a potency of 20% to 50% of the parent compound. Glycinated conjugate forms of these metabolites are eliminated renally.

Elimination: Approximately 10% of the drug is excreted in the feces and 87% in the urine. The distribution half-life is 3 to 4 hours. The elimination half-life of bupropion is approximately 21 hours.

Administration

Available Dosage Forms and Strengths

Bupropion is administered orally; tablets are available in regular or extended-release formulations. Patients may take the medication with or without meals. The tablets should be swallowed whole without crushing or dividing.

The once-daily dosage form ranges from 75 mg to 522 mg, depending on the formulation.

Immediate-release:

Available in 75 mg and 100 mg

Extended-release:

- 12-hour tablets (hydrochloride) are available in 100 mg, 150 mg, and 200 mg
- 24-hour tablets (hydrobromide) are available in 174 mg, 348 mg, and 522 mg
- 24-hour tablets (hydrochloride) are available in 150 mg, 300 mg, and 450 mg

Adult Dosage

Smoking Cessation

The initial dose for smoking cessation is 150 mg once daily for 3 days. This is increased to 150 mg twice daily for 7 to 12 weeks. The quit attempt is typically initiated after a week of therapy. The maximum daily dose is 450 mg.

Seasonal Affective Disorder

The initial dose is 150 mg (XL) once daily. After 7 days, the dose may be increased to 300 mg once daily in the morning. Treatment typically begins in autumn before depressive symptoms appear and continues through winter. Dosing is tapered to 150 mg, then discontinued in early spring. Treatment timing and duration may be adjusted based on the patient's seasonal MDD pattern. Bupropion hydrobromide can be given orally at 174 mg daily, and after 1 week, the dosage can be increased to a maintenance dose of 348 mg.

Major Depressive Disorder

Immediate-release: Treatment is initiated at 100 mg every 12 hours. This is increased to 100 mg every 8 hours on day 4. If therapeutic goals are not met on 100mg every 8 hours after several weeks, the maximum dose of 150 mg can be taken every 8 hours.

Sustained-release: Treatment is initiated at 150 mg once daily. Clinicians can consider increasing the dose to 150 mg every 12 hours starting day 4. If therapeutic goals are unmet after 4 weeks on 150 mg every 12 hours, the maximum dosage is 200 mg every 12 hours.

Extended-release: Treatment is initiated at 150 mg once daily. Clinicians may increase the dose to 300 mg once daily on day 4. If no clinical improvement is observed after 4 weeks, the dosage may be increased to 450 mg daily.

Maintenance treatment with all formulations typically requires several months or longer beyond the initial response; patients should be assessed periodically to determine the need and dose for maintenance.

Dosage switching considerations

Forfivo XL can be used only after titrating initially with other bupropion medications.

Patients with MDD switching from XL should be given the same daily dose divided equally: 3 times daily for IR, twice daily for SR, and once daily for the XL formulation.

When switching from hydrochloride salt formulation to hydrobromide salt (Aplenzin):

- 150 mg/day hydrochloride salt = 174 mg/day hydrobromide salt
- 300 mg/day hydrochloride salt = 348 mg/day hydrobromide salt
- 450 mg/day hydrochloride salt = 522 mg/day hydrobromide salt

Specific Patient Populations

Hepatic impairment: According to the American Association for the Study of Liver Diseases (AASLD), antidepressants should be started at low doses in individuals with chronic liver disease (CLD). For patients receiving bupropion, the dose should be reduced by 50%, with subsequent adjustments based on the balance between therapeutic response and adverse effects.

Renal impairment: For patients with renal impairment, the elimination of bupropion metabolites is reduced. Therefore, bupropion should be used cautiously, and dose adjustments are required. The maximum recommended dose for patients with an eGFR of 30 to 60 mL/min is 150 mg daily.

Pregnancy considerations: Bupropion is a pregnancy class C drug. Treating pregnant women with depression requires balancing the risks of fetal medication exposure with the potential harms of untreated depression. Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are first-line treatments for these patients. Selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, and sertraline are preferred medications due to their proven efficacy and safety. Bupropion is generally avoided due to limited safety data.

Breastfeeding considerations: Bupropion and its metabolites are secreted into breast milk.Maternal doses of up to 300 mg daily result in minimal bupropion levels in breast milk and are unlikely to cause adverse effects in breastfed infants. However, due to limited data and case reports suggesting potential risks, such as seizures in partially breastfed infants, bupropion should be used with caution. Alternative medications may be preferred, especially for patients with breastfeeding newborns or preterm infants, and close monitoring for symptoms such as vomiting or sedation is recommended.

Pediatric patients: Bupropion is used off-label for children with attention deficit hyperactivity disorder. The usual starting dose is 3 mg/kg daily, which can be titrated to a maximum of 6 mg/kg daily. The maximum recommended dose for these patients is 150 mg. Children receiving bupropion should be monitored closely.

Older patients: Bupropion is metabolized in the liver and excreted by the kidneys, so dose adjustments and renal function monitoring are advised, especially for older adults with impaired renal function.

Adverse Effects

Various adverse effects have been reported in patients receiving bupropion. Many of these side effects occur in more than 10% of patients.

Cardiovascular

- Hypertension
- Tachycardia [36]

Respiratory

- Rhinitis
- Pharyngitis [37]

Central nervous system

- Insomnia
- Headache
- Agitation
- Dizziness [38][39]

Dermatologic

- Pruritus
- Diaphoresis [40]

Endocrine

Weight loss [41]

Gastrointestinal

- Constipation
- Dry mouth
- Nausea [42]

Musculoskeletal

- Tremor [43]
- Arthritis [44]

Ophthalmologic

Blurred vision [43]

The most severe adverse effects include a lowered seizure threshold and worsening suicidal ideation.

Clinicians and researchers first noted epileptic seizures occurring in the 1980s; bupropion was subsequently removed from the market from 1986 through 1989. The immediate-release preparation, especially in higher doses, appears to have the highest likelihood of causing seizures. Bupropion is one of the very few antidepressants that does not cause sexual dysfunction.

Drug-Drug Interactions

CYP2B6 inducers: Bupropion is metabolized by CYP2B6, so dose adjustments may be needed with inducers like ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin.[47]

CYP2D6 substrates: Bupropion inhibits CYP2D6 (dose-dependent), potentially increasing levels of drugs such as venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline, haloperidol, risperidone, thioridazine, metoprolol, propafenone, and flecainide. A dose reduction of these drugs may be required.[48]

Digoxin: Bupropion may reduce plasma levels of digoxin; these levels should be monitored closely.[47]

Drugs reducing seizure threshold: Use bupropion cautiously with medications that lower the seizure threshold, including antipsychotics, antidepressants, theophylline, and systemic corticosteroids. Bupropion should be initiated at low doses and increased gradually.

Dopaminergic Drugs: Coadministration with dopaminergic drugs like levodopa and amantadine may lead to CNS toxicity.[49] Patients receiving these drugs should be monitored for symptoms such as restlessness, agitation, tremors, ataxia, gait disturbance, vertigo, and dizziness.

Monoamine Oxidase Inhibitors (MAOIs): Using bupropion with MAOIs can increase the risk of hypertensive reactions.[50]

Contraindications

Patients who are hypersensitive or allergic to bupropion or its constituents should not use the medication.

Bupropion is contraindicated for patients with seizure disorder. Additionally, bupropion is also contraindicated for any other factors predisposing to seizures, ie, discontinuation of alcohol or sedatives, arteriovenous malformations, severe head injury, severe stroke, brain tumor, or other significant central nervous system disease.

Patients taking monoamine oxidase inhibitors, linezolid, or methylene blue should not take bupropion. Additionally, Canadian regulations prohibit the concomitant use of thioridazine.

Patients with a history of bulimia or anorexia nervosa should not take bupropion.

Box Warnings

Bupropion has an FDA-issued box warning related to suicidal thoughts and behavior in children, adolescents, and young adults. All patients who have depressive symptoms and begin any new medication should be monitored closely for suicidal signs. If symptoms worsen or overt suicidality ensues, the clinician should stop therapy. In December 2016, researchers released a safety review; data from a large clinical trial convinced the FDA that the severe mood and behavior effects of bupropion are lower than previously represented. As a result, the FDA warning for bupropion for smoking cessation changed. However, the report notes that these reactions remain concerning, especially in patients with severe mood disorders or schizophrenia. This FDA report was explicitly related to the use of bupropion in smoking cessation.

Warnings and Precautions

- False positive amphetamine urine drug screens have been reported with the administration of bupropion; urine assays should be interpreted with caution before diagnosing substance use.[55]
- The doses and preparations of bupropion prescribed for the treatment of depression should be prescribed cautiously.[56]

Monitoring

Bupropion does not require monitoring with serum testing, and there are no firmly established therapeutic concentrations of the drug. Patients should be monitored clinically for serious adverse effects. Some patients tolerate bupropion better at lower serum concentrations; therefore, clinicians should attempt lower initial doses in all patients.

Due to its metabolism by CYP enzymes, bupropion interacts with various medications. Before prescribing, the provider should determine if any existing medications interact with bupropion. Medicines known to interact with bupropion include antidepressants, clopidogrel, and other drugs that lower the seizure threshold. Patients need to limit alcohol intake while on bupropion.

Toxicity

Signs and Symptoms of Overdose

There is extensive published data regarding bupropion overdose. The more severe exposures typically occur in an intentional overdose setting. With supportive care, unintentional overdoses usually lead to no significant effects. Accidental exposures in children are rare; a proposed 10 mg/kg safety threshold is proposed to reduce the use of healthcare resources.

Seizures occur in 10% to 15% of intentional overdoses and typically occur within the first 6 hours after exposure. In overdoses of extended-release formulations, experts recommend an observation period of 24 hours due to the potential for delayed seizure onset. Though agitation and tremor often precede seizures, delayed seizures with no prior symptoms have been observed. Other effects include hallucinations, mental status changes, agitation, and arrhythmias. The treating clinician should rule out the presence of coingestants. Bupropion misuse is rare but has been reported.

Management of Overdose

Seizures should be treated with intravenous benzodiazepines. Bupropion and hydroxybupropion are highly lipid-soluble, and intravenous lipid emulsion therapy can help treat bupropion overdose. Successful use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been documented in patients with severe cardiotoxicity associated with bupropion overdose.

Enhancing Healthcare Team Outcomes

Physicians and nurse practitioners frequently prescribe bupropion. However, all healthcare workers who prescribe this agent must be familiar with its associated adverse effects, which occur in at least 10% of patients. The most severe adverse effects include a lowered seizure threshold and the potential worsening of suicidal ideation. Clinicians should perform a mental health assessment of patients at each visit and educate them on what to do if and when a seizure develops. Pharmacists and nurses should also participate in these monitoring activities, perform medication reconciliation before drug administration, and inform the rest of the team of any concerns. This type of collaboration and communication can lead to more successful outcomes with bupropion therapy. An interprofessional team approach and communication among clinicians, pharmacists, and nurses are crucial to decreasing potential adverse effects and improving patient outcomes related to bupropion therapy.

Review Questions

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Disclosure: Martin Huecker declares no relevant financial relationships with ineligible companies.

Disclosure: Abbey Smiley declares no relevant financial relationships with ineligible companies.

Disclosure: Abdolreza Saadabadi declares no relevant financial relationships with ineligible companies.