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Tyler K. Wilson, Jayson Tripp

Continuing Education Activity

Buspirone is an anxiolytic drug. Originally, the drug was developed as an antipsychotic but was found ineffective for psychosis, but it had useful anxiolytic features. Buspirone has recently come into favor, primarily due to its decreased side-effect profile compared to other anxiolytic treatments. Buspirone is primarily used to treat generalized anxiety disorder. It is a United States Food and Drug Administration-approved medicine for managing anxiety disorders or the short-term relief of anxiety symptoms. Off-labeled buspirone is used for the augmentation of unipolar depression. This activity reviews the mechanism of action, adverse event profile, toxicity, dosing, pharmacodynamics, and monitoring of buspirone, pertinent for interprofessional team members for treating patients where buspirone is indicated.

Objectives:

- Describe the mechanism of action of buspirone.
- Outline the indications for initiating buspirone.
- Summarize the contraindications associated with initiating buspirone.
- Review interprofessional team strategies for improving care coordination and communication to advance the use of buspirone and improve outcomes in disorders where indicated.

Access free multiple choice questions on this topic.

Indications

Buspirone is an anxiolytic first synthesized in 1968 and patented in 1975. Initially, the drug was being developed as an antipsychotic but was found ineffective for psychosis, but it had useful anxiolytic features. Buspirone has recently come back into favor. This return to favor is primarily due to its decreased side-effect profile compared to other anxiolytic treatments.

United States Food and Drug Administration-Approved Indication: Management of anxiety disorders or the short-term relief of anxiety symptoms. The efficacy of buspirone has been demonstrated in controlled clinical trials of outpatients whose diagnosis corresponds to generalized anxiety disorder (GAD). Buspirone's use is primarily for treating GAD. Typically, it is used as a second-line agent behind selective serotonin reuptake inhibitors (SSRIs) when a patient does not respond to or cannot tolerate the side effects of SSRIs. Buspirone has also been used as an augmentation agent to reduce SSRI's sexual side effects. Unlike benzodiazepines and

barbiturates, there is no associated risk of physical dependence or withdrawal with buspirone use due to the lack of effects on gamma-aminobutyric acid (GABA) receptors. However, buspirone has little efficacy as an acute anxiolytic as the clinical effect typically takes 2 to 4 weeks to achieve. It is as effective as benzodiazepine treatment for GAD.

Off-label Clinical Use: Buspirone is used for the augmentation of unipolar depression. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed evidence suggesting that buspirone could be effective as augmentation, alongside SSRIs, for unipolar depression. Further studies have also found some utility in subduing the sexual side effects of SSRIs and use as a single agent for the treatment of depression. Although the FDA does not approve these uses, evidence supports that buspirone combined with melatonin can treat major depressive disorder and promote neurogenesis.

It is essential to recognize that buspirone has no use in treating withdrawal symptoms from benzodiazepines, barbiturates, or alcohol. Again, this relates to the lack of GABA receptor activity. Furthermore, the effects of buspirone have been shown to diminish in patients who have had previous treatment with benzodiazepines. A randomized controlled trial concluded that buspirone improves central apnea, apnoea-hypopnoea index, and oxygen saturation in patients with heart failure. Another study identified buspirone as a useful agent for treating gastroparesis and functional dyspepsia. However, significant research in clinical trials is necessary before approving the use of buspirone for the indications mentioned above in clinical practice.

Mechanism of Action

Buspirone is classified in the azapirone drug class. It has a strong affinity for serotonin 5HT1a receptors, where it acts as a partial agonist, which some researchers believe produces the preponderance of clinical effects. It also has a weak affinity for serotonin 5HT2 receptors and acts as a weak antagonist of dopamine D2 autoreceptors. There is no effect on benzodiazepine GABA receptors. The underlying mechanism behind how the partial 5HT1a agonism translates into clinical results remains largely unknown. It is proposed from increased serotonergic activity in the amygdala and other parts of the brain's anxiety/fear circuitry. Due to the delayed anxiolytic effects seen clinically, buspirone likely provides relief through adaptations in 5HT1a receptors.

Buspirone is primarily used to treat generalized anxiety disorder; however, it appears that buspirone may be useful in various other neurological and psychiatric disorders. Examples include attenuating side effects of Parkinson's disease therapy, ataxia, depression, social phobia, behavior disturbances following brain injury, and those accompanying Alzheimer disease, dementia, and attention deficit disorders. However, additional effectiveness studies are warranted before using buspirone for the disorders mentioned above.

Pharmacokinetics

Absorption: Buspirone is rapidly absorbed and undergoes extensive first-pass metabolism. Peak plasma levels are attained within 40 to 90 minutes.

Distribution: Buspirone has approximately 86% plasma protein binding.

Metabolism: Buspirone is metabolized primarily by oxidation by CYP3A4 and converts to hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP).

Excretion: The elimination half-life of unchanged buspirone is approximately 2 to 3 hours. Buspirone is excreted in the urine as metabolites(29% to 63%); fecal excretion accounts for 18% to 38% of the dose.

Administration

Buspirone is available in 5 mg, 7.5 mg, 10 mg, 15 mg, and 30 mg oral tablets. The initial recommended dose for GAD treatment is 15 mg daily, given as either 7.5 mg twice per day or 5 mg three times per day. Every 2 to 3 days, the dosage may be increased by 5 mg until the desired clinical response is achieved. The maximum daily dosage is 60 mg per day. In clinical trials, a typical range of therapeutic effects was between 20 to 30 mg per day in divided doses.

Buspirone has seen occasional off-label use for pediatric anxiety disorders. The dosage has not been well established. In a pilot study of children aged 6 to 14, they were started on a daily dose of 5 mg and increased by 5 mg every week to a maximum daily dose of 20 mg. Another more extensive study with patients aged 6 to 17 had a higher maximum daily dose of 60 mg. Food increases the bioavailability of buspirone; hence clinicians should counsel the patients to take buspirone with food or take it on an empty stomach. Consistency of dosage patterns is important. Buspirone gets metabolized by cytochrome P450 (CYP3A4); hence evaluate potential drug-drug interactions before an initial prescription.

Use in Specific Patient Population

Patients with hepatic impairment: The measured bioavailability (using the steady-state area under the curve) increased 13-fold in patients with hepatic impairment; consider dose reduction in patients with hepatic impairment.

Patients with renal impairment: The bioavailability of buspirone is increased fourfold in patients with renal impairment (creatine clearance=10 to 70 mL/min/1.73 m); consequently, consider dose reduction in patients with renal impairment.

Pregnancy considerations: Buspirone is a Category B risk in pregnancy. On June 30, 2015, the FDA began implementation of the Pregnancy and Lactation Labeling Rule, which replaced the pregnancy letter category system (A, B, C, D, and X) with integrated narrative summaries of the

risks of using a drug or biological product during pregnancy and lactation. The effect of buspirone use during pregnancy on labor and delivery is unknown. However, reproductive studies in rats did not cause any adverse effects on animals.

Breastfeeding considerations: Limited data indicate that maternal doses of buspirone up to 45 mg daily produce low levels of milk. No information is available on the long-term use of buspirone during breastfeeding; an alternate medication may be preferred, particularly while nursing a newborn or preterm infant.

Adverse Effects

Dizziness is a common side effect that occurs in over 10% of patients.

According to FDA product labeling, the following reports of adverse events occurred in 1% to 10% of patients.

- Central nervous system: Abnormal dreams, ataxia, confusion, dizziness, drowsiness, excitement, headache, nervousness, numbness, outbursts of anger, paresthesia
- Ophthalmic: Blurred vision
- Otic: Tinnitus
- Cardiovascular: Chest pain
- Respiratory: Nasal congestion
- Dermatologic: Diaphoresis, skin rash
- Gastrointestinal: Diarrhea, nausea, sore throat
- Neuromuscular and skeletal: Musculoskeletal pain, tremor, weakness
- Hepatic: isolated cases of serum enzyme elevations without jaundice [17]

Clinicians can mitigate these adverse drug reactions by continuing therapy and gradual titration to an optimal therapeutic dose. Of note, buspirone has minimal sexual side effects. It has even been shown to help relieve the adverse sexual effects of SSRIs when given as an augmenting agent. Patients should receive a warning about the possibility of central nervous system depression. In addition, clinicians should inform patients of the rare potential for akathisia (likely due to central dopamine antagonism) and serotonin syndrome. Postmarketing surveillance reports cases of somnambulism (sleepwalking) associated with buspirone. However, altered neurobiology due to psychiatric disorders should also be considered. QT prolongation has also been reported in patients with preexisting cardiac disorders.

Contraindications

Contraindications for Buspirone include the following:

- History of hypersensitivity reaction with buspirone in the past
- Avoid the use of monoamine oxidase inhibitors (MAOI) within 14 days before or after buspirone therapy. The aforementioned is due to the risk of developing serotonin syndrome and/or elevated blood pressure[22]
- Avoid buspirone in patients receiving reversible MAOIs such as linezolid or IV methylene blue due to the risk of serotonin syndrome.[23]

Monitoring

Offer frequent follow-ups after initiating treatment to assess for therapeutic and adverse effects. Encourage patients to stay consistent with their medication schedule and whether they take it with food. As mentioned before, a therapeutic effect typically takes 2 to 4 weeks for therapeutic effect. Often, many of the adverse effects will also lessen over time. However, healthcare providers should closely monitor signs and symptoms of anaphylaxis, akathisia, and serotonin syndrome.

Buspirone is a substrate of CYP3A4; clinicians should check for interactions that can alter its plasma concentration; this includes grapefruit juice, which can increase its concentration. Alcohol use can worsen any CNS sedation, and its use requires strict monitoring as well. Assess anxiety levels using the GAD-7 (general anxiety disorder-7) tool at baseline and follow-up visits to assess response to therapy. Similarly, clinicians can use the Hamilton Anxiety Scale (HAM-A)to objectify and rate a patient's anxiety severity. ISMP (Insitute for Safe Medical Practice) notes that buspirone may be easily confused with bupropion, and this dispensing error can be prevented using tall man lettering. Consequently, healthcare providers should monitor each visit for accurate dispensing.

Toxicity

Relative to other anxiolytics, buspirone has low toxicity and potential for abuse. There have been no deaths reported from a buspirone overdose alone. In pharmacological trials, healthy male patients were given up to 375 mg daily and developed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. While buspirone overdose typically resolves with complete recovery, high suspicion of other medication overdoses should be maintained and investigated. In a literature review, multiple reports of movement disorders, including dyskinesia, akathisia, myoclonus, parkinsonism, and dystonia, have been reported.

In case of movement disorder induced by buspirone, the drug should be discontinued, and in some instances, it may require therapy with trihexyphenidyl/benztropine(centrally acting anticholinergic medication) and additional supportive treatment. Clinicians should use

symptomatic and supportive measures and immediate gastric lavage in acute overdose. Healthcare providers must monitor respiration, pulse, and blood pressure, as in all drug overdose cases. Seizures can occur in rare instances which require treatment with benzodiazepines. It is important to note that no specific antidote is known for buspirone.

Enhancing Healthcare Team Outcomes

Before initiating buspirone therapy, it is essential to understand proper indications, dosing, adverse drug reactions, and toxicity. The clinician should prescribe buspirone and counsel the patient on the risk vs. benefit ratio. The pharmacist must educate the patient on the safe use of the drug and ensure proper dosing. Additionally, the pharmacist must communicate with the physician if there is evidence of drug misuse in rare instances. In an era where drug abuse results in high mortality, healthcare workers are responsible for ensuring that patients only use buspirone for legitimate purposes. The literature review suggests that buspirone has negligible abuse potential.

Nurses should monitor for the signs and symptoms of anxiety during each follow-up visit. Nursing staff can also provide patient counseling to reinforce the pharmacists' advice. Residents and medical students should counsel the patient not to combine buspirone with other sedatives or alcohol. Patients who continue to get refills should be encouraged to seek counseling from a psychiatrist. Encourage individuals to be patient at the initiation of therapy and follow up within a month to assess the effectiveness of buspirone therapy.

The attending psychiatrist should evaluate the patient regularly and share their findings with the healthcare team. For example, emergency physicians and triage nurses should establish patent airway, breathing, and circulation in an overdose of buspirone. Moreover, the emergency department physician should notify the psychiatrist if the overdose is deliberate.

Healthcare professionals should use evidence-based medicine and be well-informed about the latest guidelines regarding the current status of buspirone in treating generalized anxiety disorder. As depicted above, clinicians, specialists, nurses, pharmacists, and other healthcare providers should closely collaborate with the patient on buspirone therapy. An interprofessional team approach can achieve optimal therapeutic results with minimal adverse effects leading to better patient outcomes. A systematic review and meta-analysis of seven randomized controlled trials concluded that interprofessional care and communication between clinicians, psychiatrists, specialty-trained nurses, and psychologists could significantly improve patient outcomes in anxiety disorders.

Review Questions

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