

11 - 29.11 Buspirone

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dosage should not exceed 450 mg. The maximum of 400 mg of the sustained-release version should be used as a twice-a-day regimen of either 200 mg twice daily or 300 mg in the morning and 100 mg in the afternoon. A starting dosage of the sustained-release version, 100 mg once a day, can be increased to 100 mg twice a day after 4 days. Then 150 mg twice a day may be used. A single dose of sustained-release bupropion should never exceed 300 mg. The maximum dosage is 200 mg twice a day of the immediate-release or extended-release formulations. An advantage of the extended-release preparation is that after appropriate titration, a total of 450 mg can be given all at once in the morning. For smoking cessation, the patient should start taking 150 mg a day of sustained-release bupropion 10 to 14 days before quitting smoking. On the fourth day, the dosage should be increased to 150 mg twice daily. Treatment generally lasts 7 to 12 weeks.

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29.11 Buspirone Buspirone hydrochloride (BuSpar) is classified as an azapirone and is chemically distinct

from other psychotropic agents. It acts on two types of receptors, serotonin (5-HT) and dopamine (D). It has high affinity for the 5-HT_{1A} serotonin receptor, acting as an agonist or partial agonist, and moderate affinity for the D₂ dopamine receptor, acting as both an agonist and an antagonist. The approved indication for this psychotropic drug is for the treatment of GAD. It was initially believed to be a better alternative to the benzodiazepine drug group because buspirone does not possess anticonvulsant and muscle relaxant effects. Reports continue to appear that some patients benefit from the addition of buspirone to their antidepressant regimen. Its use in this role is more common than its use as an anxiolytic. Interestingly, the antidepressant drug vilazodone (Viibryd) inhibits 5-HT reuptake and acts as a 5-HT_{1A} receptor partial agonist.

PHARMACOLOGIC ACTIONS

Buspirone is well absorbed from the GI tract, but absorption is delayed by food ingestion. Peak plasma levels are achieved 40 to 90 minutes after oral administration. At doses of 10 to 40 mg, single-dose linear pharmacokinetics are observed. Nonlinear pharmacokinetics are observed after multiple doses. Because of its short half-life (2 to 11 hours), buspirone is dosed three times daily. An active metabolite of buspirone, 1-pyrimidinylpiperazine (1-PP), is about 20 percent less potent than buspirone but is up to 30 percent more concentrated in the brain than the parent compound. The elimination half-life of 1-PP is 6 hours. Buspirone has no effect on the GABA-associated chloride ion channel or the serotonin reuptake transporter, targets of other drugs that are effective in GAD. Buspirone also has activity at 5-HT₂ and dopamine type 2 (D₂) receptors, although the significance of the effects at these receptors is unknown. At D₂ receptors, it has properties of both an agonist and an antagonist.

THERAPEUTIC INDICATIONS

Generalized Anxiety Disorder Buspirone is a narrow-spectrum antianxiety agent with demonstrated efficacy only in the treatment of GAD. In contrast to the SSRIs or venlafaxine, buspirone is not effective in the treatment of panic disorder, OCD, or social phobia. Buspirone, however, has an advantage over these agents in that it does not typically cause sexual dysfunction or weight gain. Some evidence suggests that compared with benzodiazepines, buspirone is generally more effective for symptoms of anger and hostility, equally effective for psychic symptoms of anxiety, and less effective for somatic symptoms of anxiety. The full benefit of buspirone is evident only at dosages above 30 mg a day. Compared with the benzodiazepines, buspirone has a delayed onset of action and lacks any euphoric effect. Unlike benzodiazepines, buspirone has no immediate effects, and patients should be told that a full clinical response may take 2 to 4 weeks. If an immediate response is needed,

patients can be started on a benzodiazepine and then withdrawn from the drug after buspirone's effects begin. Sometimes the sedative effects of benzodiazepines, which are not found with buspirone, are desirable; however, these sedative effects may cause impaired motor performance and cognitive deficits. Other Disorders Many other clinical uses of buspirone have been reported, but most have not been confirmed in controlled trials. Evidence of the efficacy of high-dosage buspirone (30 to 90 mg a day) for depressive disorders is mixed. Buspirone appears to have weak antidepressant activity, which has led to its use as an augmenting agent in patients who have failed standard antidepressant therapy. In a large study, buspirone augmentation of SSRIs worked as well as other commonly used strategies. Buspirone is sometimes used to augment SSRIs in the treatment of OCD. There are reports that buspirone may be beneficial against the increased arousal and flashbacks associated with posttraumatic stress disorder. Because buspirone does not act on the GABA-chloride ion channel complex, the drug is not recommended for the treatment of withdrawal from benzodiazepines, alcohol, or sedative-hypnotic drugs, except as treatment of comorbid anxiety symptoms. Scattered trials suggest that buspirone reduces aggression and anxiety in persons with organic brain disease or traumatic brain injury. It is also used for SSRI-

induced bruxism and sexual dysfunction, nicotine craving, and ADHD. **PRECAUTIONS AND ADVERSE REACTIONS** Buspirone does not cause weight gain, sexual dysfunction, discontinuation symptoms, or significant sleep disturbance. It does not produce sedation or cognitive and psychomotor impairment. The most common adverse effects of buspirone are headache, nausea, dizziness, and (rarely) insomnia. No sedation is associated with buspirone. Some persons may report a minor feeling of restlessness, although that symptom may reflect an incompletely treated anxiety disorder. No deaths have been reported from overdoses of buspirone, and the median lethal dose is estimated to be 160 to 550 times the recommended daily dose. Buspirone should be used with caution by persons with hepatic and renal impairment, pregnant women, and nursing mothers. Buspirone can be used safely by the elderly. **DRUG INTERACTIONS** The coadministration of buspirone and haloperidol (Haldol) results in increased blood concentrations of haloperidol. Buspirone should not be used with MAOIs to avoid hypertensive episodes, and a 2-week washout period should pass between the discontinuation of MAOI use and the initiation of treatment with buspirone. Drugs or foods that inhibit CYP3A4, for example, erythromycin (E-mycin), itraconazole (Sporanox), nefazodone (Serzone), and grapefruit juice, increase buspirone plasma

concentrations. **LABORATORY INTERFERENCES** Single doses of buspirone can cause transient elevations in growth hormone, prolactin, and cortisol concentrations, although the effects are not clinically significant. **DOSAGE AND CLINICAL GUIDELINES** Buspirone is available in single-scored 5- and 10-mg tablets and triple-scored 15- and 30mg tablets; treatment is usually initiated with either 5 mg orally three times daily or 7.5 mg orally twice daily. The dosage can be raised 5 mg every 2 to 4 days to the usual dosage range of 15 to 60 mg a day. Buspirone should not be used in patients with past hypersensitivity to buspirone, in cases of diabetes-associated metabolic acidosis, or in patients with severely compromised liver or renal function. Switching from a Benzodiazepine to Buspirone Buspirone is not cross-tolerant with benzodiazepines, barbiturates, or alcohol. A common clinical problem, therefore, is how to initiate buspirone therapy in a person who is currently taking benzodiazepines. There are two alternatives. First, the clinician can start buspirone treatment gradually while the benzodiazepine is being withdrawn. Second, the clinician can start buspirone treatment and bring the person up to a therapeutic dosage for 2 to 3 weeks while the person is still receiving the regular dosage of the benzodiazepine and then slowly taper the benzodiazepine dosage. Patients who have received benzodiazepines in the past, especially in recent months, may find that buspirone is not as effective as the benzodiazepines in the treatment of their anxiety. This might be explained by the absence of the immediate mildly euphoric and sedative effects of the benzodiazepines. The coadministration of buspirone and benzodiazepines may be effective in the treatment of persons with anxiety disorders who have not responded to treatment with either drug alone. **REFERENCES** Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: Results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry*. 2001;62:448. Benyamina A, Lecacheux M, Blecha L, Reynaud M, Lukasiewicz M. Pharmacotherapy and psychotherapy in cannabis withdrawal and dependence. *Expert Rev Neurother*. 2008;8:479. Faber J, Sansone RA. Buspirone: A possible cause of alopecia. *Innov Clin Neurosci*. 2013;10(1):12-13. Le Foll B, Boileau I. Repurposing buspirone for drug addiction treatment. *Int J Neuropsychopharmacol*. 2013;16(2):251- 253. Levitt AJ, Schaffer A, Lanctôt KL. Buspirone. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th edition. Vol. 2. Philadelphia: Lippincott Williams & Wilkins: 2009:3060.

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