

DRUGDEX-EV 2467

MICROMEDEX

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BUSPIRONE

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0.0] Overview

1] Class

a)] This drug is a member of the following class(es):

Antianxiety

2] Dosing Information

a)] [Buspirone](#) Hydrochloride

1] Adult

a)] Anxiety

1)] 5 mg ORALLY 2 to 3 times a day OR 7.5 mg ORALLY twice a day; may increase the dosage by 5 mg/day every 2 to 3 days as needed (usual dose 20 to 30 mg/day (2 to 3 divided doses), MAX dose 60 mg/day)

b)] Depression

1)] 5 mg ORALLY 3 times a day; may increase the dosage by 5 to 10 mg/day every 2 to 3 days as needed (usual dose 40 to 55 mg/day (3 divided doses), MAX dose 90 mg/day)

2] Pediatric

a)] safety and efficacy in children under the age of 18 has not been established

3] Contraindications

a)] [Buspirone](#) Hydrochloride

1)] hypersensitivity to [buspirone](#) hydrochloride [64]

4)) Serious Adverse Effects**a)) [Buspirone](#) Hydrochloride**

- 1))** Cerebrovascular accident
- 2))** [Congestive heart failure](#)
- 3))** [Myocardial infarction](#)

5)) Clinical Applications**a)) [Buspirone](#) Hydrochloride**

- 1))** FDA Approved Indications
 - a))** Anxiety
- 2))** Non-FDA Approved Indications
 - a))** Depression

1.0) Dosing Information

[Drug Properties](#)
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1.1) Drug Properties

A)) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B)) Synonyms

[Buspirone](#)
[Buspirone HCl](#)
[Buspirone Hydrochloride](#)

C)) Physicochemical Properties**1)) Molecular Weight**

a)) [Buspirone](#) hydrochloride: 421.97 [306]

2)) Solubility

a)) Systemic: [Buspirone](#) hydrochloride is very [205] water soluble [204] [205].

1.2) Storage and Stability**A)) [Buspirone](#) Hydrochloride**

1)) Oral route**a)) Tablet**

1)) Store at USP controlled room temperature, 25 degrees Celsius (77 degrees Fahrenheit), with excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit) [101].

1.3] Adult Dosage**1.3.1] Normal Dosage****1.3.1.A] Buspirone Hydrochloride****1.3.1.A.1] Oral route****1.3.1.A.1.a] Anxiety****1)) IMPORTANT NOTE**

a)) **BUSPIRONE** does not prevent the symptoms of benzodiazepine withdrawal. If **BUSPIRONE** is intended to replace long-term or chronic benzodiazepine therapy, gradually withdraw the patient from the first drug before initiating **BUSPIRONE**.

2)) DOSING

a)) The manufacturer recommends an initial oral dose of 7.5 milligrams twice daily, increasing the dosage by 5 milligrams/day at 2 to 3-day intervals as needed. The daily dosage should not exceed 60 milligrams/day (Prod Info BuSpar(R), 2001). The efficacy of once daily dosing has not been investigated.

b)) The optimal dose of oral **buspirone** for treatment of ANXIETY appears to be 20 to 30 milligrams daily, in divided doses two or three times daily [11] [5] [6] [10] [18]. Doses of up to 60 milligrams/day have been used [19].

c)) The efficacy of oral **buspirone** in anxiety was reported using 5 milligrams twice daily initially, increasing to 5 milligrams three times a day after 4 days, then increasing again after 1 week to 5 milligrams four times a day. Mean orally effective doses were 20 milligrams daily [6].

3)) DIAZEPAM EQUIVALENT

a)) Oral **buspirone** has been reported to be equipotent to **diazepam** in the treatment of anxiety, on a milligram-milligram basis [20] [6] [10].

1.3.1.A.1.b)) IMPORTANT NOTE

1)) **BUSPIRONE** does not prevent the symptoms of benzodiazepine withdrawal. If **BUSPIRONE** is intended to replace long-term or chronic benzodiazepine therapy, gradually withdraw the patient from the first drug before initiating **BUSPIRONE**.

1.3.2] Dosage in Renal Failure**A)) Buspirone Hydrochloride**

1J) The manufacturer does not recommend the administration of **buspirone** to patients with severe **renal impairment** (Prod Info **BuSpar**(R), 2001).

2J) In patients with mild to severe renal dysfunction, **buspirone** clearance may be decreased up to 50%; however, there is not a clear relationship between the degree of **renal impairment** and the degree of change in **buspirone** clearance [59]. Patients with **renal impairment** should be monitored closely and may require a dosage reduction.

3J) Based upon the kinetics of **buspirone** in patients with **impaired renal function**, dose reductions are not required in patients with mild-to-moderate renal dysfunction [60]. However, as serum concentrations of the active metabolite of **buspirone** (1-PP) were elevated in patients with **anuria** as compared to healthy subjects or patients with mild-to-moderate **renal impairment**, it is suggested that the dose of **buspirone** be reduced by 25% to 50% in anuric patients.

1.3.3] Dosage in **Hepatic Insufficiency**

AJ) **Buspirone** Hydrochloride

1J) The manufacturer does not recommend the administration of **buspirone** to patients with severe **hepatic impairment** (Prod Info **BuSpar**(R), 2001).

2J) Significant increases in the AUC and plasma levels of **buspirone** were reported following single oral doses of 20 milligrams in cirrhotic patients [61]. An increase in the elimination half-life of the drug was also observed. A second peak plasma level of **buspirone** was observed in 8 of 12 cirrhotic patients and in 7 of 12 normal subjects in this study, suggesting biliary excretion of intact **buspirone**. Dose reductions should be considered in patients with severe **cirrhosis**.

1.3.4] Dosage in **Geriatric Patients**

AJ) **Buspirone** Hydrochloride

1J) **Buspirone** does not appear to have any age-related alterations in pharmacokinetic parameters. However, greater sensitivity of some older patients cannot be ruled out (Prod Info **BuSpar**(R), 2001).

2J) In a double-blind, placebo-controlled study of **buspirone** for **major depression** in the elderly, patients were started on **buspirone** 10 milligrams (mg) twice daily for one week, increased to 10 mg three times daily for one week, then increased to 40 mg/day, with a maximum of 60 mg/day. The authors conclude the 10 mg twice daily starting dose may be excessive for the elderly, according to the overall higher dropout rate for **buspirone**, and six patients who dropped out during the first week of therapy, primarily due to dizziness [31].

3J) Based upon the pharmacokinetics of **buspirone** in elderly men and women (65 years or older), there is no need to alter the initial dose of **buspirone** based solely upon patient age [62]. No significant differences were observed in **buspirone** and 1-pyrimidinylpiperazine (active metabolite) pharmacokinetics in elderly subjects as compared to younger subjects (21 to 40 years of age) in this study [31].

1.4] **Pediatric Dosage**

1.4.1] **Normal Dosage**

1.4.1.A] **Buspirone** Hydrochloride

1.4.1.A.1] Oral route**1.4.1.A.1.a] Anxiety**

1]) Prepubertal hospitalized patients with anxiety symptoms and moderately severe aggression, age 5 to 12 years of age, were treated with a 5-milligram (mg)/day starting dose with titration upward by 5 to 10 mg every 3 days to a maximum dose of 50 mg/day. Mean optimal dosage was 28 mg/day administered in two divided doses [21].

1.4.1.A.1.b] Behavioral syndrome

1]) Prepubertal hospitalized patients with anxiety symptoms and moderately severe aggression, age 5 to 12 years of age, were treated with a 5-milligram (mg)/day starting dose with titration upward by 5 to 10 mg every 3 days to a maximum dose of 50 mg/day. Mean optimal dosage was 28 mg/day administered in two divided doses [21].

1.4.1.A.1.c] Pervasive developmental disorder

1]) In pediatric patients, 6 to 17 years of age, with [pervasive developmental disorders](#), [buspirone](#) has been used at an initial dose of 5 milligrams (mg) three times daily, with the maximum dosage of 45 mg/day reached within three weeks. Mean dosage was 29.3 mg/day during the 6 to 8 week evaluation [42].

2.0] Pharmacokinetics[Onset and Duration](#)[Drug Concentration Levels](#)[ADME](#)**2.1] Onset and Duration****A]) Onset****1]) Initial Response**

a]) 1 week [201] [202] [203].

2.2] Drug Concentration Levels**A]) Time to Peak Concentration**

1]) 40 to 90 minutes (Prod Info [BuSpar\(R\)](#), 2001).

a]) Nonlinear pharmacokinetics have been suggested (Prod Info [BuSpar\(R\)](#), 2001).

2.3] ADME**2.3.1] Absorption****A]) Bioavailability**

1]) low (Prod Info [BuSpar\(R\)](#), 2001).

a) Undergoes extensive first-pass metabolism (Prod Info BuSpar(R), 1998).

b) Absorption from tablet form is about 90% of that from an equivalent dose in solution (Prod Info BuSpar(R), 2001).

B) Effects of Food

1) increases peak plasma concentration and area under the curve (AUC) (Prod Info BuSpar(R), 2001)

a) Administration of BUSPIRONE with food results in a decreased rate of absorption but an increase in the total amount of unchanged drug reaching the systemic circulation [206] [207]. This is felt to be due to a decrease in the extent of "first-pass" metabolism.

b) Buspirone should be taken consistently, either with food or always without food (Prod Info BuSpar(R), 2001).

c) Large amounts of grapefruit juice should be avoided during treatment with buspirone (Prod Info BuSpar(R), 2001).

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

a) 86% (Prod Info BuSpar(R), 2001).

1) Sixty-nine percent of the bound BUSPIRONE is bound to albumin; the remainder is bound to alpha-1-acid glycoprotein [210].

B) Distribution Kinetics

1) Volume of Distribution

a) 5.3 L/kg [211].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, extensive first-pass metabolism (Prod Info BuSpar(R), 2001).

a) Metabolized primarily by oxidation mediated by cytochrome P450 3A4 (Prod Info BuSpar(R), 2001).

B) Metabolites

1) 1-pyrimidinyl piperazine (1-PP), active [213].

a) Probably not significant in humans (Prod Info BuSpar(R), 2001).

2) hydroxylated derivatives

3)) glucuronides

2.3.4] Excretion

A)) Kidney

1)) Renal Excretion (%)

a)) 29% to 63% (Prod Info [BuSpar\(R\)](#), 2001)

2)) Twenty-nine to sixty-three percent of a dose is eliminated within 24 hours, primarily as metabolites (Prod Info [BuSpar\(R\)](#), 2001).

3)) Less than 1% of an orally administered dose of [BUSPIRONE](#) is excreted unchanged in the urine, with 10% being excreted as hydrolyzable conjugates [207] [214].

B)) Other

1)) Feces, 18% to 38% (Prod Info [BuSpar\(R\)](#), 2001).

2.3.5] Elimination Half-life

A)) Parent Compound

1)) ELIMINATION HALF-LIFE

a)) 2.4 to 2.7 hours [215] [207] [216].

B)) Metabolites

1)) 1-pyrimidinyl [piperazine](#), 4.8 to 6.1 hours [217] [218]

2.3.6] Extracorporeal Elimination

A)) [Hemodialysis](#)

1)) Dialyzable: No [214]

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.1] Contraindications

A)) [Buspirone](#) Hydrochloride

1)) hypersensitivity to [buspirone](#) hydrochloride [64]

3.2] Precautions

A)) [Buspirone](#) Hydrochloride

1) CNS-depressant drugs should be withdrawn gradually before starting therapy with [buspirone](#); [buspirone](#) will not block the withdrawal syndrome often seen with cessation of sedative/hypnotic drugs [64]

2) concomitant use with alcohol, MAOI, or consumption of large amounts of grapefruit juice; use should be avoided [64]

3) [hepatic impairment](#), severe; use not recommended due to increased plasma levels and $t(1/2)$ [64]

4) [renal impairment](#), severe; use not recommended due to increased plasma levels and $t(1/2)$ [64]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Buspirone](#) Hydrochloride

3.3.1.A.1] [Congestive heart failure](#)

a) Incidence: less than 0.1% [64]

b) In pooled data of approximately 3000 patients who received [buspirone](#) hydrochloride during premarketing evaluation, [congestive heart failure](#) occurred rarely, in less than 0.1% of patients [64].

3.3.1.A.2] [Myocardial infarction](#)

a) Incidence: less than 0.1% [64]

b) In pooled data of approximately 3000 patients who received [buspirone](#) hydrochloride during premarketing evaluation, [myocardial infarction](#) occurred rarely, in less than 0.1% of patients [64].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] [Buspirone](#) Hydrochloride

3.3.3.A.1] [Hyperprolactinemia](#)

a) Dose-dependent increases in serum prolactin have been described with [buspirone](#) [71].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Buspirone](#) Hydrochloride

3.3.4.A.1] [Diarrhea](#)

a) Incidence: 2% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, diarrhea was reported in 2% of adult patients who received [buspirone](#) (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.4.A.2] [Nausea](#)

a) Incidence: 8% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, nausea was reported in 8% of adult patients who received [buspirone](#) (n=477) compared with 5% of patients who received placebo (n=464) [64].

c) Gastrointestinal disturbance, primarily nausea, was reported as reason for discontinuation in 1.2% of approximately 2200 patients who received buspirone during clinical trials in the treatment of anxiety [64].

3.3.9] Neurologic Effects

3.3.9.A] Buspirone Hydrochloride

3.3.9.A.1] Akathisia

a) Incidence: 0.1% to 1% [64]

b) In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, akathisia occurred infrequently, in 0.1% to 1% of patients [64].

c) Akathisia has been reported in postmarketing experience with buspirone therapy [64].

3.3.9.A.2] Cerebrovascular accident

a) Incidence: less than 0.1% [64]

b) In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, cerebrovascular accident occurred rarely, in less than 0.1% of patients [64].

3.3.9.A.3] Confusion

a) Incidence: 2% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, confusion was reported in 2% of adult patients who received buspirone (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.9.A.4] Dizziness

a) Incidence: 12% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, dizziness was reported in 12% of adult patients who received buspirone (n=477) compared with 3% of patients who received placebo (n=464) [64].

c) CNS disturbances, including dizziness, insomnia, nervousness, drowsiness, and lightheadedness, were reported as reason for discontinuation in 3.4% of approximately 2200 patients who received buspirone during clinical trials in the treatment of anxiety [64].

3.3.9.A.5] Dyskinesia

a) Dyskinesias, acute and tardive, have been reported in postmarketing experience with buspirone therapy [64].

b) In a trial consisting of 22 pediatric patients with pervasive developmental disorders, 1 child developed abnormal involuntary movements of the mouth, cheeks, and tongue following treatment with buspirone 20 mg/day for 10 months. The child was diagnosed with buspirone-associated orofacial-lingual dyskinesia following extensive evaluation. Within 2 weeks of discontinuation, the abnormal movements disappeared completely [65].

c) Oral dyskinesia was described in an 85-year-old woman with degenerative dementia after receiving buspirone (5 mg orally twice daily) for the treatment of continuous agitation. On day 3 of therapy, the patient developed continuous tongue thrusting, lip smacking, and side-to-side mouth movements. Buspirone was discontinued but dyskinesia persisted, despite therapy with benztropine 0.5 mg orally twice daily. At 4-month follow-up, the dyskinesia still persisted although somewhat diminished in intensity. It is possible that buspirone may induce dyskinesia via effects on dopaminergic systems,

similar to neuroleptic agents. However, a definite cause-effect relationship could not be established in this case [66].

3.3.9.A.6] Dystonia

- a)] **Dystonia** has been reported in postmarketing experience with **buspirone** therapy [64].
- b)] Two patients experienced movement disorders during **buspirone** treatment. The first patient experienced cervical-cranial **dystonia** and tremors and the second patient experienced an exacerbation of spasmodic torticollis and **tardive dyskinesia**. Both patients' symptoms improved upon discontinuation of **buspirone** and treatment with suppressive therapy but were still present 1 year later and 5 years later, respectively [67].
- c)] A 64-year-old woman developed painful **dystonia** of the left hand 3 to 4 weeks after starting **buspirone** 10 mg 4 times daily and **trazodone** 150 mg daily for anxiety and depression, respectively. About 12 weeks later, she complained of pain in the left wrist and hand that remitted during sleep. On physical examination, she had **focal dystonia** of the upper left extremity, increased axial and upper extremity tone, a mildly shuffling gait, and an asymmetrical upper extremity athetosis, but no evidence of inflammation in the painful hand. Discontinuation of **buspirone** provided partial improvement, while **levodopa/carbidopa** caused increased symptoms. Trihexyphenidyl and **baclofen** were tried separately without success. Although the patient improved, with athetosis and gait abnormality gone after 3 to 4 months off **buspirone**, she continued to have local **dystonia** and rigidity a year after discontinuation of **buspirone** and an unstated period after discontinuation of **trazodone**. The patient had previously developed extrapyramidal symptoms (shuffling gait and mild bradykinesia) during therapy with **amitriptyline** and **haloperidol** or **thioridazine**, although these agents had been discontinued and the extrapyramidal symptomatology had resolved several months before initiation of **buspirone**. However, it is possible that the patient had an extrapyramidal syndrome before therapy with neuroleptics; thus, **buspirone** may have worsened an **extrapyramidal disorder** rather than caused it to appear de novo [68].

3.3.9.A.7] Excitement

- a)] Incidence: 2% [64]
- b)] In pooled data from 17 short-term, placebo-controlled clinical trials, excitement was reported in 2% of adult patients who received **buspirone** (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.9.A.8] Headache

- a)] Incidence: 6% [64]
- b)] In pooled data from 17 short-term, placebo-controlled clinical trials, headache was reported in 6% of adult patients who received **buspirone** (n=477) compared with 3% of placebo-treated patients (n=464) [64].
- c)] Miscellaneous disturbances, including headache and fatigue, were reported as reason for discontinuation in 1.1% of approximately 2200 patients who received **buspirone** during clinical trials in the treatment of anxiety [64].

3.3.9.A.9] Insomnia

- a)] CNS disturbances, including dizziness, insomnia, nervousness, drowsiness, and lightheadedness, were reported as reason for discontinuation in 3.4% of approximately 2200 patients who received **buspirone** during clinical trials in the treatment of anxiety [64].

3.3.9.A.10] Lightheadedness

- a) Incidence: 3% [64]
- b) In pooled data from 17 short-term, placebo-controlled clinical trials, lightheadedness was reported in 3% of adult patients who received **buspirone** (n=477) compared with less than 1% of patients who received placebo (n=464) [64].
- c) Central nervous system disturbances, including dizziness, insomnia, nervousness, drowsiness, and lightheadedness, were reported as reason for discontinuation in 3.4% of approximately 2200 patients who received **buspirone** during clinical trials in the treatment of anxiety [64].

3.3.9.A.11] Numbness

- a) Incidence: 2% [64]
- b) In pooled data from 17 short-term, placebo-controlled clinical trials, numbness was reported in 2% of adult patients who received **buspirone** (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.9.A.12] Paresthesia

- a) Incidence: 1% [64]
- b) In pooled data from 17 short-term, placebo-controlled clinical trials, paresthesia was reported in 1% of adult patients who received **buspirone** (n=477) compared with less than 1% of placebo-treated patients (n=464) [64].
- c) In an 8-week, placebo-controlled study of **buspirone** in patients with **major depression** with moderate anxiety (n=155) which allowed rapid titration of daily **buspirone** doses up to 90 mg/day (mean dose, 56 mg/day in patients completing at least 1 week of the trial), 10% of patients in the **buspirone** group reported paresthesia compared with 0% in the placebo group [69].

3.3.9.A.13] Seizure

- a) Incidence: 0.1% to 1% [64]
- b) In pooled data of approximately 3000 patients who received **buspirone** hydrochloride during premarketing evaluation, seizures occurred infrequently, in 0.1% to 1% of patients [64].
- c) In a study using **buspirone** in the treatment of **alcohol withdrawal syndrome**, 1 patient with a history of alcohol-related seizures reported an unwitnessed seizure [70].

3.3.9.A.14] Somnolence

- a) Incidence: 10% [64]
- b) In pooled data from 17 short-term, placebo-controlled clinical trials, drowsiness was reported in 10% of adult patients who received **buspirone** (n=477) compared with 9% of placebo-treated patients (n=464) [64].
- c) CNS disturbances, including dizziness, insomnia, nervousness, drowsiness, and lightheadedness, were reported as reason for discontinuation in 3.4% of approximately 2200 patients who received **buspirone** during clinical trials in the treatment of anxiety [64].

3.3.10] Ophthalmic Effects**3.3.10.A] **Buspirone** Hydrochloride****3.3.10.A.1] Blurred vision**

a) Incidence: 2% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, blurred vision was reported in 2% of adult patients who received buspirone (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.11] Otic Effects

3.3.11.A] Buspirone Hydrochloride

3.3.11.A.1] Tinnitus

a) Incidence: at least 1% [64]

b) In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, tinnitus occurred frequently, in at least 1% of patients [64].

3.3.12] Psychiatric Effects

3.3.12.A] Buspirone Hydrochloride

3.3.12.A.1] Dream disorder

a) Incidence: at least 1% [64]

b) In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, dream disturbances occurred frequently, in at least 1% of patients [64].

3.3.12.A.2] Dysphoric mood

a) Incidence: at least 1% [64]

b) In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, dysphoria occurred frequently, in at least 1% of patients [64].

c) Dysphoria, accompanied by vertigo and dizziness, was reported in 4 of 5 Japanese male volunteers given a single dose of buspirone 20 mg after previous exposure to a single dose of buspirone, up to 10 mg, did not produce dysphoria [75].

d) High single doses of oral buspirone (ie, 40 mg) have induced dysphoria, which was not seen with administration of buspirone 10 mg 3 times daily in repeated doses [76] [19] [77] [78] [79].

3.3.12.A.3] Feeling angry

a) Incidence: 2% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, anger was reported in 2% of adult patients who received buspirone (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.12.A.4] Feeling nervous

a) Incidence: 5% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, nervousness was reported in 5% of adult patients who received buspirone (n=477) compared with 1% of patients who received placebo (n=464) [64].

c) CNS disturbances, including dizziness, insomnia, nervousness, drowsiness, and lightheadedness, were reported as reason for discontinuation in 3.4% of approximately 2200 patients who received buspirone during clinical trials in the treatment of anxiety [64].

3.3.12.A.5] Hostile behavior

a) Incidence: 2% [64]

b) In pooled data from 17 short-term, placebo-controlled clinical trials, hostility was reported in 2% of adult patients who received [buspirone](#) (n=477) compared with less than 1% of patients who received placebo (n=464) [64].

3.3.12.A.6] Mania

a) Mania with flight of ideas, pressured speech, and elated mood have been reported with the therapeutic use of [buspirone](#). In this case the patient was also taking [disulfiram](#) 400 mg/day which may be a contributing factor [72].

b) Symptoms of racing thoughts, pressured speech, and sleep disturbances including 1 case of insomnia appeared as early as the second dose of [buspirone](#) and as late as the 40th day of therapy. All patients stopped taking [buspirone](#) and the symptoms resolved 1 to 5 days later. None of the patients was rechallenged with the drug. Further studies are needed to determine whether these symptoms are a reaction to [buspirone](#) alone or whether an interaction occurs between [buspirone](#) and [alprazolam](#) [73] [74].

3.3.12.A.7] Panic attack

a) An acute panic attack, with [hypertension](#), was reported on 2 occasions following single doses of [buspirone](#) 10 mg in a 40-year-old man with a history of [panic disorder](#). On the first occasion, [buspirone](#) was added to [clomipramine](#) therapy, and a panic attack with hypertensive symptoms was observed 20 hours following the [buspirone](#) dose. Prior to the second occasion, the patient was switched from [clomipramine](#) to [trimipramine](#); the patient was given [trimipramine](#) on day 1 (50 mg infusion), followed by [buspirone](#) 10 mg on day 2. Eight hours following the [buspirone](#) dose, a panic attack with [hypertension](#) was observed. The patient responded to [nifedipine](#) (10 mg sublingually) with a reduction in blood pressure and suppression of anxiety symptoms [80].

3.3.12.A.8] Psychotic disorder

a) Incidence: less than 0.1% [64]

b) In pooled data of approximately 3000 patients who received [buspirone](#) hydrochloride during premarketing evaluation, [psychosis](#) occurred rarely, in less than 0.1% of patients [64].

c) Two cases of [psychosis](#) were reported in children during treatment with [buspirone](#) [81].

3.3.13] Renal Effects

3.3.13.A] [Buspirone](#) Hydrochloride

3.3.13.A.1] Dysuria

a) Incidence: 0.1% to 1% [64]

b) In pooled data of approximately 3000 patients who received [buspirone](#) hydrochloride during premarketing evaluation, dysuria occurred infrequently, in 0.1% to 1% of patients [64].

3.3.13.A.2] Nocturia

a) Incidence: less than 0.1% [64]

b) In pooled data of approximately 3000 patients who received [buspirone](#) hydrochloride during premarketing evaluation, [nocturia](#) occurred rarely, in less than 0.1% of patients [64].

3.3.13.A.3] Nocturnal enuresis

- a)] Incidence: less than 0.1% [64]
- b)] In pooled data of approximately 3000 patients who received buspirone hydrochloride during premarketing evaluation, enuresis occurred rarely, in less than 0.1% of patients [64].

3.3.14] Reproductive Effects**3.3.14.A] Buspirone Hydrochloride****3.3.14.A.1] Orgasm incapacity**

- a)] One of 10 patients with obsessive-compulsive disorder noted onset of anorgasmia after buspirone (mean dose, 54 mg/day) was added to fluoxetine therapy (mean dose, 78 mg/day). The anorgasmia could not be definitely attributed to the buspirone or to an interaction between the 2 agents [82].

3.3.14.A.2] Priapism

- a)] Priapism and acute urinary retention were reported in a man after receiving buspirone 15 to 30 mg/day for 6 months [83].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding**A)] Teratogenicity/Effects in Pregnancy****1)] U.S. Food and Drug Administration's Pregnancy Category: Category B (All Trimesters)**

- a)] Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

2)] Australian Drug Evaluation Committee's (ADEC) Category: B1

- a)] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3)] Crosses Placenta: Unknown**4)] Clinical Management**

- a)] There are no data on the use of buspirone in pregnant women. The effects, if any, on the developing fetus are unknown. In animal studies, there was no evidence of fetal harm or impaired fertility with buspirone exposure. Because data regarding buspirone use during pregnancy are limited, the drug should be used during pregnancy only if clearly needed [101].

5)] Literature Reports

a)] There are no adequate and well-controlled studies of [buspirone](#) use during pregnancy. In animal reproduction studies, there was no evidence of fetal harm or impaired fertility when rats and rabbits were administered [buspirone](#) at doses approximately 30 times the maximum recommended human dose [101].

B)] Breastfeeding

1)] Micromedex Lactation Rating: Infant risk cannot be ruled out.

a)] Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2)] Clinical Management

a)] Adequate studies of [buspirone](#) use in nursing mothers are lacking. In rat studies, [buspirone](#) and its metabolites were shown to be excreted in breast milk. Therefore, [buspirone](#) should not be used by a nursing woman unless the drug is clinically necessary [101].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] [Almotriptan](#)

1)] Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2)] Summary: [Buspirone](#) use has been associated with [serotonin syndrome](#) in postmarketing evaluations [64], while [almotriptan](#) is known to affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment and at dosage increases is recommended if [almotriptan](#) and [buspirone](#) are used concurrently [154]. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99].

3)] Severity: major

4)] Onset: unspecified

5)] Substantiation: theoretical

6)] Clinical Management: Use caution with concomitant administration of [almotriptan](#) and [buspirone](#), as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, monitoring of patient during treatment and dosage increases is recommended [154].

7)] Probable Mechanism: additive serotonergic effect

3.5.1.B] [Amiodarone](#)

- 1) Interaction Effect: increased CYP1A2, CYP2C9, CYP2D6, CYP3A4, or P-glycoprotein substrate exposure
- 2) Summary: Concomitant use of [amiodarone](#) (an inhibitor of CYP1A2, CYP2C9, CYP2D6, CYP3A4, and of P-glycoprotein efflux transport) and drugs that are substrates of these metabolic enzymes and transporter may increase the exposure of these drugs. As [amiodarone](#) has a variable and long half-life, potential drug interaction may occur even after [amiodarone](#) is discontinued [140]. If [amiodarone](#) is used concomitantly (or after [amiodarone](#) is discontinued) with any of these drugs, use with caution, monitor for increased adverse effects, and consider dose adjustment as appropriate.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amiodarone](#) (an inhibitor of CYP1A2, CYP2C9, CYP2D6, CYP3A4, and of P-glycoprotein efflux transport) and drugs that are substrates of these metabolic enzymes and transporter may increase the exposure of these drugs [140]. If [amiodarone](#) is used concomitantly with any of these drugs, use with caution, monitor for increased adverse effects, and consider dose adjustment as appropriate.
- 7) Probable Mechanism: inhibition of CYP1A2-, CYP2C9-, CYP2D6-, or CYP3A4-mediated metabolism, or P-glycoprotein-mediated efflux transport by [amiodarone](#)

3.5.1.C] Amitriptyline

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amitriptyline](#), a serotonin reuptake inhibitor [115], and [buspirone](#) affect the serotonergic neurotransmitter systems. [Serotonin syndrome](#) has been associated with [buspirone](#) use during postmarketing surveillance [64]. Concomitant use should be approached with caution due to the additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amitriptyline](#) and [buspirone](#) are used concurrently. Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, and diarrhea), and mental status changes (eg, agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with concomitant administration of [amitriptyline](#) and [buspirone](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#) [115] [64]. If coadministration is required, appropriate monitoring may be warranted.
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.D] Amoxapine

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Both [amoxapine](#) [163] and [buspirone](#) affect the serotonergic neurotransmitter systems. [Serotonin syndrome](#) has been reported with [buspirone](#) use during postmarketing surveillance [64]. Concomitant use should be approached with caution due to additive serotonergic effects and the potential for increased risk of [serotonin syndrome](#). Symptoms of [serotonin syndrome](#) include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and

shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99]. Monitoring for signs and symptoms of [serotonin syndrome](#) during treatment may be warranted if [amoxapine](#) and [buspirone](#) are used concurrently.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of [amoxapine](#) and [buspirone](#), as it may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effect

3.5.1.EJ [Carbamazepine](#)

1J) Interaction Effect: decreased exposure of CYP3A4 substrates

2J) Summary: Concomitant use of [carbamazepine](#) (a potent CYP3A4 inducer) and a CYP3A4 substrate may result in decreased exposure of the CYP3A4 substrate. If used concomitantly, monitoring of the CYP3A4 substrate concentrations or dose adjustments may be needed [143] [144].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [carbamazepine](#), a potent CYP3A4 inducer, and a CYP3A4 substrate may result in decreased exposure of the CYP3A4 substrate. If used concomitantly, monitoring of the CYP3A4 substrate concentrations or dose adjustments may be needed [143] [144].

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism by [carbamazepine](#)

3.5.1.FJ [Carbinoxamine](#)

1J) Interaction Effect: additive CNS effects

2J) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects [116] [117]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended [116] [117]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.

7J) Probable Mechanism: additive effects on the CNS

3.5.1.GJ [Citalopram](#)

1J) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: An isolated case has been reported of [serotonin syndrome](#) and [hyponatremia](#) after ingesting higher than prescribed doses of [citalopram](#) and [buspirone](#). Notably, [citalopram](#) alone has been associated with post-marketing reports of [serotonin syndrome](#), [hyponatremia](#), and syndrome of inappropriate

antidiuretic hormone (SIADH) [134]. [Serotonin syndrome](#) can result in death if it is not recognized and correctly treated [135].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor patients receiving concurrent [buspirone](#) and [citalopram](#) for signs and symptoms of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes). The risk of developing [serotonin syndrome](#) may increase as dose increases.

7) Probable Mechanism: serotonin reuptake inhibition

8) Literature Reports

a) A 69-year-old female with recurrent [depressive episodes](#) was treated with [citalopram](#) 40 mg daily for approximately 18 months. [Buspirone](#) 10 mg daily was initiated, and the patient developed signs of [serotonin syndrome](#) in six weeks. She became disoriented, confused, hyperactive, agitated, and experienced auditory and visual hallucinations. She also could not stand or walk, and experienced involuntary tremors of her arms and legs. Upon admission to the hospital, her serum sodium level was 121 mmol/L. Following the discontinuation of [citalopram](#) and [buspirone](#), the neuromuscular and psychiatric symptoms gradually disappeared, and her serum sodium level increased to 137 mmol/L without specific treatment. It was discovered that the patient had been taking higher than prescribed doses of both [citalopram](#) and [buspirone](#) in the few days before her symptoms appeared. Four days after the discontinuation of [citalopram](#), her serum concentration was 155 nmol/L. Although the [citalopram](#) level was not measured upon admission, it was extrapolated to be more than 1200 nmol/L. By comparison, 33 patients receiving [citalopram](#) 40 mg daily had a mean steady state [citalopram](#) level of 256 nmol/L [133].

3.5.1.H] Clorgyline

1) Interaction Effect: [hypertensive crisis](#)

2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) clorgyline is not recommended [107]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [buspirone](#) with monoamine oxidase inhibitors (MAOI), including clorgyline, is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of [buspirone](#).

7) Probable Mechanism: unknown

8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing,

headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [106].

3.5.1.I] Clozapine

- 1) Interaction Effect: an increased risk of [gastrointestinal bleeding](#) and [hyperglycemia](#)
- 2) Summary: A 33-year old male who was taking [clozapine](#) for more than a year without adverse effects, but developed [gastrointestinal bleeding](#) and severe [hyperglycemia](#) when [buspirone](#) therapy was also instituted, has been reported [139]. Since [clozapine](#) can cause [gastric ulcer](#) and [hyperglycemia](#) by itself, it is possible that [buspirone](#) augmented the serum level of [clozapine](#), either by enzyme inhibition or by displacing [clozapine](#) from its binding sites.
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be observed when [clozapine](#) and [buspirone](#) are coadministered. Monitor blood glucose levels and watch for signs and symptoms of bleeding, especially from the gastrointestinal tract.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 33-year old institutionalized paranoid schizophrenic male was placed on [clozapine](#) 600 mg daily for hallucinations and serious assaultiveness. A series of other medications failed to control his feelings of anxiety, so [buspirone](#) therapy was initiated at a dose of 5 mg three times daily. His [clozapine](#) serum level was 390 ng/mL (range 100-700 ng/mL) prior to [buspirone](#) therapy. One month after [buspirone](#) was started, the dose was increased to 20 mg daily, and the patient began to complain of nausea and epigastric pain. After an episode of coffee-grounds emesis, he was transferred to the intensive care unit, where he was found to have severe [acidosis](#). His blood glucose level was over 1300 mg/dL, and hematocrit had dropped to 31 mL/dL. Both the [clozapine](#) and [buspirone](#) were discontinued. An [upper gastrointestinal series](#) did not reveal a source of the bleeding, and the patient required [insulin](#) therapy until his blood glucose level eventually returned to normal. [Clozapine](#) was reinitiated because of his assaultiveness, and he had no recurrence of adverse effects [139].

3.5.1.J] Cobicistat

- 1) Interaction Effect: increased [buspirone](#) exposure
- 2) Summary: Cobicistat is a strong CYP3A4 inhibitor. Caution is advised when using cobicistat together with a CYP3A4 substrate such as [buspirone](#) as this may result in elevated plasma concentrations of [buspirone](#). If concomitant use is required, [buspirone](#) should be initiated at a lower dose [171] and clinical monitoring is recommended [172]. A dose reduction for [buspirone](#) may be required [171] [172].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised when using cobicistat together with a CYP3A4 substrate such as [buspirone](#) as this may result in elevated plasma concentrations of [buspirone](#). If concomitant use is required, [buspirone](#) should be initiated at a lower dose [171] and clinical monitoring is recommended [172]. A dose reduction for [buspirone](#) may be required [171] [172].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [buspirone](#)

3.5.1.K] Crizotinib

- 1) Interaction Effect: increased [buspirone](#) plasma concentrations
- 2) Summary: The concomitant use of crizotinib (a moderate CYP3A inhibitor) with [buspirone](#) (a CYP3A substrate) may increase [buspirone](#) plasma concentrations. Dose reduction of [buspirone](#) may be required when coadministered with crizotinib [108].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [buspirone](#) with crizotinib may cause increased [buspirone](#) plasma concentrations. If concomitant use is required, dose reduction may be warranted for [buspirone](#) [108].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [buspirone](#) metabolism by crizotinib

3.5.1.L] Dabrafenib

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of dabrafenib (a CYP3A4 inducer) with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. During drug interaction studies, dabrafenib decreased the AUC of [midazolam](#) (a CYP3A4 substrate) by 74%. Because a similar reaction can be expected with other CYP3A4 substrates, use of a drug other than a CYP3A4 substrate is recommended. If concomitant use cannot be avoided, monitor patients for loss of efficacy [150].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of dabrafenib, a CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If possible, substitute the use of CYP3A4 substrates during dabrafenib therapy. If concomitant use of dabrafenib and a CYP3A4 substrate is required, monitor patients for loss of efficacy [150].
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by dabrafenib
- 8) Literature Reports

- a) Administration of dabrafenib 150 mg twice daily for 15 days with a single 3 mg [midazolam](#) dose, decreased [midazolam](#) AUC by 74%. Dabrafenib is a CYP3A4 inducer, while [midazolam](#) is a CYP3A4 substrate [150].

3.5.1.M] Deferasirox

- 1) Interaction Effect: reduced [buspirone](#) plasma concentrations
- 2) Summary: Although the [buspirone/deferasirox](#) interaction has not been studied, concomitant use of [deferasirox](#), a potential CYP3A4 inducer, and [midazolam](#), another CYP3A4 substrate, resulted in decreases in [midazolam](#) Cmax and AUC by 23% and 17%. Therefore, caution should be used when [buspirone](#) and [deferasirox](#) are coadministered due to the potential for reduced [buspirone](#) plasma concentrations [86].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [buspirone](#) and [deferasirox](#) may decrease [buspirone](#) plasma concentrations. Therefore, caution should be used when [buspirone](#) and [deferasirox](#) are coadministered [86].

7J) Probable Mechanism: induction of CYP3A4-mediated [buspirone](#) metabolism by [deferasirox](#)

3.5.1.N] Desvenlafaxine

1J) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: Desvenlafaxine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during treatment initiation and dose increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [165].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use extreme caution with coadministration of desvenlafaxine and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Immediate discontinuation of both agents and supportive symptomatic treatment is warranted if [serotonin syndrome](#) develops [165].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.O] Diltiazem

1J) Interaction Effect: an increased risk of enhanced [buspirone](#) effects

2J) Summary: [Diltiazem](#) has been shown to increase the area under the concentration-time curve (AUC) and the maximum concentration (C_{max}) of [buspirone](#) by 5.5-fold (range 3.3-fold to 7.4-fold) and 4.1-fold, respectively. Because the elimination half-life of [buspirone](#) was not altered by the presence of [diltiazem](#), it can be assumed that this interaction is a result of inhibition of the cytochrome P450 3A4-mediated first-pass metabolism of [buspirone](#) in the gut wall and liver [174].

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Monitor patients who are receiving [diltiazem](#) and [buspirone](#) for enhanced sedative effects of [buspirone](#). Low doses of [buspirone](#) should be employed.

7J) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated first-pass metabolism of [buspirone](#)

8J) Literature Reports

aJ) Nine healthy volunteers participated in a randomized, placebo-controlled, three-phase crossover study to investigate possible interactions of [buspirone](#) with [verapamil](#) and [diltiazem](#). Subjects received [verapamil](#) 80 mg, [diltiazem](#) 60 mg, or placebo orally three times daily for five doses, with [buspirone](#) 10 mg being administered orally following the fifth dose. During the placebo phase, the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of [buspirone](#) was 2.6 ng/mL and 6.9 ng/mL/hr, respectively. In the presence of [diltiazem](#), the C_{max} was 10.3 ng/mL and the AUC was 36.8 ng/mL/hr. The elimination half-life and the time to C_{max} (t_{max}) were not significantly altered by [diltiazem](#). While this pharmacokinetic interaction was

associated with only a minor [impairment of psychomotor](#) performance, an increased frequency of side effects of [buspirone](#) was seen in the [diltiazem](#) phase [173].

3.5.1.P| [Erythromycin](#)

- 1) Interaction Effect: increased [buspirone](#) plasma concentrations; increased [buspirone](#) side effects (impaired psychomotor performance, sedation)
- 2) Summary: Peak plasma concentrations and bioavailability of [buspirone](#) were significantly increased by [erythromycin](#) in eight healthy females in a double blind randomized study [152]. If concomitant administration is necessary, low doses of [buspirone](#) (2.5 mg twice daily) should be utilized and further dose adjustments should be based on clinical assessment [153].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: [Erythromycin](#) should be avoided in patients treated with [buspirone](#). If this combination cannot be avoided, low doses of [buspirone](#) (2.5 mg twice daily) are recommended. Also monitor the patient for side effects of [buspirone](#).
- 7) Probable Mechanism: inhibition by [erythromycin](#) of cytochrome P450 3A4-mediated metabolism of [buspirone](#)
- 8) Literature Reports

a) Peak plasma concentrations and bioavailability of [buspirone](#) were significantly increased by [erythromycin](#) in eight healthy females in a double blind randomized study. Patients were randomized to receive either [erythromycin](#) 500 mg three times daily or placebo for four days. On the fourth day a single dose of [buspirone](#) 10 mg was given with the last dose of [erythromycin](#). Compared to placebo, the average peak plasma level of [buspirone](#) was increased from 1 ng/mL to 5 ng/mL by [erythromycin](#). The average area under the plasma concentration time curve from time zero to infinity was increased from 3.3 ng/mL h for placebo to 19.5 ng/mL h with [erythromycin](#). The elimination half-life of [buspirone](#) was not effected by [erythromycin](#). This may be because the [erythromycin](#) was discontinued when the [buspirone](#) was given. Performance in psychomotor tests was significantly impaired in subjects receiving both [erythromycin](#) and [buspirone](#) compared to subjects receiving [buspirone](#) and placebo. [Erythromycin](#) should be avoided in patients treated with [buspirone](#) [151].

3.5.1.Q| [Eslicarbazepine Acetate](#)

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [94], use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [94], use caution and monitor the patient closely.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by eslicarbazepine acetate

3.5.1.R| [Fentanyl](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) and increased risk of CNS depression

2) Summary: Concurrent use of [buspirone](#) and [fentanyl](#) may cause additive CNS depression [124] and can potentially cause [serotonin syndrome](#). [Fentanyl](#) is considered proserotonergic and has been associated with [serotonin syndrome](#) when coadministered with serotonergic drugs [125]. [Serotonin syndrome](#) has been reported with [buspirone](#), and in vitro studies have shown that it has a high affinity of for 5-hydroxytryptamine-1 receptors [64]. During coadministration, use caution, reduce the dose of [buspirone](#) or [fentanyl](#), and monitor for sedation or [respiratory depression](#), especially when initiating therapy with [fentanyl](#) [124]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities, autonomic hyperactivity, and mental status changes. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care [99].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [buspirone](#) and [fentanyl](#) may cause additive CNS depression, including [respiratory depression](#), hypotension, and profound sedation or coma [124], and may potentially cause [serotonin syndrome](#) [125]. When [buspirone](#) and [fentanyl](#) are coadministered, use with caution, reduce the dose of one or both drugs, and monitor for signs and symptoms of sedation and [respiratory depression](#), especially when initiating therapy with [fentanyl](#) [124]. Monitor patients for symptoms of [serotonin syndrome](#), including neuromuscular abnormalities (eg, hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (eg, [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (eg, agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99].

7) Probable Mechanism: additive serotonergic effects; additive CNS depression

3.5.1.S] [Fluoxetine](#)

1) Interaction Effect: worsening of psychiatric symptoms

2) Summary: In a number of case reports, the concomitant use of [buspirone](#) and [fluoxetine](#) has been reported to result in a worsening of the patient's underlying anxiety/or [obsessive-compulsive disorder](#) [187] [188] [189]. One case report describes a patient maintained on [fluoxetine](#) who presented with symptoms of [serotonin syndrome](#), including confusion, diaphoresis, incoordination, diarrhea, and myoclonus after [buspirone](#) was added to his drug regimen [190].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If possible, the combination of [fluoxetine](#) and [buspirone](#) should be avoided; however, if deemed clinically appropriate, monitor for worsening of psychiatric symptoms.

7) Probable Mechanism: possible inhibition of [buspirone](#) serotonergic effects

8) Literature Reports

a) One of 10 patients with [obsessive-compulsive disorder](#) experienced [anorgasmia](#) after [buspirone](#) (mean maximum dose, 54 mg daily) was added to [fluoxetine](#) therapy (mean maximum dose, 78 mg daily). The [anorgasmia](#) could not be definitely attributed to the [buspirone](#) or to an interaction between the two agents. Both [fluoxetine](#) and [buspirone](#) have reported a low incidence of sexual dysfunction when taken as monotherapy [182] [183] [184].

b) Three cases of potentiation of the antidepressant effects of [fluoxetine](#) by [buspirone](#) have been reported [185]. All three patients had treatment-resistant symptoms of depression, obsessional traits, anxiety, and a history of eating disorder prior to adding [buspirone](#) to the treatment regimen.

c) A case report describes a 37-year-old male patient maintained on fluoxetine 20mg per day who began combination treatment with buspirone to augment the actions of fluoxetine. The starting dose of buspirone was gradually increased from 5mg twice a day to 30mg twice a day over approximately five weeks. After five days at this dose, the patient complained of confusion, diaphoresis, incoordination, diarrhea, and myoclonus, which was thought to be serotonin syndrome. The patient's symptoms resolved shortly after discontinuation of buspirone [186].

3.5.1.T] Ginkgo

- 1) Interaction Effect: changes in mental status
- 2) Summary: The addition of Ginkgo biloba and/or St. John's Wort to therapy with buspirone and fluoxetine may have precipitated a hypomanic episode in a case report [85]. It is unclear if Ginkgo or St. John's Wort, the combination of both, or other patient factors, contributed to the effect. Caution is advised.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution patients taking buspirone to discuss the use of nonprescription medicines, herbs, and dietary supplements with their doctor or pharmacist. If a patient presents with hypomanic symptoms when taking buspirone, inquire about the use of nonprescription medicines, herbs, and dietary supplements. It is recommended to avoid Ginkgo in patients taking buspirone, especially in combination with other psychotropic medicines.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of fluoxetine, buspirone, Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild traumatic brain injury with fluoxetine 20 milligrams (mg) twice daily and buspirone 15 mg twice daily. Several weeks prior to presentation, buspirone was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, melatonin, and St. John's Wort in unspecified doses. Melatonin was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the brain injury was considered a possible contributor [84].

3.5.1.U] Haloperidol

- 1) Interaction Effect: increased haloperidol concentrations
- 2) Summary: Concurrent administration of buspirone, a CYP3A4 substrate [101] and haloperidol may increase the plasma concentrations of haloperidol via interference of CYP3A4-mediated haloperidol metabolism. In pharmacokinetic studies, coadministration of CYP3A4 or CYP2D6 substrates or inhibitors and haloperidol resulted in mild to moderate increases in haloperidol plasma concentrations [160]. If the 2 drugs are coadministered, monitoring and dose adjustments may be required.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable

6) Clinical Management: Concurrent administration of buspirone and haloperidol may increase the plasma concentrations of haloperidol [160]. If the 2 drugs are coadministered, monitoring and dose adjustments may be required.

7) Probable Mechanism: interference with CYP3A4-mediated haloperidol metabolism

8) Literature Reports

a) In a study of normal volunteers, coadministration of buspirone and haloperidol resulted in increased serum haloperidol concentrations [101].

b) In pharmacokinetic studies, coadministration of CYP3A4 or CYP2D6 substrates or inhibitors and haloperidol resulted in mild to moderate increases in haloperidol plasma concentrations [160] [161].

3.5.1.V] Hydrocodone

1) Interaction Effect: increased risk of CNS depression (ie, respiratory depression, profound sedation, coma)

2) Summary: Use caution with the concomitant use of hydrocodone and a CNS depressant as this may result in additive CNS effects and increase the risk of respiratory depression, profound sedation, coma, and/or death. If combination therapy is required, reduce the initial hydrocodone dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of respiratory depression, sedation, or hypotension [145].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of hydrocodone and a CNS depressant may result in additive CNS effects and increase the risk of respiratory depression, profound sedation, coma, and/or death. If combination therapy is required, reduce the initial hydrocodone dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of respiratory depression, sedation, or hypotension [145].

7) Probable Mechanism: additive CNS depression

3.5.1.W] Hydromorphone

1) Interaction Effect: an increase in CNS or respiratory depression

2) Summary: The concomitant use of hydromorphone and other CNS depressants, such as sedatives and hypnotics, may result in additive CNS depressant effects, including respiratory depression, hypotension, profound sedation, and coma. When administering hydromorphone and a sedative or hypnotic together, dose reduction of one or both of the medications should be considered [181].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of hydromorphone and other CNS depressants, such as sedatives or hypnotics, may result in respiratory depression, hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered [181].

7) Probable Mechanism: additive effects

3.5.1.X] Hydroxytryptophan

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes)

2J) Summary: **Buspirone** use has been associated with **serotonin syndrome** in postmarketing evaluations [64]. Concomitant use of **buspirone** and hydroxytryptophan, another serotonergic agent, should be approached with caution due to the additive effects and the potential for increased risk of **serotonin syndrome**. Monitoring for signs and symptoms of **serotonin syndrome** may be warranted if **buspirone** and hydroxytryptophan are used concurrently.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant administration of **buspirone** and hydroxytryptophan, as this may result in additive serotonergic effects and may increase the risk of **serotonin syndrome**. If coadministration is required, appropriate monitoring may be warranted.

7J) Probable Mechanism: additive serotonergic effects

3.5.1.Y| Ioflupane I 123

1J) Interaction Effect: interference with ioflupane I 123 imaging

2J) Summary: The ioflupane component of ioflupane I 123 binds to the **dopamine** transporter allowing for striatal **dopamine** transport visualization using **single photon emission computed tomography** (SPECT) **brain imaging**. Because **buspirone** binds with high affinity to the **dopamine** transporter, there is the potential for interference with ioflupane I 123 imaging. It is unknown whether discontinuing **buspirone** prior to ioflupane I 123 administration may minimize this interference [164]. The potential for imaging interference should be considered when administering ioflupane I 123 to patients who are already receiving **buspirone**.

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of **buspirone** and ioflupane I 123 may result in interference with ioflupane I 123 imaging. It is unknown whether discontinuing **buspirone** prior to ioflupane I 123 administration may minimize the interference [164]. Consider the potential for imaging interference when administering ioflupane I 123 to patients who are already receiving **buspirone**.

7J) Probable Mechanism: unknown

3.5.1.Z| Iproniazid

1J) Interaction Effect: **hypertensive crisis**

2J) Summary: Concurrent administration of **buspirone** with the monoamine oxidase inhibitor (MAOI) iproniazid is not recommended [159]. Cases of **hypertensive crisis** have occurred when MAOIs have been administered simultaneously with **buspirone**. This interaction may be mediated by the affinity of **buspirone** for serotonin receptors.

3J) Severity: major

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Coadministration of **buspirone** with monoamine oxidase inhibitors (MAOI), including iproniazid, is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of **buspirone**.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) **Increased blood pressure** has been reported in patients receiving concomitant **buspirone** and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving **phenelzine** 30 mg to 45 mg daily.

After a single dose of buspirone 5 mg, the patient's blood pressure increased to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving tranlycypromine for approximately three weeks before initiating buspirone 15 mg daily. Three days after beginning buspirone, his blood pressure increased from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on tranlycypromine 10 mg three times daily. Buspirone 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking phenelzine 15 mg three times daily was given buspirone 5 mg daily. After three days, the blood pressure increased to 160/110 mmHg. Discontinuation of buspirone in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of buspirone for serotonin receptors [158].

3.5.1.AA] Isocarboxazid

- 1) Interaction Effect: hypertensive crisis
- 2) Summary: Concurrent administration of buspirone with the monoamine oxidase inhibitor (MAOI) isocarboxazid is contraindicated [103] [104]. Cases of hypertensive crisis have occurred when MAOIs have been administered simultaneously with buspirone. This interaction may be mediated by the affinity of buspirone for serotonin receptors.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of buspirone with monoamine oxidase inhibitors (MAOI) is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of buspirone.
- 7) Probable Mechanism: increased norepinephrine availability
- 8) Literature Reports

a) Increased blood pressure has been reported in patients receiving concomitant buspirone and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving phenelzine 30 mg to 45 mg daily. After a single dose of buspirone 5 mg, the patient's blood pressure increased to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving tranlycypromine for approximately three weeks before initiating buspirone 15 mg daily. Three days after beginning buspirone, his blood pressure increased from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on tranlycypromine 10 mg three times daily. Buspirone 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking phenelzine 15 mg three times daily was given buspirone 5 mg daily. After three days, the blood pressure increased to 160/110 mmHg. Discontinuation of buspirone in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of buspirone for serotonin receptors [102].

3.5.1.AB] Itraconazole

- 1) Interaction Effect: increased buspirone plasma concentrations; increased buspirone side effects (impaired psychomotor performance, sedation)
- 2) Summary: Peak plasma concentrations and bioavailability of buspirone were significantly increased by itraconazole in eight healthy females in a double blind randomized study [110]. If concomitant administration of buspirone and itraconazole is necessary, low doses of buspirone (2.5 mg twice daily)

should be utilized and further dosing adjustments should be based on clinical assessment [111]. Significant increases in plasma concentrations of **buspirone** occurs when coadministered with **itraconazole** [112].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: **Itraconazole** should be avoided in patients treated with **buspirone**. If this combination cannot be avoided, low doses of **buspirone** (2.5 mg twice daily) should be used. Monitor the patient for side effects of **buspirone**.

7) Probable Mechanism: inhibition by **itraconazole** of cytochrome P450 3A4-mediated metabolism of **buspirone**

8) Literature Reports

a) Peak plasma concentrations and bioavailability of **buspirone** were significantly increased by **itraconazole** in eight healthy females in a double blind randomized study. Patients were randomized to receive either **itraconazole** 100 mg two times daily or placebo for four days. On the fourth day a single dose of **buspirone** 10 mg was given with the last dose of **itraconazole**. Compared to placebo, the average peak plasma level of **buspirone** was increased from 1 ng/mL to 13.4 ng/mL by **itraconazole**. The average area under the plasma concentration time curve from time zero to infinity was increased from 3.3 ng/mL h for placebo, to 63.2 ng/mL h with **itraconazole**. The elimination half-life of **buspirone** was not effected by **itraconazole**. This may be because the **itraconazole** was discontinued when the **buspirone** was given. Performance in psychomotor tests was significantly impaired in subjects receiving both **itraconazole** and **buspirone**, compared to subjects receiving **buspirone** and placebo. **Itraconazole** should be avoided in patients treated with **buspirone** [109].

3.5.1.AC] **Ketoconazole**

1) Interaction Effect: increased **buspirone** exposure

2) Summary: Use caution when coadministering **buspirone**, a CYP3A4 substrate, and **ketoconazole**, a CYP3A4 inhibitor, as this may result in increased **buspirone** exposure and possibly increase the risk of **buspirone** adverse effects. If concomitant use is required, initiate **buspirone** treatment at a lower dose and adjust subsequent doses based on clinical assessment. Monitor patients for adverse effects [162].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of **buspirone**, a CYP3A4 substrate, and **ketoconazole**, a CYP3A4 inhibitor, should be undertaken with caution as this may result in increased **buspirone** exposure and possibly increase the risk of adverse effects. If coadministration is required, initiate **buspirone** treatment at a lower dose and adjust subsequent doses based on clinical assessment. Monitor patients carefully for adverse effects [162].

7) Probable Mechanism: inhibition of CYP3A-mediated **buspirone** metabolism

3.5.1.AD] **Levomilnacipran**

1) Interaction Effect: increased risk of **serotonin syndrome** (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Levomilnacipran is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of potentially life-threatening **serotonin syndrome** and should be approached with extreme caution. If coadministration is required, monitor closely for signs and symptoms of **serotonin syndrome**, especially during initiation of the

coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [177].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use extreme caution with coadministration of levomilnacipran and another serotonergic drug, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [177].

7) Probable Mechanism: additive serotonergic effects

3.5.1.AE] [Linezolid](#)

1) Interaction Effect: increased risk of [serotonin syndrome](#) (incoordination, cognitive dysfunction, [hyperpyrexia](#), hyperreflexia) and increased risk for elevated blood pressure

2) Summary: Spontaneous reports of [serotonin syndrome](#) associated with the co-administration of [linezolid](#) and serotonergic agents have been reported. Concomitant use of these agents may cause symptoms of [serotonin syndrome](#) such as cognitive dysfunction, [hyperpyrexia](#), hyperreflexia, and incoordination. If these agents are used concomitantly, the patient should be monitored for [serotonin syndrome](#) effects. If symptoms occur, discontinuation of either one or both of the agents may be necessary [100]

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [buspirone](#) and [linezolid](#) is contraindicated, as it may result in [serotonin syndrome](#). However, if concomitant use is clinically warranted, monitor for signs and symptoms of [serotonin syndrome](#), such as neuromuscular abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including [tachycardia](#), mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and [delirium](#)). [Serotonin syndrome](#) can be life-threatening. If [serotonin syndrome](#) develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99] [100]. If concomitant use with [buspirone](#) is discontinued, monitor for symptoms of discontinuation, including central nervous system disturbances (dizziness, insomnia, nervousness, drowsiness), light-headedness; nausea, headache, and fatigue [101].

7) Probable Mechanism: [linezolid](#) inhibition of monoamine oxidase resulting in an increased concentration of serotonin

3.5.1.AF] [Lorcaserin](#)

1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [tachycardia](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: Lorcaserin is a serotonergic drug and concomitant use with another agent that affects the serotonergic neurotransmitter system, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, may result in an increased risk of [serotonin syndrome](#) and should be approached with extreme caution. [Serotonin syndrome](#) may be life threatening and symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered

drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [138].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use extreme caution with concomitant administration of lorcaserin and another serotonergic drug, such as an SSRI, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant, as this may result in additive serotonergic effects and may increase the risk of [serotonin syndrome](#). If coadministration is required, careful monitoring is recommended, especially during treatment initiation and dose increases. Drug discontinuation and supportive symptomatic treatment is recommended if [serotonin syndrome](#) develops [138].

7J) Probable Mechanism: additive serotonergic effects

3.5.1.AG| [Loxapine](#)

1J) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of [respiratory depression](#), hypotension, oversedation, and syncope

2J) Summary: Concomitant use of [loxapine](#), a CNS depressant, and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and other CNS depressants are used concurrently, consider a dose reduction of the CNS depressant [136] and use with caution [137].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [loxapine](#) and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and CNS depressants are used concurrently, consider a dose reduction of the CNS depressant [136] and use with caution [137].

7J) Probable Mechanism: additive CNS depression

3.5.1.AH| [Meclizine](#)

1J) Interaction Effect: an increase in CNS depression or [respiratory depression](#)

2J) Summary: Concomitant use of [meclizine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives may potentiate CNS depression cognitive and motor effects. Avoid concurrent use of alcohol while taking [meclizine](#) [167] [168] [169] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [meclizine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may potentiate CNS depression. Avoid concurrent use of alcohol with [meclizine](#) [167] [168] [169] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

7J) Probable Mechanism: additive effects

3.5.1.AI| [Methylene Blue](#)

1J) Interaction Effect: an increased risk of [serotonin syndrome](#) (labile blood pressure, [hyperthermia](#), neuromuscular abnormalities, mental status changes, gastrointestinal symptoms)

2) Summary: Concurrent use of [buspirone](#) and methylene blue (an MAOI) is not recommended [101]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [130]. In settings where urgent treatment with methylene blue is not required, discontinue [buspirone](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [buspirone](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [buspirone](#) must be discontinued immediately. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Buspirone](#) may be resumed 24 hours after the last dose of methylene blue has been given [131].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of [buspirone](#) and methylene blue (an MAOI) is not recommended [101]. Concurrent administration may result in potentially fatal [serotonin syndrome](#) [130]. In settings where urgent treatment with methylene blue is not required, discontinue [buspirone](#) at least 14 days prior to initiating treatment with methylene blue. If no alternative pharmacological or non-pharmacological treatment is available and urgent treatment with methylene blue is required in a patient on [buspirone](#) therapy, and the potential benefits outweigh the risk of [serotonin syndrome](#), [buspirone](#) must be discontinued immediately. Monitor for [serotonin syndrome](#) for 2 weeks or until 24 hours after the last dose of methylene blue has been administered, whichever comes first. [Buspirone](#) may be resumed 24 hours after the last dose of methylene blue has been given [131].

7) Probable Mechanism: inhibition of MAO-mediated serotonin metabolism by methylene blue

3.5.1.AJ] [Mitotane](#)

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [146] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [146] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [mitotane](#)

3.5.1.AK] [Moclobemide](#)

1) Interaction Effect: [hypertensive crisis](#)

2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) moclobemide is not recommended [96]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [buspirone](#) with monoamine oxidase inhibitors (MAOI) is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of [buspirone](#).

7) Probable Mechanism: unknown

8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [95].

3.5.1.AL] [Nefazodone](#)

1) Interaction Effect: increased [buspirone](#) plasma concentrations

2) Summary: Concomitant administration of [buspirone](#) 2.5 mg or 5 mg twice daily and [nefazodone](#) 250 mg twice daily resulted in large increases in the [buspirone](#) plasma concentration in healthy volunteers. Maximum concentration (C_{max}) was increased up to 20-fold and the area under the concentration-time curve (AUC) was elevated by as much as 50-fold. In addition, plasma concentrations of 1-PP, a [buspirone](#) metabolite, were decreased by 50%. If concomitant administration of [buspirone](#) and [nefazodone](#) is necessary, low doses of [buspirone](#) (2.5 mg twice daily) should be utilized and further dosing adjustments should be based on clinical assessment [122] [123].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: [Nefazodone](#) should be avoided in patients treated with [buspirone](#). If this combination cannot be avoided, low doses of [buspirone](#) (2.5 mg twice daily) should be used. Monitor the patient for side effects of [buspirone](#).

7) Probable Mechanism: inhibition by [nefazodone](#) of cytochrome P450 3A4-mediated metabolism of [buspirone](#)

3.5.1.AM] [Nialamide](#)

1) Interaction Effect: [hypertensive crisis](#)

2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) [nialamide](#) is not recommended [127]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Coadministration of buspirone with monoamine oxidase inhibitors (MAOI), including nialamide, is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of buspirone.

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased blood pressure has been reported in patients receiving concomitant buspirone and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving phenelzine 30 mg to 45 mg daily. After a single dose of buspirone 5 mg, the patient's blood pressure increased to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving tranylcypromine for approximately three weeks before initiating buspirone 15 mg daily. Three days after beginning buspirone, his blood pressure increased from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on tranylcypromine 10 mg three times daily. Buspirone 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking phenelzine 15 mg three times daily was given buspirone 5 mg daily. After three days, the blood pressure increased to 160/110 mmHg. Discontinuation of buspirone in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of buspirone for serotonin receptors [126].

3.5.1.AN] Oxycodone

1) Interaction Effect: an increase in CNS or respiratory depression

2) Summary: Concomitant use of oxycodone with other CNS depressants, such as sedatives or hypnotics, may result in respiratory depression, hypotension, profound sedation, and coma. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate oxycodone controlled-release tablets at one-third to one-half of the usual dosage [90] and initiate extended-release oxycodone hydrochloride/acetaminophen at one-half the usual dose [91].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of oxycodone with other CNS depressants, such as sedatives or hypnotics, may result in respiratory depression, hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate oxycodone controlled-release tablets at one-third to one-half of the usual dosage [90] and initiate extended-release oxycodone hydrochloride/acetaminophen at one-half the usual dose [91].

7) Probable Mechanism: additive effects

3.5.1.AO] Paclitaxel

1) Interaction Effect: altered paclitaxel plasma concentrations

2) Summary: Paclitaxel metabolism is catalyzed via CYP3A4 isoenzymes. Use caution if paclitaxel is administered to a patient who is taking buspirone (a CYP3A4 substrate), as concomitant use may result in altered paclitaxel plasma concentrations [170]. Monitoring for therapeutic effect of paclitaxel and paclitaxel dose adjustment may be warranted if concomitant use with buspirone is required.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Use caution if [paclitaxel](#) is administered to a patient who is taking a known substrate of CYP3A4, such as [buspirone](#) [170]. If concomitant use is required, monitoring and dose adjustment of [paclitaxel](#) may be warranted.

7) Probable Mechanism: interference with CYP3A-mediated [paclitaxel](#) metabolism

3.5.1.AP] Pargyline

1) Interaction Effect: [hypertensive crisis](#)

2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) pargyline is not recommended [129]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Coadministration of [buspirone](#) with monoamine oxidase inhibitors (MAOI), including pargyline, is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of [buspirone](#).

7) Probable Mechanism: unknown

8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [128].

3.5.1.AQ] Perampanel

1) Interaction Effect: potentiation of impaired cognitive and motor effects

2) Summary: Caution is advised if perampanel is coadministered with CNS depressants. Although not studied with other CNS depressants, perampanel had additive or supra-additive effects to alcohol on complex tasks (eg, driving), enhanced alcohol's effect on alertness and vigilance, and increased levels of anger, confusion, and depression in a pharmacodynamic study with healthy volunteers. Concomitant use of perampanel may potentiate the impaired cognitive and motor effects of CNS depressants [141].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised if perampanel is coadministered with CNS depressants. Concomitant use of perampanel may potentiate the impaired cognitive and motor effects of CNS depressants [141].

7) Probable Mechanism: additive CNS depression

3.5.1.AR] Phenelzine

- 1) Interaction Effect: [hypertensive crisis](#)
- 2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) [phenelzine](#) is contraindicated [93]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) [phenelzine](#) is contraindicated. Allow 14 days to elapse between withdrawal of the MAOI and administration of [buspirone](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [92].

3.5.1.AS] Piperazine

- 1) Interaction Effect: increased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised with administration of a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [175]. If concomitant administration is required, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised with administration of a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [175]. If concomitant administration is required, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by piperazine

3.5.1.AT] Primidone

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: **Primidone** is metabolized to **phenobarbital** [147] (a strong CYP3A4 inducer). Concomitant use of **primidone** with certain CYP3A4 substrates may result in decreased exposure of the CYP3A4 substrate and should be avoided if clinically possible. If concomitant administration is required, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use if clinically possible. If coadministration is required, use caution and monitor the patient closely.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by **primidone**

3.5.1.AU] Procarbazine

- 1) Interaction Effect: **hypertensive crisis**
- 2) Summary: Concurrent administration of **buspirone** with the monoamine oxidase inhibitor (MAOI) **procarbazine** is not recommended [156]. Cases of **hypertensive crisis** have occurred when MAOIs have been administered simultaneously with **buspirone**. This interaction may be mediated by the affinity of **buspirone** for serotonin receptors.
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of **buspirone** with monoamine oxidase inhibitors (MAOI) is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of **buspirone**.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) **Increased blood pressure** has been reported in patients receiving concomitant **buspirone** and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving **phenelzine** 30 mg to 45 mg daily. After a single dose of **buspirone** 5 mg, the patient's **blood pressure increased** to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving **tranylcypromine** for approximately three weeks before initiating **buspirone** 15 mg daily. Three days after beginning **buspirone**, his **blood pressure increased** from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on **tranylcypromine** 10 mg three times daily. **Buspirone** 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking **phenelzine** 15 mg three times daily was given **buspirone** 5 mg daily. After three days, the **blood pressure increased** to 160/110 mmHg. Discontinuation of **buspirone** in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of **buspirone** for serotonin receptors [155].

3.5.1.AV] Ranolazine

- 1) Interaction Effect: increased **buspirone** plasma concentrations

- 2) Summary: Concurrent administration of [buspirone](#) and [ranolazine](#) may increase the plasma concentration of [buspirone](#) via inhibition of CYP3A4-mediated [buspirone](#) metabolism. Dosage adjustment of [buspirone](#) may be required when coadministered with [ranolazine](#) [176].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [buspirone](#) and [ranolazine](#) may increase the plasma concentrations of [buspirone](#); therefore, a reduction in the [buspirone](#) dose may be required [176].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [buspirone](#) metabolism by [ranolazine](#)

3.5.1.AW] [Rifampin](#)

- 1) Interaction Effect: reduced anxiolytic effects of [buspirone](#)
- 2) Summary: In a study to determine the effects of [rifampin](#) on [buspirone](#) pharmacokinetics and pharmacodynamics, [rifampin](#) significantly induced the metabolism of [buspirone](#), resulting in reduced anxiolytic effects. [Rifampin](#) is a potent inducer of cytochrome P450 3A4 enzymes, and [buspirone](#) is suspected of being a substrate of CYP3A4 [98].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving [buspirone](#) and [rifampin](#) for [buspirone](#) efficacy. Doses of [buspirone](#) may need to be increased when [rifampin](#) is coadministered.
- 7) Probable Mechanism: induction of cytochrome P450 3A4-mediated first-pass metabolism of [buspirone](#)
- 8) Literature Reports

a) Ten healthy volunteers participated in a randomized, placebo-controlled, cross-over study design to determine the effects of [rifampin](#) on the pharmacokinetics and pharmacodynamics of [buspirone](#). Subjects ingested [rifampin](#) 600 mg or matching placebo once daily for five days, and then received [buspirone](#) 30 mg as a single oral dose on day 6. Although the normal dose of [buspirone](#) is 5 mg to 10 mg, 30 mg was used in this study to allow more accurate determinations of plasma [buspirone](#) concentrations after [rifampin](#) administration. Maximum concentrations (C_{max}) of [buspirone](#) averaged 6.6 ng/mL during the placebo phase, but decreased to 0.84 ng/mL following [rifampin](#) pretreatment. Time to C_{max} (t_{max}) also decreased from 1.5 hours to 0.5 hours. Half-life of [buspirone](#) was reduced from 2.8 hours to 1.3 hours in the [rifampin](#) phase, and the area under the concentration-time curve (AUC) also decreased from 22 ng/mL/h to 1.64 ng/mL/h. Results of psychomotor tests, including the digit symbol substitution test, critical [flicker fusion test](#), postural sway test measures, and subjective drowsiness and overall drug effect, revealed that [rifampin](#) greatly decreased the sedative and anxiolytic effect of [buspirone](#). These results were consistent with what would be expected from the pharmacokinetic changes seen in [buspirone](#) following [rifampin](#) pretreatment [97].

3.5.1.AX] [Ritonavir](#)

- 1) Interaction Effect: an increased risk of extreme sedation, [respiratory depression](#) and confusion
- 2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [buspirone](#), causing a potential risk of extreme sedation and [respiratory depression](#). A decrease in [buspirone](#) dose may be needed [191].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical

- 6) Clinical Management: Monitor patients for signs and symptoms of [buspirone](#) toxicity (sedation, confusion, [respiratory depression](#)). Reduce doses of [buspirone](#) as required.
- 7) Probable Mechanism: increased [buspirone](#) serum concentrations due to decreased [buspirone](#) metabolism

3.5.1.AY] [Selegiline](#)

- 1) Interaction Effect: [hypertensive crisis](#)
- 2) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) [selegiline](#) is not recommended [88] [89]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors.
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [buspirone](#) with [selegiline](#) is not recommended. Allow 14 days to elapse between withdrawal of [selegiline](#) and administration of [buspirone](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [87].

3.5.1.AZ] [St John's Wort](#)

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes) or [hypomania](#)
- 2) Summary: One case of possible [serotonin syndrome](#) associated with concomitant use of [buspirone](#) and [St. John's Wort](#) has been reported [120]. The addition of [St. John's Wort](#) and/or [Ginkgo](#) to therapy with [buspirone](#) and [fluoxetine](#) may have precipitated a hypomanic episode in a case report [121]. It is unclear if [Ginkgo](#) or [St. John's Wort](#), the combination of both, or other patient factors, contributed to the effect. Caution is advised.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution patients taking [buspirone](#) to discuss the use of nonprescription medicines, herbs, and dietary supplements with their doctor or pharmacist. If a patient presents with hypomanic or serotonergic symptoms when taking [buspirone](#), inquire about the use of nonprescription

medicines, herbs, and dietary supplements. It is recommended to avoid St. John's Wort in patients taking [buspirone](#), especially in combination with other psychotropic medicines.

7j) Probable Mechanism: additive serotonergic effect

8j) Literature Reports

a) A 27-year-old female experienced symptoms suggestive of [serotonin syndrome](#) after 2 months of adding St. John's Wort to her [buspirone](#) therapy. She was prescribed [buspirone](#) 30 milligrams (mg) daily for [generalized anxiety disorder](#) and she self-medicated with St. John's Wort (Hypericum 2000 Plus(R), Herb Valley, Australia) three tablets daily (containing hypericin 1 mg, tyrosine 250 mg, and magnesium 25 mg per tablet). She experienced symptoms of nervousness, aggressiveness, hyperactivity, insomnia, blurred vision, confusion, disorientation, and changes in vocal tone. St. John's Wort was tapered and discontinued and her symptoms resolved within one week [118].

b) A 42-year-old female experienced symptoms consistent with a mixed hypomanic episode following concomitant use of [fluoxetine](#), [buspirone](#), Ginkgo biloba, and St. John's Wort. The symptoms resolved following discontinuation of Ginkgo and St. John's Wort. The patient was being treated for depression following a mild [traumatic brain injury](#) with [fluoxetine](#) 20 milligrams (mg) twice daily and [buspirone](#) 15 mg twice daily. Several weeks prior to presentation, [buspirone](#) was increased to 20 mg twice daily for persistent anxiety and the patient began taking Ginkgo biloba, [melatonin](#), and St. John's Wort in unspecified doses. [Melatonin](#) was considered unlikely to have contributed to her symptoms. Ginkgo and St. John's Wort were considered possible contributors since they may potentiate antidepressants, and considering the temporal relationship between the use of the herbs and onset of symptoms and discontinuation of the herbs and resolution of symptoms. However, the [brain injury](#) was considered a possible contributor [119].

3.5.1.BA] Tapentadol

1j) Interaction Effect: an increase in central nervous system and [respiratory depression](#)

2j) Summary: The concomitant use of tapentadol with central nervous system depressants including sedatives (eg, [alprazolam](#), [midazolam](#), or [zolpidem](#)) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma. When administering tapentadol and a sedative together, dosage of one or both agents may be reduced [132].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: theoretical

6j) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when tapentadol and sedatives are used in combination. A reduction in dose of one or both drugs may be necessary [132].

7j) Probable Mechanism: additive effects

3.5.1.BB] Toloxatone

1j) Interaction Effect: [hypertensive crisis](#)

2j) Summary: Concurrent administration of [buspirone](#) with the monoamine oxidase inhibitor (MAOI) toloxatone is not recommended [114]. Cases of [hypertensive crisis](#) have occurred when MAOIs have been administered simultaneously with [buspirone](#). This interaction may be mediated by the affinity of [buspirone](#) for serotonin receptors. As a reversible and selective monoamine oxidase inhibitor, toloxatone may not potentiate the effects of [buspirone](#) to the same frequency, extent, and duration observed with other MAOIs. However, until further studies confirm the safety and efficacy of this combined therapy, concomitant use is contraindicated.

- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [buspirone](#) with monoamine oxidase inhibitors (MAOI), including tolloxatone, is not recommended. Allow 14 days to elapse between withdrawal of the MAOI and administration of [buspirone](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) [Increased blood pressure](#) has been reported in patients receiving concomitant [buspirone](#) and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving [phenelzine](#) 30 mg to 45 mg daily. After a single dose of [buspirone](#) 5 mg, the patient's [blood pressure increased](#) to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving [tranlycypromine](#) for approximately three weeks before initiating [buspirone](#) 15 mg daily. Three days after beginning [buspirone](#), his [blood pressure increased](#) from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on [tranlycypromine](#) 10 mg three times daily. [Buspirone](#) 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking [phenelzine](#) 15 mg three times daily was given [buspirone](#) 5 mg daily. After three days, the [blood pressure increased](#) to 160/110 mmHg. Discontinuation of [buspirone](#) in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of [buspirone](#) for serotonin receptors [113].

3.5.1.BC] [Tramadol](#)

- 1) Interaction Effect: increased risk of [serotonin syndrome](#)
- 2) Summary: Use caution when coadministering [tramadol](#), including use within the recommended dose range, and a serotonergic agent as this may increase the risk for [serotonin syndrome](#). If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dosage increases [105].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [tramadol](#), including use within the recommended dose range, with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of [tramadol](#) with a serotonergic agent is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation and dosage increases [105].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.BD] [Tranlycypromine](#)

- 1) Interaction Effect: [hypertensive crisis](#)
- 2) Summary: The use of [tranlycypromine](#) in patients receiving [buspirone](#) has resulted in [increased blood pressure](#). The concurrent use of these two medications is contraindicated [149].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable

6) Clinical Management: The concurrent use of buspirone and tranylcypromine is contraindicated. Wait at least two weeks after stopping an MAO inhibitor before starting buspirone therapy, or at least ten days after stopping buspirone before initiating therapy with an MAO inhibitor.

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased blood pressure has been reported in patients receiving concomitant buspirone and monoamine oxidase inhibitors. To date, four cases have been described. In the first, a 76-year-old female with a history of labile blood pressure was receiving phenelzine 30 mg to 45 mg daily. After a single dose of buspirone 5 mg, the patient's blood pressure increased to 170/110 mmHg, remained elevated for several hours, then returned to baseline. The second patient, a male in his 30's, was receiving tranylcypromine for approximately three weeks before initiating buspirone 15 mg daily. Three days after beginning buspirone, his blood pressure increased from 110/86 mmHg to 160/100 mmHg. The third patient was a 42-year-old male on tranylcypromine 10 mg three times daily. Buspirone 5 mg daily was added after a few weeks and the patient developed flushing, headache, and elevation of blood pressure to 180/110 mmHg. In the final case, a 35-year-old male who was taking phenelzine 15 mg three times daily was given buspirone 5 mg daily. After three days, the blood pressure increased to 160/110 mmHg. Discontinuation of buspirone in all four patients resulted in a return of blood pressure to baseline. It is speculated that the mechanism of this interaction may be related to the affinity of buspirone for serotonin receptors [148].

3.5.1.BE] Trazodone

1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Both buspirone and trazodone affect the serotonergic neurotransmitter systems. Concomitant use should be approached with caution due to the additive effects and the potential for increased risk of serotonin syndrome [157]. Monitoring for signs and symptoms of serotonin syndrome may be warranted if buspirone and trazodone are used concurrently. Symptoms of serotonin syndrome include neuromuscular abnormalities (including hyperreflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivity (including tachycardia, mydriasis, diaphoresis, the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). Serotonin syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therapy as necessary [99].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant administration of buspirone and trazodone, as this may result in additive serotonergic effects and may increase the risk of serotonin syndrome [157]. If coadministration is required, appropriate monitoring may be warranted.

7) Probable Mechanism: additive serotonergic effect

3.5.1.BF] Verapamil

1) Interaction Effect: an increased risk of enhanced buspirone effects

2) Summary: Verapamil has been shown to increase both the area under the concentration-time curve (AUC) and the maximum concentration (Cmax) of buspirone by 3.4-fold. Because the elimination half-life of buspirone was not altered by the presence of verapamil, it can be assumed that this interaction is a result of inhibition of the cytochrome P450 3A4-mediated first-pass metabolism of buspirone in the gut wall and liver [180].

3) Severity: moderate

- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients who are receiving [verapamil](#) and [buspirone](#) for enhanced sedative effects of [buspirone](#). Low doses of [buspirone](#) should be employed.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated first-pass metabolism of [buspirone](#)
- 8) Literature Reports

a) Nine healthy volunteers participated in a randomized, placebo-controlled, three-phase crossover study to investigate possible interactions of [buspirone](#) with [verapamil](#) and [diltiazem](#). Subjects received [verapamil](#) 80 mg, [diltiazem](#) 60 mg, or placebo orally three times daily for five doses, with [buspirone](#) 10 mg being administered orally following the fifth dose. During the placebo phase, the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of [buspirone](#) was 2.6 ng/mL and 6.9 ng/mL/hr, respectively. In the presence of [verapamil](#), the C_{max} was 8.8 ng/mL and the AUC was 24.3 ng/mL/hr. The elimination half-life and the time to C_{max} (t_{max}) were not significantly altered by [verapamil](#). While this pharmacokinetic interaction was associated with only a minor [impairment of psychomotor](#) performance, an increased frequency of side effects of [buspirone](#) was seen in the [verapamil](#) phase as compared to placebo [179].

3.5.1.BG| Vilazodone

- 1) Interaction Effect: increased risk of [serotonin syndrome](#) or [neuroleptic malignant syndrome](#)
- 2) Summary: Concurrent use of [buspirone](#) with vilazodone may result in [serotonin syndrome](#) or a [neuroleptic malignant syndrome](#) (NMS)-like reaction, which may be life-threatening. Symptoms may include agitation, hallucinations, coma, incoordination, [tachycardia](#), labile blood pressure, [hyperthermia](#), hyperreflexia, nausea, vomiting, and diarrhea. If treatment with [buspirone](#) and vilazodone is required, use caution and monitor patient for signs and symptoms of [serotonin syndrome](#) or NMS. Immediately discontinue both agents if a reaction occurs [142].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [buspirone](#) with vilazodone may result in [serotonin syndrome](#) or a [neuroleptic malignant syndrome](#) (NMS)-like reaction through additive serotonergic effects. Use caution if the coadministration of [buspirone](#) with vilazodone is required. Closely monitor for signs and/or symptoms of [serotonin syndrome](#) or NMS, especially during treatment initiation and dose increases, and immediately discontinue both agents if symptoms occur [142].
- 7) Probable Mechanism: additive serotonergic effect

3.5.1.BH| Vortioxetine

- 1) Interaction Effect: an increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: Vortioxetine is a serotonergic drug; concomitant use with another agent that affects the serotonergic neurotransmitter system may result in an increased risk of [serotonin syndrome](#) and should be approached with caution. [Serotonin syndrome](#) may be life-threatening. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, [tachycardia](#), labile blood pressure, [hyperthermia](#)), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If coadministration is required, monitor closely for signs and symptoms of [serotonin syndrome](#), especially during initiation of the coadministered drug and during dosage increases of either drug. If [serotonin syndrome](#) develops, discontinue both agents and initiate supportive symptomatic therapy [166].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of vortioxetine with serotonergic agents may increase the risk for [serotonin syndrome](#) and should be undertaken with caution. If concomitant use of vortioxetine with a serotonergic agent is clinically warranted, close monitoring of the patient is recommended, particularly during treatment initiation and dosage increases. If [serotonin syndrome](#) develops, discontinue vortioxetine and concomitant serotonergic agents and initiate supportive care [166].
- 7) Probable Mechanism: additive serotonergic effects

3.5.1.BI] [Zolpidem](#)

- 1) Interaction Effect: an increase in central nervous system depressant effects
- 2) Summary: The concomitant use of [zolpidem](#) with any central nervous system depressant agent including sedatives (eg, [alprazolam](#), [diazepam](#), or [midazolam](#)) may result in additive CNS depressant effects. Systematic evaluations of [zolpidem](#) in combination with other CNS-active drugs is limited. When administering [zolpidem](#) and a sedative together, dosage adjustments of one or both agents may be necessary [178].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Dosage adjustments may be necessary when [zolpidem](#) is administered with sedative/hypnotic drugs because of the potentially additive effects [178].
- 7) Probable Mechanism: additive effects

3.5.2] Drug-Food Combinations

3.5.2.A] Grapefruit Juice

- 1) Interaction Effect: an increased risk of [buspirone](#) toxicity (dizziness, sedation)
- 2) Summary: In a study involving ten healthy volunteers, grapefruit juice increased the peak plasma concentrations of [buspirone](#) by 4.3-fold and also resulted in an increase in the subjective overall drug effect. Although [buspirone](#) has a wide therapeutic index, patients should be cautioned against the ingestion of large quantities of grapefruit juice [193].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Patients receiving [buspirone](#) should be cautioned against the consumption of large quantities of grapefruit juice.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [buspirone](#) first-pass metabolism
- 8) Literature Reports

a) In a randomized, two-phase crossover study, ten healthy volunteers (four male and six female) ingested 200 mL of double-strength grapefruit juice or water three times daily for two days. On day 3, each participant was given [buspirone](#) 10 mg with grapefruit juice or water, followed by more grapefruit juice or water at 30 minutes and 90 minutes after [buspirone](#). Maximum concentration (C_{max}) increased from 1.96 ng/mL to 8.40 ng/mL and area under the concentration-time curve (AUC) rose from 4.32 ng/mL/hr to 29.8 ng/mL/hr during the grapefruit juice phase. Pharmacodynamically, the effect of [buspirone](#) as measured by the visual analog scale for subjective overall drug effect was significantly greater during the grapefruit juice phase than in the water phase. Large interindividual variability was seen between subjects, with the two female subjects

who were also receiving oral contraceptives showing a lesser extent of interaction. Although [buspirone](#) possesses a wide therapeutic index, patients should be cautioned against consuming large quantities of grapefruit juice with [buspirone](#) [192].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A) [Buspirone](#) Hydrochloride

1) Therapeutic

a) Physical Findings

1) Improvement in symptoms of anxiety (eg, motor tension, autonomic hyperactivity, apprehensive expectation, vigilance and scanning) indicates efficacy.

2) Periodically reassess efficacy with extended use (more than 3 to 4 weeks) [64].

4.2] Patient Instructions

A) [Buspirone](#) (By mouth)

[Buspirone](#)

Treats anxiety.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [buspirone](#).

How to Use This Medicine:

Tablet

Your doctor will tell you how much of this medicine to take and how often. Do not take more medicine or take it more often than your doctor tells you to.

You may take this medicine with or without food, but take it the same way each time.

You may need to take this medicine for 1 or 2 weeks before you begin to feel better.

If a Dose is Missed:

If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose.

Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine at room temperature, away from heat, moisture, and direct light.

Keep all medicine out of the reach of children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

You should not use [buspirone](#) when you are also using an MAO inhibitor (such as [Eldepryl®](#), [Marplan®](#), [Nardil®](#), [Parnate®](#)).

Do not eat grapefruit, drink grapefruit juice, or drink alcohol while you are using [buspirone](#).

Make sure your doctor knows if you are also using [cimetidine](#) ([Tagamet®](#)), [dexamethasone](#) ([Decadron®](#)), [diltiazem](#) ([Cardizem®](#), [Tiazac®](#)), [erythromycin](#) ([Erythro-Tab®](#)), [itraconazole](#) ([Sporanox®](#)), [nefazodone](#) ([Serzone®](#)), [rifampin](#) ([Rifadin®](#), [Rifamate®](#), [Rifater®](#)), [verapamil](#) ([Calan®](#), [Covera®](#)), or medicine for seizures (such as [Dilantin®](#), [Luminal®](#), [Tegretol®](#)).

Make sure your doctor knows if you are using any medicines that make you sleepy (such as sleeping pills, cold and allergy medicine, narcotic pain relievers, or sedatives).

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have kidney or liver disease.

Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- Fast or pounding heartbeat
- Numbness or tingling feeling
- Tremors or shaking

If you notice these less serious side effects, talk with your doctor:

- Drowsiness or weakness
- Dry mouth
- Feeling restless or nervous, trouble sleeping
- Headache
- Nausea, constipation, upset stomach

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Compared with [diazepam](#), [buspirone](#) produces less sedation, less effect on psychomotor and psychologic function, and a lower propensity for interaction with ethanol and CNS depressants, suggesting its use in patients for whom a sedative component is undesirable, or in the elderly who are generally more sensitive to the sedative effects of benzodiazepines. [Buspirone](#) appears to lack the abuse liability of [diazepam](#) and other benzodiazepines. Physical dependency and withdrawal symptoms have not been reported; thus, the drug may be desirable in patients prone to drug addiction. Due to minimal effects of [buspirone](#) in combination with ethanol, as compared with benzodiazepines, the drug may also be beneficial in the treatment of anxiety and anxiety/depression in the alcoholic.

B) [Buspirone](#) appears to be useful in anxious patients with a history of drug abuse due to its low abuse potential. Impairment of cognitive performance and functioning is less with [buspirone](#) as compared to benzodiazepines, and withdrawal and dependence do not appear to occur with [buspirone](#). The drug could provide advantages over benzodiazepines in patients with specific illnesses, such as [pulmonary disease](#). Controversial issues include a possibly slower onset of action with [buspirone](#) as compared to benzodiazepines. [Buspirone](#) lacks muscle relaxant properties and has a lower sedative potential as compared to benzodiazepines. In addition, it is unclear whether previous benzodiazepine use will render patients resistant to [buspirone](#), and more studies are required. Although the drug has not been associated with withdrawal symptoms when stopped abruptly following administration for up to 6

months, it has failed to prevent withdrawal symptoms from benzodiazepine use in several studies; the drug is not indicated as substitution therapy for benzodiazepines when benzodiazepines are discontinued abruptly.

C) At least several days of regular dosing with [buspirone](#) may be required for anxiolytic efficacy to become apparent. Implications include the need to advise patients not to expect immediate benefit, and the inappropriateness of attempting to use [buspirone](#) to treat brief anxious states on an as-needed basis [257] or where a rapid onset of action is otherwise needed [258]. Studies in a rat model suggest that acute [buspirone](#) doses achieve greater anxiolytic efficacy when administered against a background of established, chronic [buspirone](#) treatment [259], supporting the proposal that repeated administration of [buspirone](#) is required for optimal anxiolytic effect.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) [Buspirone](#), a nonbenzodiazepine anxiolytic agent, is chemically unrelated to any existing psychotropic agents. The drug is an azaspirodecanedione derivative, with the chemical name of 8-(4-(4-(2-pyrimidinyl)-1-piperazinyl) butyl-2-azaspiro(4,5) decane-7,9-dione [215]. The drug is pharmacologically different from phenothiazines, butyrophenones, tricyclic antidepressants, MAO inhibitors, and benzodiazepines [227]. [Buspirone](#) appears to produce anxiolytic effects via serotonergic and dopaminergic effects.

2) [Buspirone](#) was initially investigated as an antipsychotic agent [228] [215]; however, studies in schizophrenic patients were disappointing [229]. Subsequently anxiolytic effects with minimal development of ataxia or psychomotor dysfunction were observed in animals [215] [227] and clinical studies have demonstrated fewer side effects from [buspirone](#) as compared to [clorazepate](#) or [diazepam](#) [230].

3) The mechanism of action of [buspirone](#) remains obscure [231]. The drug lacks the anticonvulsant, sedative, and muscle relaxant effect of benzodiazepines [232] [233] [207], and has been termed "anxiolytic" because of these characteristics [234]. [Buspirone](#) does not bind to the benzodiazepine-GABA-chloride ion receptor complex in vitro [235]. [Buspirone](#) has potent effects on the dopaminergic system, interacting with [dopamine](#) receptors in vitro [236] and acting pharmacologically as an agonist, antagonist, or both (in vivo and in vitro) [215] [236] [213]. [Buspirone](#) appears to block presynaptic [dopamine](#) receptors selectively and causes an increased firing rate in midbrain [dopamine](#) neurons [237] [236]. The drug has been shown to lower [acetylcholine](#) in selected parts of the brain, whereas benzodiazepines increase brain [acetylcholine](#) [238]. It has been felt that the interaction of [buspirone](#) with dopaminergic pathways may account for its anxiolytic effects [239]. However, MJ 13805, a derivative of [buspirone](#), does not affect dopaminergic pathways, but produces similar antiaggressive and anticonflict actions [215], indicating that effects of [buspirone](#) on dopaminergic pathways may not be the primary mechanism of action [240].

4) Neurochemical studies have shown that [buspirone](#) has no affinity for benzodiazepine receptors and that it does not bind to [GABA](#) or alpha-2 adrenergic receptors (Garrattini et al, 1982) [236], suggesting that it does not bind to receptors typically associated with the anxiolytic effects of drugs [213]. Additionally, the action of [buspirone](#) is not blocked by the benzodiazepine receptor antagonist [flumazenil](#) [241] [242] [240]. Other investigators have demonstrated in vivo that high doses of [buspirone](#) can increase the binding of benzodiazepines, suggesting an effect of [buspirone](#) or a metabolite on the GABA-benzodiazepine receptor-chloride ionophore complex [240] [242] [207]. However, more recent studies (both in vitro and in vivo) have not found any effect of the drug on the binding of benzodiazepines [243]. A metabolite of [buspirone](#), 1-pyrimidinyl [piperazine](#) (1-PP), is present in the brain at higher concentrations than the parent drug, and may contribute to the pharmacologic effect of [buspirone](#) [213] [231]. The mechanism of the anxiolytic effects of [buspirone](#) is complex, and further studies are required.

5) An effect of [buspirone](#) on decreasing the activity of serotonergic neurons in the nuclei raphe has also been observed, as well as an increase in the impulse flow in the locus ceruleus, the center of noradrenergic

activity [207]. Both [buspirone](#) and its metabolite 1-PP have high affinity for serotonin receptors. These mechanisms have been thought to be involved in the drug's therapeutic effects. [Buspirone](#) has been classified as a "midbrain modulator" with selective anxiolytic activity by some investigators due to its variety of effects on midbrain-receptor systems [244] [207].

6J) [Buspirone](#) has been classified as a selective serotonin subtype 1A (5-HT1A) partial agonist, with activity at both presynaptic and postsynaptic 5-HT1A receptors in vitro [235].

BJ) REVIEW ARTICLES

1J) Reviews of the non-benzodiazepine anxiolytics, including [buspirone](#), have been published [245] [246] [247] [248] [241]. Other similar agents being evaluated are trazolate, zopidone, CL218,872, CGS9896, MK-801, fenobam, and gepirone.

2J) Reviews of the efficacy and toxicity of [buspirone](#) have been provided [249] [250] [251]; (Taylor, 1988) [252].

3J) The use of [buspirone](#) in smoking cessation has been reviewed [253].

4J) A review of the dependence and abuse potential and the effects of [buspirone](#) withdrawal in animals and man has been provided [254].

5J) A review of animal studies that evaluate the abuse and addiction potential of [buspirone](#) and summarized anecdotal and clinical evidence of the low abuse liability of [buspirone](#) in humans has been provided [255].

6J) [Buspirone](#) has been reviewed as an alternative to benzodiazepines in anxiety related disorders [256].

7J) The efficacy of [buspirone](#) has been reviewed in the treatment of alcohol dependence (Malec et al, 1996).

4.5J Therapeutic Uses

4.5.AJ [Buspirone](#)

4.5.A.1J [Dementia](#)

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF [DEMENTIA](#)

4.5.BJ [Buspirone](#) Hydrochloride

4.5.B.1J [Alcoholism](#)

aJ) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

bJ) Summary:

May not directly decrease alcohol craving and consumption in alcoholic subjects

May improve the accompanying psychological symptoms associated with alcohol abuse

c) Adult:

1) **Buspirone** did not have a direct effect on alcohol craving and consumption in a double-blind, placebo-controlled, 12-week study in 36 alcoholic subjects, but there was improvement in associated psychopathological symptoms (Malec et al, 1996). **Buspirone** 10 milligrams (mg) twice daily (BID) was given for the first 2 weeks, then increased to 20 mg BID for the remainder of the study. Of 57 original subjects, 9 in the placebo group and 12 in the **buspirone** group dropped out. There was a significant decrease in ethanol consumption in both groups. Five scales on the Hopkins Symptoms Check List 90-Revised (global severity index, obsessive compulsive, interpersonal sensitivity, depression, and hostility) were significantly improved in the **buspirone** group. Dizziness, lightheadedness, drowsiness, and nausea occurred significantly more often in the buspirone-treated group. The findings of this study were limited by the small sample size, high dropout rate, and lack of randomization of subject characteristics.

2) In a randomized, double-blind, placebo-controlled study of 50 outpatients meeting DSM-III criteria for chronic alcohol abuse, **BUSPIRONE** (mean daily dose 20.5 milligrams) was reported to produce significantly greater decreases in alcohol craving and reported alcohol consumption, as well as improvements on a variety of psychiatric rating scales and evaluations by both physicians and subjects, compared with placebo [1]. These findings must be interpreted in light of the high dropout rate in the placebo group (64% versus 20% for the **BUSPIRONE** group) and the small sample size. Further, patients with other substance abuse problems were excluded, self-reports of alcohol use were not corroborated by other means, and the subjects, though not abstinent at time of entry, had to have expressed a desire to stop or reduce their alcohol use.

3) **BUSPIRONE** was effective in **alcohol detoxification** in a nonrandom sample of 100 patients, based on: a) both patients and detoxification unit staffers evaluations and b) lack of progression of alcohol withdrawal symptoms (except for a report of an unwitnessed seizure by one patient with a prior history of "alcohol-related seizures") [2]. Several important features of the study and the report make it difficult to draw firm conclusions about the drug's efficacy in this setting. These include: the non-blinded, noncomparative, uncontrolled nature of the study; the ambiguity in the information on the **BUSPIRONE** regimen used (noted to be "5 milligrams every 4 hours while awake" and yet "administered p.r.n."); the statement that 68% of the patients had a "cross addiction" (addiction to a substance other than ethanol), although patients with histories of **dependence on benzodiazepines** or **barbiturates** had been excluded; and lack of information on other withdrawal syndromes in this largely "cross-addicted" sample.

4.5.B.2] Anxiety

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; **Pediatric, Class III**

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

Indicated for the treatment of anxiety
Effective for anxiety and anxiety with depression

c) Adult:

1) Controlled studies comparing oral **BUSPIRONE** with placebo or other antianxiety agents have demonstrated its efficacy in the treatment of anxiety and anxiety and depression [3]; (Pecknold et al, 1985 Riblet et al, 1983) [4] [5] [6] [7] [8] [9] [10]. **Buspirone** was considered highly effective in outpatients with combined anxiety and substance abuse disorder (Oliveria et al, 1990). Optimal doses of oral **BUSPIRONE** appear to be 15 to 30 milligrams daily, and **BUSPIRONE** appears to be equipotent to **DIAZEPAM** on a milligram-milligram basis (Rakel, 1990 Rickels et al, 1982) [10]. One study reported the comparable efficacy of **BUSPIRONE** 16 milligrams daily and **CLORAZEPATE** 20 mg/day [5].

2) In a randomized, double-blind study in 120 patients, **buspirone** 15 milligrams twice daily was as effective as **buspirone** 10 milligrams three times daily [11]. Both groups demonstrated significant reductions in mean Hamilton rating Scale for Anxiety scores and improvement on Clinical Global Impression measures.

3) In at least one study [6], **BUSPIRONE** appeared to be more effective in previously untreated female patients (married, positive family adjustment, and low level of depression). In this study **DIAZEPAM** produced equal improvement in both males and females. It has been suggested that patients who respond to **BUSPIRONE** may have different characteristics than those responding to benzodiazepines (Uhlenhuth, 1982).

4) The long-term efficacy of oral **BUSPIRONE** in the treatment of **generalized anxiety disorder** was reported in an open study involving 700 patients (16 to 84 years of age) [12]. **BUSPIRONE** 5 to 60 milligrams daily was reported to maintain efficacy over a period of 12 months with a low incidence of side effects. Improvement in anxiety symptoms appeared to be more pronounced with continued therapy. Optimal doses in this study were 15 to 30 milligrams daily. A similar study has also reported long-term (up to 12 months' use) safety and efficacy of **BUSPIRONE** [13].

5) An analysis of data from 6 trials included in the New Drug Application (NDA) for **BUSPIRONE** revealed that patients generally showed improvement in psychic symptoms of anxiety (**anxious mood**, depressed mood, tension, fears, insomnia, and cognitive changes) sooner than in somatic symptoms (gastrointestinal, genitourinary, autonomic, somatic (sensory), somatic (muscular), cardiovascular, and respiratory) [14].

6) Resistance to the antianxiety effects of **BUSPIRONE** in patients with a history of benzodiazepine use has been reported (Schweizer et al, 1986). These authors observed that long-time benzodiazepine users had significantly less improvement than those without a history of past benzodiazepine use. Patients receiving benzodiazepine therapy within one month of beginning **buspirone** therapy experienced less improvement in symptoms of **generalized anxiety disorder**, a greater incidence of adverse effects, and a significantly higher (p less than 0.05) rate of attrition compared to patients with no prior benzodiazepine treatment or treatment discontinued at least one month prior to initiation of **buspirone** (DeMartinis, 2000). Similar results were reported in a small, uncontrolled, open label study [15]. The influence of prior treatment on therapeutic response to **BUSPIRONE** deserves examination.

7) **Buspirone** was efficacious in a small sample of elderly subjects with anxious symptoms due to an anxiety state or **neurotic depression** (Bohm et al, 1990). All patients studied in this double-blind,

placebo-controlled trial had additional medical conditions ([hypertension](#), [diabetes](#), [congestive heart failure](#), [hyperlipidemia](#)) and received other medications.

8) **BUSPIRONE** 5 milligrams orally 4 times a day was reported effective in the treatment of [transvestic fetishism](#) in a 46-year-old male with [generalized anxiety disorder](#) [16].

d) Pediatric:

1) In a case report, [buspirone](#) therapy of a 4-year-old boy with anxiety associated with [laryngomalacia](#) and [pharyngeal dysphagia](#) resulted in a decrease in anxiety, weight gain and improved self-feeding skills [17]. An open trial of [buspirone](#) was used with the dose gradually increased to 12.5 milligrams in divided doses over 22 weeks. The parents reported a decrease in separation anxiety, social anxiety, and eating-associated anxiety.

4.5.B.3] Autistic disorder

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: **Pediatric, Class IIb**

Strength of Evidence: Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

May improve symptoms of AGGRESSION and HYPERACTIVITY associated with [autism](#)

c) Pediatric:

1) **BUSPIRONE** in doses of 15 milligrams daily was reported beneficial in the treatment of [autism](#) in children, particularly with symptoms of aggression and hyperactivity, during a small open study involving 4 patients [22]. Improvement in severity of tantrums, pica, and self-injury has been reported in a profoundly mentally retarded adult with [autism](#) after initiation of **BUSPIRONE** 5 milligrams three times daily [23]. Controlled clinical trials are required to evaluate **BUSPIRONE** in autistic children and adults.

4.5.B.4] Behavioral syndrome

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; **Pediatric, Class IIb**

Strength of Evidence: Adult, Category C; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Useful for treating agitation, irritability, hostility, or aggression associated with [neurological disorders](#)

Useful for treating aggressive and self-injurious behaviors in developmentally disabled adults (Ratey et al 1991; Ratey et al, 1989)

Not very useful in treating children with aggression

c) Adult:

1) A 74-year-old man with [Huntington's disease](#) experiencing worsening [dementia](#) and escalation of aggressive behavior was helped by [buspirone](#) [24]. In the past, he had been managed on [haloperidol](#) but increasing doses were unsuccessful. He was started on [buspirone](#) 5 milligrams (mg) three times daily and increased to 10 mg three times daily after 4 days. He immediately became less aggressive and more compliant.

2) [BUSPIRONE](#) 10 to 15 milligrams orally three times daily was reported effective in reducing aggressive and agitated behavior in a 74-year-old woman with [primary degenerative dementia](#) of senile onset [25]. More studies are required to evaluate the efficacy of [BUSPIRONE](#) in such patients.

d) Pediatric:

1) [Buspirone](#) treatment in an open-label study involving 25 prepubertal hospitalized pediatric patients (5 to 12 years old) produced limited, but significant therapeutic effects on AGGRESSION, anxiety, and depression. Children with anxiety and aggressive behavior were treated with an initial dosage of 5 milligrams (mg)/day and titrated upward over 3 weeks by 5 to 10 mg every 3 days to a maximum of 50 mg/day for a 6-week maintenance phase. The mean optimal dose for the 19 patients who completed the study was 28 mg/day. After 6 weeks of maintenance therapy, depressive symptoms were reduced by 52% (P less than 0.001, Children's Depression Inventory) and aggressivity by 29% (P less than 0.02, Measure of Aggression, Violence, and Rage in Children). Four children experienced increased aggression and agitation while 2 developed euphoric mania. Only 3 children improved sufficiently to continue [buspirone](#) therapy after the study period [21].

4.5.B.5] Benzodiazepine withdrawal

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Not effective in preventing the symptoms of benzodiazepine withdrawal

c) Adult:

1) [Buspirone](#) was not effective in a small, placebo-controlled, double-blind study. [BUSPIRONE](#) 5 milligrams three times daily was compared with placebo, given for 4 weeks before, 4 weeks during, and 4 weeks after inpatient withdrawal of [DIAZEPAM](#), in a double-blind study of 23

subjects who had taken benzodiazepines chronically for at least 6 months [54]. The dropout rate was significantly higher in the **BUSPIRONE** group (7 of 11) than in the placebo group (1 of 12). At 6 and 12 months, 11 of 12 placebo patients and 6 of 11 **BUSPIRONE** patients were off benzodiazepines. Although the authors do not address this, it appears that some patients who dropped out of the **BUSPIRONE** group were considered successfully off benzodiazepines at follow-up. No withdrawal reactions were seen when **BUSPIRONE** was discontinued in the few remaining patients after 12 weeks. Although the mean benzodiazepine withdrawal scores were higher (though generally not significantly so) in the **BUSPIRONE** group at many points during the study, the fact that this difference was apparent even before the start of benzodiazepine withdrawal was not explained. Although the mean daily **DIAZEPAM** intake was significantly higher in the **BUSPIRONE** group at study entry, the authors found that the initial **DIAZEPAM** intake was not significantly related to study completion or to outcome at follow-up. Although the differences in patient groups and the small size of the study make it difficult to conclude that **BUSPIRONE** worsens benzodiazepine withdrawal, the study provides more evidence that **BUSPIRONE** is not effective in this setting, even when withdrawal does not take place until **BUSPIRONE** has been given for a sufficient time to allow onset of effects.

2)) Oral **BUSPIRONE** was reported ineffective in suppressing benzodiazepine withdrawal symptoms in one study [55]. The drug was not cross-tolerant with benzodiazepines and, compared with placebo, was not beneficial in helping patients undergoing benzodiazepine withdrawal despite evidence of an anxiolytic effect. Similar results from an open-label trial involving 15 patients were reported [56].

3)) However, in a double-blind, placebo-controlled study of 44 patients fulfilling Diagnostic Style Manual-III-R criteria for **generalized anxiety disorder** and with a Hamilton Rating Scale for Anxiety (HRSA) score higher than 18, **buspirone** 15 milligrams (mg)/day during 2 weeks of **lorazepam** taper was superior to placebo in prevention of significant rebound anxiety or benzodiazepine-withdrawal syndrome. The patients had been on a continuous benzodiazepine regimen for 3 to 9 weeks, were stabilized on **lorazepam** 3 to 5 mg/day treatment for 5 weeks, then randomly assigned to **buspirone** 15 mg/day or placebo for 6 weeks. Fewer adverse effects were observed during **buspirone** treatment than **lorazepam** and the profile was similar to placebo [57].

4)) **BUSPIRONE** 10 milligrams three times a day orally was ineffective in preventing abstinence symptoms following abrupt withdrawal of **LORAZEPAM** in a 74-year-old male [58]. Reinstitution of **LORAZEPAM** therapy (0.5 mg TID) was effective in producing prompt resolution of withdrawal symptoms.

4.5.B.6] **Bruxism**

a)) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b)) Summary:

Alleviates [bruxism](#) and associated symptoms in 4 case reports

c) Adult:

1) [Buspirone](#) was shown to relieve [bruxism](#) induced by [sertraline](#) therapy (100 milligrams to 150 milligrams). Four patients (3 female, 1 male) ages 32, 61, 38, and 35 years received [sertraline](#) for severe [postpartum depression](#), depressed mood, low mood with sleep disturbances, and depressive and obsessional symptoms, respectively. [Bruxism](#) and associated symptoms such as headaches and sore jaws developed within weeks of starting [sertraline](#) therapy. Treatment with [buspirone](#) 20 mg to 50 mg daily resulted in relief of [bruxism](#) and associated symptoms. The response to [buspirone](#) occurred between 1 week and 2 months of therapy [26].

4.5.B.7] Depression

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Effective in the treatment of depression, as well as depression accompanied by anxiety

c) Adult:

1) An analysis of 5 placebo-controlled, double-blind studies of a total of 382 adults with [major depression](#) found [BUSPIRONE](#) significantly more effective than placebo in improving Hamilton depression (HAM-D) or anxiety (HAM-A) scale scores and Clinical Global Impression-Global Improvement scale ratings (Schweizer et al, 1986). In contrast, one study found a more dramatic response among patients with melancholic-type depression [28]. Another interesting outcome was that patients with higher initial HAM-D or HAM-A scores responded better to [BUSPIRONE](#) than did patients with less severe illness. The dosing scheme used for [BUSPIRONE](#) began with 15 milligrams/day, with rapid titration allowed (increases of 5 to 10 mg every 2 to 3 days) to a maximum of 90 mg/day. Such rapid dose increases may have overestimated the doses required for efficacy in this study. The median daily dose for patients who responded to [BUSPIRONE](#) was 40 mg/day during the first week of response and 50 mg/day during the final week of the 8-week trial. Studies comparing [BUSPIRONE](#) to established antidepressants are needed, as well as studies to determine this agent's antidepressant dosing range.

2) [BUSPIRONE](#) was significantly more effective than placebo in the treatment of [major depression](#) accompanied by at least moderate anxiety [29] [30]. This 8-week, double-blind trial allowed fairly rapid titration from an initial [BUSPIRONE](#) dose of 5 milligrams three times daily to a maximum of 90 mg/day, but the mean dose among those completing the study was 56.5 mg/day. Melancholic patients accounted for only 15% of the 155 subjects, and thus an analysis of this subgroup was not possible. Improvement in measures of depression, anxiety, or global impression did not become significantly different for the treatment conditions until 4 weeks into the trial, which followed a 1- to 4-week washout period. Patients were excluded if they had used benzodiazepines regularly within 4 weeks of study entry, or for more than 6 weeks during the year

preceding the trial. This may have allowed a better evaluation of the therapeutic benefits of the drug, relatively unclouded by patients' expectation of the effects of an anxiolytic agent.

d) GERIATRIC

1) Imipramine was more effective than placebo (p less than 0.01) while buspirone trended towards being more effective than placebo (p less than 0.1) for the treatment of major depression in elderly outpatients. The 8-week, randomized, double-blind, placebo-controlled study involved 177 patients aged 65 years and over. Beginning dosages were imipramine 25 milligrams (mg) twice daily or buspirone 10 mg twice daily, increased to imipramine 25 mg three times daily and buspirone 10 mg three times daily after one week. If tolerated after the second week, imipramine was increased to 100 mg/day and buspirone to 40 mg/day in divided doses. A daily maximum dose of 150 mg of imipramine and 60 mg of buspirone could be reached based on clinical response, with the mean optimal dose of 89 mg/day for imipramine and 38 mg/day for buspirone. Following 8 weeks of treatment, moderate to marked global improvement occurred in 61% of buspirone patients, 70% of imipramine patients, and 42% of placebo patients [31].

2) Three geriatric patients, unresponsive to antidepressant therapy with either trazodone or fluvoxamine, responded favorably to augmentation with BUSPIRONE. All of the elderly patients showed signs and symptoms of both anxiety and depression that improved within two weeks of the addition of buspirone; doses used were 15 to 40 milligrams/day [32].

4.5.B.8] Depression, Refractory

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Questionable efficacy as adjunctive therapy for refractory depression

c) Adult:

1) As an augmentation treatment, buspirone may have speeded the response to SSRI (selective serotonin reuptake inhibitor) therapy in patients with refractory depression. Patients (n=102) diagnosed with a major depressive episode (DSM-IV) who had failed to respond to at least 6 weeks of therapy with citalopram or fluoxetine were randomly assigned to receive buspirone (initially 10 milligrams (mg) twice daily, maximum 60 mg/day) or placebo for 6 weeks, in a double-blind manner. A 2-week, single-blind wash-in period with placebo preceded double-blind treatment. SSRI therapy continued throughout the study period. During the placebo wash-in, there was a significant improvement (p less than 0.01) in scores on the Montgomery Asberg Depression Rating Scale (MADRS) for both groups. At 1 week after the start of the double-blind treatment, there was a statistically significant (p=0.034) improvement in MADRS score (compared to the score at the end of the wash-in period) in the buspirone group but not in the placebo group. Both groups showed improvement over the study period, and by the end of the study, there was no difference between groups in MADRS scores. According to the response criterion of a reduction of 2 or

more points on the Clinical Global Impression-Severity of Illness scale, 33% of the buspirone-treated patients and 31% of the placebo-treated patients were responders. In the buspirone group, there was a positive correlation between initial MADRS score and change in MADRS score ($r=0.4$, $p=0.004$); there was no such correlation in the placebo group. The authors concluded that buspirone may have produced a faster onset of recovery and may be particularly effective in patients with more severe depression [51].

2) In this placebo-controlled, double-blinded study, the addition of buspirone to paroxetine or citalopram antidepressant therapy did not appear to demonstrate any improvement in response when compared to placebo [52]. Treatment-refractory patients were randomized to receive either buspirone 10 milligrams/day (mg/day) ($n=57$) or placebo ($n=60$) in addition to their paroxetine or citalopram for 4 weeks. Doses of buspirone and placebo were titrated by up to 10 mg of buspirone or 1 tablet of placebo every 3 days to a maximum of 60 mg/day of buspirone or corresponding placebo dose. The mean daily doses of buspirone and placebo at the end of the 4 weeks were 49 mg and 5.1 tablets, respectively. There were no significant differences in response rate ("much improved" or "very much improved" on the Clinical Global Impressions scale) between the 2 groups (50.9% in the buspirone group, 46.7% in the placebo group). There were also no differences found in the Montgomery-Asberg Depression Rating Scale, the Global Assessment of Functioning Scale, or the 4 visual analogue scales. In a follow-up report, it was noted that 47 of these patients had reported sexual dysfunction at the beginning of the study [53]. During the 4 weeks of treatment, 58% of buspirone patients and 30% of placebo patients had improvement. This was seen after week 1 of buspirone therapy and was significant in women during weeks 1 and 3 (for both weeks $p=0.048$).

3) In this open-label study, buspirone appeared to be effective as augmentation therapy in patients who did not respond to an adequate trial of fluoxetine, paroxetine, citalopram, or imipramine monotherapy (Dimitriou et al, 1998). Buspirone 15 milligrams/day (mg/day) was added to patients' existing antidepressant regimen for 4 to 5 weeks and was titrated to 20 to 30 mg/day at week 2 as tolerated. The mean daily dose of buspirone used was 27 mg/day. Complete or partial response was achieved in 18 out of the 30 patients treated. An equal number of patients showed complete and partial response. Mean Clinical Global Impressions (CGI) Severity score decreased significantly from 4.7 to 1.7 (64% reduction; p less than 0.0001). The Hamilton Rating Scale for Depression (HAM-D) was also used in 16 out of the 30 patients. There were 9 out of 16 patients classified as responders (56%): 7 out of 16 were complete responders, 2 out of 16 were partial responders. Mean HAM-D scores decreased from 25.4 to 11.8 (54% reduction; p less than 0.0001).

4.5.B.9] Nicotine dependence

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b) Summary:

May offer some benefit in patients wishing to quit smoking

Available data is limited and only report short-term efficacy

c) Adult:

1) **BUSPIRONE** was reported effective in the amelioration of short-term withdrawal symptoms associated with smoking cessation [46]. In a double-blind, randomized, placebo-controlled trial involving 40 patients, **buspirone** 10 milligrams three times daily offered significant benefit over placebo. After three weeks of therapy, patients were instructed to stop smoking with drug therapy continued for an additional week. Seventy-nine percent of buspirone-treated patients were able to abstain from smoking as compared with fifty percent of placebo-treated patients. A similar study was unable to demonstrate benefit of **buspirone** versus placebo in terms of withdrawal symptoms; however, buspirone-treated patients did report a significantly decreased urge to smoke [47].

4.5.B.10| Obsessive-compulsive disorder

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Despite early data which suggested that **buspirone** may be beneficial in the treatment of **obsessive compulsive disorder**, subsequent controlled trials have demonstrated no advantage over placebo

c) Adult:

1) **BUSPIRONE** was found to be no better than placebo in reducing obsessive-compulsive, depressive, or anxiety symptoms in a double-blind, placebo-controlled trial involving 33 patients with **obsessive compulsive disorder** refractory to **FLUVOXAMINE** therapy alone, [33]. **Buspirone** was added to **fluvoxamine** in doses of 15 to 60 milligrams daily based on clinical response and side effects. The authors concluded that addition of **buspirone** to serotonin reuptake inhibitors is not an effective treatment strategy in the majority of patients with **obsessive compulsive disorder** who are refractory to treatment with serotonin reuptake inhibitors alone. Similar results were demonstrated in a group of **FLUOXETINE**-treated patients given adjuvant **buspirone** therapy [34].

4.5.B.11| Panic disorder

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Not been shown to be superior to placebo in the treatment of [panic disorders](#)

Case reports and at least one open label study have noted benefit of [buspirone](#) in patients with [panic disorders](#) with inadequate response to other agents

c) Adult:

1) The safety and efficacy of [alprazolam](#) and [buspirone](#) were compared in the treatment of [panic disorder](#) in an 8-week double-blind, placebo-controlled trial. [Alprazolam](#) was superior to [buspirone](#) and placebo in improvement of panic attacks, anxiety, phobias, and disability. [Buspirone](#) (mean dose 61 milligrams) was not superior to placebo in any of the outcome measures [35].

2) [Buspirone](#) was found to be effective in an open study of eleven patients with [atypical depression](#) with panic attacks [36]. Many of the patients had previously no or little response to therapy with monamine oxidase inhibitors or benzodiazepines. [Buspirone](#) was initiated at a dose of 20 milligrams daily and gradually advanced to 60 milligrams daily, in divided doses, after one month. All of the patients improved with therapy based on the CGI scale, with maximum benefit seen with daily doses greater than 40 milligrams. Panic attacks, as well as phobic and depressive symptoms, were significantly improved in the majority of patients. Two patients were unable to advance past a daily dose of 15 milligrams due to side effects, but still noted benefit.

3) In one study, 55 adults with [panic disorder](#) were randomly assigned to receive [BUSPIRONE](#), [IMIPRAMINE](#), or placebo in an 8-week, double-blind trial [37]. After a placebo washout, subjects received initial daily doses of [BUSPIRONE](#) 10 milligrams (mg), [IMIPRAMINE](#) 50 mg, or placebo 2 capsules, given twice daily. Doses could be titrated to a daily maximum of 60 mg, 30 mg, and 12 capsules, respectively. At the end of the trial, mean daily doses were 57.2 mg for [BUSPIRONE](#) and 291.7 mg for [IMIPRAMINE](#). [IMIPRAMINE](#) was not statistically superior to placebo in a variety of measures. [BUSPIRONE](#) showed a tendency for greater improvement in HAM-A scores and the CGI scale compared to placebo, although such improvement was less than with [IMIPRAMINE](#). There were no significant differences between groups in absence of full-symptom or limited-symptom panic attacks at week 8. The study sample was too small to demonstrate statistical superiority of [BUSPIRONE](#) over placebo. A narrowing in the standard deviation of patients' improvement scores for [BUSPIRONE](#) and [IMIPRAMINE](#) compared to placebo appeared to be an indicator of efficacy for both active drugs in this study; this contributed to the conclusion that [BUSPIRONE](#) is a weak, though active, antipanic medication.

4.5.B.12] [Parkinson's disease](#)**a) Overview**

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

BUSPIRONE may be safely administered to parkinsonian patients, however, no significant improvement in symptoms has been observed

Worsening of parkinsonian symptoms has been reported when BUSPIRONE was administered at high doses (100 milligrams/day)

c) Adult:

1) Oral BUSPIRONE has been reported to have dopamine agonist and antagonist effects. Animal studies have demonstrated reversal of neuroleptic-induced catalepsy [38] and dose-related stimulation of noradrenergic neurons in the locus ceruleus [39]. As a result of these studies, one researcher examined the usefulness of BUSPIRONE in managing patients with idiopathic Parkinson's disease [40]. At conventional antianxiety doses of 10 to 60 milligrams/day, BUSPIRONE was well tolerated; however, no significant effects on disability, dyskinesia, anxiety, or depression were observed. When doses of BUSPIRONE were increased to 100 milligrams/day, patients developed significant worsening of their parkinsonian symptoms. This worsening was attributed to increased stimulation of central noradrenergic neurons. Although BUSPIRONE may be given safely to parkinsonian patients at conventional dosages, the drug is not effective as an antiparkinson agent and may exacerbate symptoms at higher dosages. Similar results have been reported [41].

4.5.B.13] Pervasive developmental disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

May be useful for treating anxiety and irritability symptoms in children with pervasive developmental disorder (PDD)

c) Pediatric:

1) In an open-label trial of 22 pediatric patients with pervasive developmental syndrome (PDD) (6 to 17 years old), buspirone was found to produce a beneficial response within 2 or 3 weeks, reducing anxiety, irritability, and temper outbursts. The buspirone starting dose was 5 milligrams (mg) three times daily, with maximum dosage of 45 mg/day reached within three weeks. The mean dosage was 29.3 mg/day during the 6 to 8 week evaluation. On the Clinical Global Impressions-irritability scale, 9 subjects showed a marked response, 7 showed a moderate response, and 6 failed to show a response. Side effects were minimal (including initial sedation, slight agitation, and initial nausea), while one child experienced orofacial-lingual dyskinesia at a dosage of 20 mg/day for 10 months. Controlled clinical trials are necessary to evaluate buspirone in children with PDD [42].

4.5.B.14] Posttraumatic stress disorder

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Effective in case reports

c) Adult:

1) Three patients with the diagnosis of [posttraumatic stress disorder](#) as defined by DSM-III criteria were reported as being successfully treated with [buspirone](#) [43]. Doses of 35 to 60 milligrams were administered daily in divided doses. Benefit of therapy was observed from 5 to 29 days after initiation of therapy and continued benefit was noted after one year of treatment.

4.5.B.15] [Premenstrual syndrome](#)

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Limited data suggest that [buspirone](#) may be beneficial for women suffering from [premenstrual syndrome](#)

c) Adult:

1) In one small pilot study involving 34 patients, [BUSPIRONE](#) in average doses of 25 milligrams daily, given for the last 12 days of the menstrual cycle for 3 consecutive cycles, was reported superior to placebo in alleviating symptoms of [premenstrual syndrome](#). Improvement occurred in aches and pains, fatigue, cramps, [impaired social interaction](#), and irritability. These data suggest a role for serotonergic agents in [premenstrual syndrome](#) [44].

4.5.B.16] [Sexual dysfunction](#)

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Effective in one small study

c) Adult:

1) [BUSPIRONE](#) in mean oral doses of 45 milligrams daily was reported effective in improving sexual dysfunction in patients with [generalized anxiety disorder](#) [45]. Improvement in sexual dysfunction occurred in conjunction with improvement in the anxiety disorder in 8 of 9 patients following 1 month of treatment.

4.5.B.17) [Social phobia](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Found to be ineffective for [social phobia](#)

c) Adult:

1) In a 12-week double-blind, placebo-controlled study, [buspirone](#) 30 milligrams daily was not superior to placebo in the treatment of [social phobia](#) in 30 patients [48]. Both treatment groups showed only a small decrease on psychometric scales with no statistically significant differences between them. Only 4 patients using [buspirone](#) and 2 taking placebo reported a subjective improvement.

4.5.B.18) [Tardive dyskinesia](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

A single case report suggests efficacy of [buspirone](#) in high doses in a patient with extreme [tardive dyskinesia](#)

c) Adult:

1) A 63-year-old woman had profound [neuroleptic-induced tardive dyskinesia](#) which improved during treatment with high doses of [BUSPIRONE](#) (up to 200 milligrams/day) [49]. Diarrhea occurred at 60 mg/day and worsened with increasing doses. [CYPROHEPTADINE](#) 50 mg three times daily (TID) produced improvement in the patient's diarrhea, but worsening of her [tardive dyskinesia](#). [NADOLOL](#) 20 mg TID improved the diarrhea while allowing continued escalation of the [BUSPIRONE](#) dose. The therapeutic effects of [BUSPIRONE](#) on [neuroleptic-induced tardive dyskinesia](#) need further study, both in patients no longer receiving such agents and in those who continue treatment with the agents responsible for the movement disorder.

2) A neurochemical model of the potentially therapeutic effects of [BUSPIRONE](#) in [tardive dyskinesia](#) was presented [50].

4.5.B.19] [Tension-type headache, chronic](#); Prophylaxis

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Effective for chronic [tension HEADACHE](#) prophylaxis

c) Adult:

1) Both [buspirone](#) 30 milligrams (mg)/day and [amitriptyline](#) 50 mg/day were effective in the treatment of chronic [tension headache](#) [27]. In an open, parallel group study, patients received either [buspirone](#) (N=26) or [amitriptyline](#) (N=32). A greater than 50% reduction of days with a headache per month was experienced by 60.7% in the [amitriptyline](#) group and 54.5% in the [buspirone](#) group (not significantly different). Patients treated with [amitriptyline](#), however, had a better opinion of the drug and used fewer additional drugs for acute therapy.

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Abecarnil

4.6.A.1] [Generalized anxiety disorder](#)

a) Although the ability to demonstrate compelling effects from active treatment was hampered by an unexpectedly high placebo-group response, abecarnil showed promise as an effective anxiolytic while [buspirone](#), with a later onset of action, by 6 weeks of treatment significantly relieved anxiety compared to placebo [265]. In just one week of treatment both dosage levels of abecarnil showed significant anxiolytic activity compared to placebo as determined by the Hamilton Rating Scale for Anxiety and the Clinical Global Impressions scale, but as the study progressed differences from placebo diminished and by 6 weeks no longer differed significantly in the low-dose group. Outpatients (n=464) with [generalized anxiety disorder](#) (GAD) were randomized to receive high-dose abecarnil (7.5 to 22.5 milligrams/day),

low-dose abecarnil (3.0 to 9.0 mg/day), [buspirone](#) (15 to 45 mg/day), or placebo for the 6-week acute-treatment period, after which responders could enter an optional 18-week maintenance period in which investigators maintained or adjusted original dosages. At any time patients who discontinued or completed the double-blind study phase entered a 3-week, single-blind follow-up phase during which medication was abruptly substituted with placebo. Withdrawal symptoms in patients in the abecarnil group increased with dosage and treatment duration and were significant at both dosage levels compared to placebo when treatment lasted 12 to 24 weeks. Although treatment was completed by significantly fewer high-dose abecarnil-treated than placebo-treated patients, tolerance to abecarnil and [buspirone](#) was comparable (discontinuation by 10% to 26% abecarnil group and by 19% [buspirone](#) group).

4.6.B] [Alprazolam](#)

1) Adverse Effects

a) In a double-blind study comparing [buspirone](#) (5 milligrams (mg) three times daily (TID)), placebo, and [alprazolam](#) (0.25 mg TID) for 14 days in 60 healthy elderly subjects, [buspirone](#) did not affect reaction time, vigilance, or performance on tests of psychomotor function and memory [262]. However, given that [alprazolam](#) was found to have only marginal effects on vigilance, psychomotor speed, and memory on treatment day 1, and none after 14 days of treatment, it is possible that the exclusion criteria (eg, "significant or uncontrolled" medical illness, use of a variety of CNS depressants, [neurologic disease](#), psychiatric disorders) biased the sample toward persons less likely to exhibit unwanted CNS effects of therapy, and away from persons more likely to receive the drug in clinical practice.

4.6.C] [Amitriptyline](#)

4.6.C.1] [Tension-type headache, chronic](#); Prophylaxis

a) Both [buspirone](#) 30 milligrams (mg)/day and [amitriptyline](#) 50 mg/day were effective in the treatment of chronic [tension headache](#) [275]. In an open, parallel group study, patients received either [buspirone](#) (N=26) or [amitriptyline](#) (N=32). A greater than 50% reduction of days with a headache per month was experienced by 60.7% in the [amitriptyline](#) group and 54.5% in the [buspirone](#) group (not significantly different). Patients treated with [amitriptyline](#), however, had a better opinion of the drug and used fewer additional drugs for acute therapy.

4.6.D] [Bromazepam](#)

4.6.D.1] [Anxiety](#)

a) No significant differences were observed between [buspirone](#) (15.75 milligrams (mg)/day) and bromazepam (9.03 mg/day) in a 4-week, multicenter, randomized, double-blind, parallel-group study of 108 patients fulfilling Diagnostic Statistical Manual-III criteria for [generalized anxiety disorder](#). Patients had a Hamilton Rating Scale for Anxiety (HRSA) score higher than 18. Both treatments significantly improved anxiety ($p = 0.0001$) as evaluated with HRSA scores, 100 mm Visual Analogues Scales, Clinical Global Impression Scale and Clinical Global Self Rating Scale. The adverse effect profile of bromazepam was slightly more favorable: 38% of [buspirone](#) patients reported adverse effects (dizziness, nausea and vomiting, headache) versus 28% for bromazepam (sleepiness, fatigue, dizziness) [271].

4.6.D.2) Adverse Effects

a) The effects of single doses of bromazepam 3 mg, [buspirone](#) 10 mg, and clobazam 10 mg were compared on tests of performance and memory in 20 healthy adults [272]. Free recall was altered with all drugs at 2 hours post-dose; effects persisted at 6 hours only with bromazepam. [Buspirone](#) caused more amnesic effects than did clobazam, suggesting the effect on memory may not relate to sedative

effects. Bromazepam and buspirone, but not clobazam, affected the digit/symbol substitution tests, indicating disturbed recognition and processing of sensory data. None of the drugs caused subjective sedative effects.

4.6.E] Bupropion

4.6.E.1] Depression

a) In a randomized, 12-week study comparing sustained-release bupropion (n=279) to buspirone (n=286) as augmentation therapy to citalopram for refractory depression, the medications were associated with similar rates of remission of symptoms. The study was designed as a second level of treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial. Participants who had been treated for depression with citalopram and developed intolerance or did not achieve remission after up to 14 weeks of treatment were eligible to participate in this second level study. The primary efficacy endpoint was remission of symptoms, defined as a score of 7 or less on the Hamilton Rating Scale for Depression (HAM-D). Secondary endpoints included remission, defined as a score of 5 or less on the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR-16) and response, defined as a 50% or greater reduction in QIDS-SR-16 scores from baseline to endpoint. Investigators also considered overall QIDS-SR scores at study end and tolerability. Patients (mean age, 41.1 +/- 12.7 years; mean baseline HAM-D, 15.8 +/- 7.1) were randomized to receive sustained-release bupropion or buspirone, in addition to citalopram. Citalopram doses remained constant unless dose reductions were needed due to adverse effects. Sustained-release bupropion was titrated up from 200 milligrams (mg) per day to 400 mg per day over the first 6 weeks, and buspirone was titrated up from 15 mg per day to 60 mg per day over the first 6 weeks. Both were administered in two divided doses. Patients in the buspirone group had a longer duration of depression than those in the bupropion group (17.3 +/- 13.6 years and 14.8 +/- 12.6 years, respectively; p less than 0.004). The difference in remission rates according to HAM-D scores between sustained-release bupropion and buspirone was not statistically significant (29.7% vs 30.1%, respectively; p=0.93). The difference in remission rates according to QIDS-SR-16 scores between sustained-released bupropion and buspirone was not statistically significant either (39% vs 32.9%, respectively; p=0.13). The difference in response rates between the two groups was also not significant (31.8% vs 26.9%, respectively; p=0.21). However, sustained-release bupropion resulted in a statistically significantly greater reduction in QIDS-SR-16 scores than buspirone (25.3% versus 17.1%, respectively; p less than 0.04), lower overall QIDS-SR-16 scores (8 versus 9.1, respectively; p less than 0.02), and fewer discontinuations due to adverse effects (12.5% versus 20.6%, respectively; p less than 0.001). Although the investigators report similar frequency and intensity of adverse events for both groups, there was no delineation of specific adverse events experienced [264].

4.6.F] Clobazam

4.6.F.1] Anxiety - Panic disorder

a) Comparable efficacy of buspirone (20 to 30 milligrams/day) and clobazam (20 to 30 mg/day) have been reported in a randomized, double-blind, placebo-controlled trial in anxious outpatients [263]. The authors' description of entry criteria makes it appear likely that patients with frank panic disorder were included, but these patients were not analyzed separately. This study's limitations include small sample size (20 in each group) and short duration (3 weeks of active treatment after a one-week placebo washout).

4.6.G] Clomipramine

4.6.G.1] Obsessive-compulsive disorder

a) A double-blind study comparing buspirone and clomipramine in the treatment of obsessive-compulsive disorder (OCD) was performed [270]. Eighteen of 20 study entrants completed the trial, which included an

initial 2-week placebo washout period, a 2-week titration phase (in which doses were increased as tolerated to a daily maximum of 60 mg [buspirone](#) or 250 mg [clomipramine](#)), and a 4-week dose maintenance phase; subjects then received half the maximum tolerated dose for 4 days, followed by 3-1/2 weeks of placebo. Although the study was conducted in a crossover fashion, with the alternate treatment given after the 3-1/2 week placebo washout, the trial results were analyzed as a parallel design because subjects did not return to baseline status by the beginning of the second active treatment period. The authors reported similar efficacy of the 2 active treatments, with at least half of the patients in each group evidencing a minimum of 20% improvement in several measures of OCD and one of depression. However, the small sample size may have obscured differences in efficacy. The authors noted that response was not correlated with dose of [clomipramine](#) (mean 225 +/- 49 mg/day) or of [buspirone](#) (mean 58 +/- 7 mg/day), or with previous use of benzodiazepines. [Buspirone](#) warrants further study as a possible treatment for OCD.

4.6.H] [Clorazepate](#)

1) Adverse Effects

a) Abrupt withdrawal of chlorazepate (CZ), but not [buspirone](#) (BP), after long-term treatment of anxious outpatients was shown to result in withdrawal reaction in a double blind, randomized study in 150 patients [261]. Therapy consisted of CZ 15 to 60 mg/d (n=76) or BP 10 to 40 mg/d (n=74) for 24 weeks after which the tranquilizers were suddenly replaced with placebo for 4 weeks (the withdrawal phase). BP-treated patients dropped out of the study at a significantly higher rate than CZ-treated patients (71% vs 43%), leaving 40 CZ-treated patients and 21 BP-treated patients for evaluation. Anxiety assessment scores were similar for both groups by week 4 of the study, but the high dropout rate for BP indicates less patient satisfaction with this agent. During the withdrawal phase, 11 withdrawal symptoms were identified as being significantly more common in the CZ group than the BP group. Significantly more subjects in the CZ group (16 of 40, 40%) took reserve medication during the withdrawal period than in the BP group (0 of 21). Using a criterion of 5 or more new symptoms to define withdrawal, significantly more CZ-treated subjects (27 of 40, 72%) experienced withdrawal than BP-treated subjects (2 of 21, 9%). Because the BP-treated group was so small by the withdrawal phase, Rickels et al recommended further study of the addictive and withdrawal effects of BP with a large patient population.

4.6.I] [Diazepam](#)

4.6.I.1] Anxiety

a) SUMMARY: [Buspirone](#) and [diazepam](#) appear to be similarly effective in the treatment of anxiety disorders. Onset of action is more rapid with [diazepam](#). [Buspirone](#) should not be used in patients recently treated for generalized anxiety with benzodiazepines. On a milligram-milligram basis, oral [buspirone](#) appears to be equivalent in efficacy to oral [diazepam](#) in the treatment of anxiety disorders, while producing a lower incidence of CNS side effects and [impairment of psychomotor](#) skills [276] [277] [278] [279] [280] [281] [282] [283].

b) The superiority of [diazepam](#) over [buspirone](#) was reported in the treatment of chronic anxiety in a placebo-controlled study involving 33 outpatients [284]. Oral [diazepam](#) 20 milligrams daily (mean) was superior to [buspirone](#) in the same dose, and to placebo, on most clinical rating scales; expected EEG changes were observed with [diazepam](#) but not with [buspirone](#). There were 9 dropouts from the trial, with 6 patients withdrawing due to inefficacy of [buspirone](#). Of the 24 evaluable patients, 23 had previously received long-term benzodiazepine therapy, with 10 patients being unable to tolerate the pretrial placebo washout period (7 days). These data suggest that [buspirone](#) is ineffective in the treatment of chronic generalized anxiety in patients who have recently received benzodiazepine therapy. It is suggested that this is related to lack of cross-tolerance between [buspirone](#) and [diazepam](#), resulting in failure of [buspirone](#) to

suppress the benzodiazepine withdrawal syndrome. Withdrawal symptoms in this study appeared to be maximal at the time the beneficial effects of [buspirone](#) would normally be observed, suggesting that the symptoms (resembling anxiety phenomena) were not suppressed by [buspirone](#).

c) The efficacy of [buspirone](#) and [diazepam](#), each in oral doses of 10 to 40 mg daily, was compared in the treatment of [generalized anxiety disorder](#) in a 4-week controlled study involving 66 outpatients [285]. [Buspirone](#) doses were higher than those of [diazepam](#) throughout the study, with patients receiving a mean daily [buspirone](#) dose of 16.5 milligrams, compared with 13 milligrams of [diazepam](#). The onset of efficacy was earlier with [diazepam](#) than [buspirone](#). [Diazepam](#) was considered superior to [buspirone](#) during the initial 2 weeks of treatment; however, both drugs were equivalent in efficacy after 4 weeks of treatment. Adverse effects were more frequent in [diazepam](#)-treated patients. The study was skewed in that significantly more patients received [buspirone](#) than [diazepam](#) (43 versus 13), and it is unclear whether a more balanced patient sample would have altered the outcome.

d) Compared with [diazepam](#), there is some evidence that oral [buspirone](#) may be more effective in females, as compared to males. In addition, [diazepam](#) may be more effective in reducing somatic symptoms, while [buspirone](#) might be more effective in reducing symptoms associated with cognitive and interpersonal problems [280]; however, more studies are required to delineate these differences.

e) [Buspirone](#) (average 16.5 milligrams daily orally) was compared with [diazepam](#) (15 milligrams daily orally) for the treatment of mixed anxiety and depression in a double-blind trial. Both drugs were similarly efficacious in relieving symptoms of both anxiety and depression in 100 patients; however, [buspirone](#) showed benefits over [diazepam](#) in improving impaired cognition and confusion. Side effects (sedation, drowsiness) were significantly less with [buspirone](#) [279].

4.6.J] [Hydroxyzine](#)

4.6.J.1] [Generalized anxiety disorder](#)

a) In a randomized, double-blind, placebo-controlled trial, [hydroxyzine](#) significantly improved the symptoms of [generalized anxiety disorder](#), as measured by the Hamilton Anxiety Scale, while treatment with [buspirone](#) was no different from placebo. In this study, 244 patients received 4 weeks' treatment with [hydroxyzine](#) 50 milligrams per day (mg/d) (12.5 mg in the morning and at mid-day and 25 mg in the evening) (n=81), [buspirone](#) 20 mg/d (5 mg in the morning and at mid-day and 10 mg in the evening) (n=82), or placebo (n=81). Secondary measures of anxiety using the Clinical Global Index and the Hospital Anxiety and Depression (self-rating) scales found both [hydroxyzine](#) and [buspirone](#) to be more effective than placebo. After day 28, when placebo was substituted for active drug, both [hydroxyzine](#)- and [buspirone](#)-treated patients continued to improve. The incidence of side effects were similar between groups. Somnolence was reported more frequently in [hydroxyzine](#)-treated patients than [buspirone](#)-treated patients, 9.9% versus 4.9%, respectively. Headache and migraine were reported more frequently by [buspirone](#)-treated patients than [hydroxyzine](#)-treated patients, 6.1% versus 4.9%, respectively. [Buspirone](#)-treated patients also had a higher incidence of dizziness as compared to those receiving [hydroxyzine](#) (6.1% versus 0%). The authors conclude that [hydroxyzine](#) offers an effective and safer alternative than benzodiazepines for the treatment of general anxiety disorder [260].

4.6.K] [Imipramine](#)

4.6.K.1] [Depression](#)

a) [Imipramine](#) was more effective than placebo (p less than 0.01) while [buspirone](#) trended towards being more effective than placebo (p less than 0.1) for the treatment of [major depression](#) in elderly outpatients. The 8-week, randomized, double-blind, placebo-controlled study involved 177 patients aged 65 years and over. Beginning dosages were [imipramine](#) 25 milligrams (mg) twice daily or [buspirone](#) 10 mg twice daily, increased to [imipramine](#) 25 mg three times daily and [buspirone](#) 10 mg three times daily after one week. If

tolerated after the second week, [imipramine](#) was increased to 100 mg/day and [buspirone](#) to 40 mg/day in divided doses. A daily maximum dose of 150 mg of [imipramine](#) and 60 mg of [buspirone](#) could be reached based on clinical response, with the mean optimal dose of 89 mg/day for [imipramine](#) and 38 mg/day for [buspirone](#). Following 8 weeks of treatment, moderate to marked global improvement occurred in 61% of [buspirone](#) patients, 70% of [imipramine](#) patients, and 42% of placebo patients [269].

4.6.K.2] [Panic disorder](#)

a) A placebo-controlled, double-blind study of outpatients with [panic disorder](#) or [agoraphobia with panic attacks](#) failed to show any significant differences in total biweekly numbers of panic attacks, decreases in number of attacks, and evaluations of psychopathology and of global improvement over an eight-week period between patients treated with [buspirone](#), [imipramine](#), or placebo. All groups improved. The inconclusive results may have been due to a number of factors, including small sample sizes, the episodic nature of the illness, a possible therapeutic effect of the diagnosis for the subjects (many of whom were diagnosed for the first time during the study), and the limited study duration [267]. Somewhat better results were seen for both active treatments in a study using higher doses [268].

4.6.L] [Lorazepam](#)

4.6.L.1] [Anxiety](#)

a) Few significant differences were observed between [buspirone](#) (15.2 milligrams (mg)/day) and [lorazepam](#) (3.5 mg/day) in a 4-week, multicenter, randomized, double-blind, parallel-group study of 113 patients fulfilling Diagnostic Style Manual-III criteria for [generalized anxiety disorder](#). Patients had a Hamilton Rating Scale for Anxiety (HRSA) score higher than 18. Both treatments improved anxiety ($p = 0.0001$) according to HRSA scores, 100 mm Visual Analogue Scale, Clinical Global Impression Scale (CGIS) and Clinical Global Self Rating Scale (CGSRS). [Lorazepam](#) showed significantly higher improvement in HRSA score (p less than 0.05) and CGIS ($p = 0.002$) than [buspirone](#) after 1 week. Adverse effects were reported in 38% of [buspirone](#) patients (dizziness, nausea and vomiting, headache) versus 27% in the [lorazepam](#) group (sleepiness, dizziness, fatigue) [286].

4.6.L.2) Efficacy

a) A small, randomized, double-blind, 4-week study of 14 patients (6 males, 8 females; mean age 48 years) fulfilling Diagnostic Style Manual- III criteria for [generalized anxiety disorder](#) compared the effect of [buspirone](#) 30 milligrams (mg)/day and [lorazepam](#) 6 mg/day on electroencephalographic spectral power. [Buspirone](#) showed a significantly (p less than 0.05) increased output of slow frequencies (delta and theta) and decreased fronto-central beta-2 spectral power. Clinical effects were not studied [287].

4.6.M] [Oxazepam](#)

4.6.M.1] [Generalized anxiety disorder](#)

a) [Oxazepam](#) and [buspirone](#) were equally effective in treating generalized anxiety in 206 outpatients in a double-blind, multi-center, controlled trial [266]. Patients were treated with either [buspirone](#) 5 to 10 milligrams(mg) three times/day ($n=100$) or [oxazepam](#) 10 to 20 milligrams three times/day ($n=106$) for 6 weeks; 87 and 99 patients, respectively, completed the 6-week trial. The main assessment of efficacy was based on the Hamilton Rating Scale for Anxiety (HAM-A). The mean decrease in the HAM-A scores from baseline to end of study was from 23.9 +/- 4.3 to 10.5 +/- 7.3 ([oxazepam](#)) and from 23.7 +/- 4 to 8.9 +/- 6.2 ([buspirone](#)) in those who completed the study (NS). Similar results were seen on the Hamilton Rating Scale for Depression and the Raskin-Covi Rating Scale which were also used to evaluate the treatment. The Clinical Global Impressions scale (physicians' evaluation) and the Hopkins [Symptom](#)

Checklist (patient self-rating) rated **buspirone** as significantly better than **oxazepam**. Adverse effects were similar in both groups. **Oxazepam** was compared with **buspirone** 26 patients with **generalized anxiety disorder**; mean daily doses were 22.2 mg and 55.8 mg, respectively. The onset of anxiolytic activity was slower with **buspirone**, with the only significant differences in clinical improvement noted following 2 weeks of treatment. No difference was noted in overall anxiolytic activity, antidepressant activity, or side effects during the treatment period and abrupt withdrawal produced no significant difference in rebound anxiety.

b) **Oxazepam** and **buspirone** were equally efficacious overall in a 6-week trial, but **buspirone** had a slower onset of action (Ansseau et al, 1990-91).

4.6.N] **Venlafaxine**

4.6.N.1] **Generalized anxiety disorder**

a) One small study suggests that **venlafaxine** could be an alternative to **buspirone** in patients with **generalized anxiety disorder** (GAD). As part of a larger study, patients with clinically significant signs of GAD received **venlafaxine** XR 75 milligrams (mg)/day (n=4), **venlafaxine** XR 150 mg/day (n=4), **buspirone** 30 mg/day (n=4), or placebo (n=2) for 8 weeks. Improvement was defined as a greater than 50% decline on the Hamilton Anxiety Scale. Improvement was seen in 2 **venlafaxine** 75 mg patients, 2 **venlafaxine** 150 mg patients, and in 1 **buspirone** patient. With this study's small sample size, no specific conclusions could be made [273].

b) **Venlafaxine** XR was useful for treating **generalized anxiety disorder** (GAD); for many efficacy measures, it appeared to be better than **buspirone** [274]. Patients (n=405) with GAD diagnosed by DSM-IV criteria were randomly assigned to blinded treatment with placebo, **buspirone** 30 milligrams(mg)/day, or **venlafaxine** XR 75 or 150 mg/day for 8 weeks; dosage for active treatment was titrated over 1 week. At study conclusion, the Hamilton Rating Scale for Anxiety (HAM-A) score was NOT statistically significant for any active treatment compared to placebo; however, the HAM-A psychic anxiety, HAM-A **anxious mood**, and HAM-A tension scores were significantly lower for **venlafaxine** XR at selected weeks compared to placebo. **Venlafaxine** XR was superior to placebo and **buspirone** for selected weeks on the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI Improvement scale. Active treatments were generally well tolerated although 10%, 22%, 28%, and 15% of patients treated with placebo, **venlafaxine** XR 75 mg, **venlafaxine** XR 150 mg, and **buspirone**, respectively, stopped treatment due to adverse effects.

6.0] **References**

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