21 - 29.21 Mirtazapine

29.21 Mirtazapine

pathophysiology and the role of melatonin. Recent Pat Endocr Metab Immune Drug Discov. 2013;7(1):11–25. DeMicco M, Wang-Weigand S, Zhang J. Long-term therapeutic effects of ramelteon treatment in adults with chronic insomnia: A 1-year study. Sleep. 2006;29[Suppl]:A234 [abstract]. Doghramji K. Melatonin and its receptors: A new class of sleep-promoting agents. J Clin Sleep Med. 2007;3[5 Suppl]:S17. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. Sleep Med. 2006;7(1):17. Johnson MW, Suess PE, Griffiths RR. Ramelteon: A novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psychiatry. 2006;63(10):1149. Karim A, Bradford D, Siebert F, Zhao Z. Pharmacokinetic effect of multiple oral doses of donepezil on ramelteon, and vice versa, in healthy adults. Sleep. 2007;30[Suppl]:A244 [abstract]. Kato K, Hirai K, Nishiyama K, Uchikawa O, Fukatsu K. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. Neuropharmacology. 2005;48(2):301. Lieberman JA. Update on the safety considerations in the management of insomnia with hypnotics: Incorporating modified-release formulations into primary care. Prim Care Companion J Clin Psychiatry. 2007;9(1):25. Mahajan B, Kaushal S, Chopra SC. Ramelteon: A new melatonin receptor agonist. J Anaesth Clin Pharmacol. 2008;24(4):463. Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. Sleep. 2005;28(10):1271. Natural Standard Research Collaboration. Melatonin. Medline Plus—Herbs and supplements 2007. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-melatonin.html. Norris ER, Karen B, Correll JR, Zemanek KJ, Lerman J, Primelo RA, Kaufmann MW. A double-blind, randomized, placebocontrolled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. J Affect Disord. Jan 10 2013;144(1–2):141–147. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med. 2006;7(4):312. Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. Sleep. 2005;28(3):303. Turek FW, Gillette MU. Melatonin, sleep, and circadian rhythms: Rationale for development of specific melatonin agonists. Sleep Med. 2004;5(6):523. Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med. 2007;3(5):495. 29.21 Mirtazapine Mirtazapine (Remeron) is unique among drugs used to treat major depression in that it increases both norepinephrine and serotonin through a mechanism other than reuptake blockade (as in the case of tricyclic agents or SSRIs) or monoamine oxidase inhibition (as in the case of phenelzine or tranylcypromine). Mirtazapine is also more likely to reduce rather than cause nausea and diarrhea, the result of its effects on serotonin

5-HT3 receptors. Characteristic side effects include increased appetite and sedation.
PHARMACOLOGIC ACTIONS

Mirtazapine is administered orally and is rapidly and completely absorbed. It has a halflife of about 30 hours. Peak concentration is achieved within 2 hours of ingestion, and steady state is reached after 6 days. Plasma clearance may be slowed up to 30 percent in persons with impaired hepatic function, up to 50 percent in those with impaired renal function, up to 40 percent slower in elderly men, and up to 10 percent slower in elderly women. The mechanism of action of mirtazapine is antagonism of central presynaptic α2adrenergic receptors and blockade of postsynaptic serotonin 5-HT2 and 5-HT3 receptors. The α2-adrenergic receptor antagonism causes increased firing of norepinephrine and serotonin neurons. The potent antagonist of serotonin 5-HT2 and 5-HT3 receptors serves to decrease anxiety, relieve insomnia, and stimulate appetite. Mirtazapine is a potent antagonist of histamine H1 receptors and is a moderately potent antagonist at α1adrenergic and muscarinic-cholinergic receptors. THERAPEUTIC INDICATIONS Mirtazapine is effective for the treatment of depression. It is highly sedating, making it a reasonable choice for use in depressed patients with severe or long-standing insomnia. Some patients find the residual daytime sedation associated with initiation of treatment to be quite pronounced. However, the more extreme sedating properties of the drug generally lessen over the first week of treatment. Combined with the tendency to sometimes cause a ravenous appetite, mirtazapine is well suited for depressed patients with melancholic features such as insomnia, weight loss, and agitation. Elderly depressed patients in particular are good candidates for mirtazapine; young adults are more likely to object to this side effect profile. Mirtazapine’s blockade of 5-HT3 receptors, a mechanism associated with medications used to combat the severe gastrointestinal side effects of cancer chemotherapy agents, has led to the use of the drug in a similar role. In this population, sedation and stimulation of appetite clearly could be seen as being beneficial instead of unwelcome side effects. Mirtazapine is often combined with SSRIs or venlafaxine to augment antidepressant response or counteract serotonergic side effects of those drugs, particularly nausea, agitation, and insomnia. Mirtazapine has no significant pharmacokinetic interactions with other antidepressants. PRECAUTIONS AND ADVERSE REACTIONS Somnolence, the most common adverse effect of mirtazapine, occurs in more than 50 percent of persons (Table 29.21-1). Persons starting mirtazapine should thus exercise caution when driving or operating dangerous machinery and even when getting out of bed at night. This adverse effect is why mirtazapine is almost always given before sleep. Mirtazapine potentiates the sedative effects of other CNS depressants, so potentially

sedating prescription or over-the-counter drugs and alcohol should be avoided during use of mirtazapine. Mirtazapine also causes dizziness in 7 percent of persons. It does not appear to increase the risk for seizures. Mania or hypomania occurred in clinical trials at a rate similar to that of other antidepressant drugs. Table 29.21-1 Adverse Reactions Reported with Mirtazapine Mirtazapine increases appetite in about one-third of patients. Mirtazapine may also increase serum cholesterol concentration to 20 percent or more above the upper limit of normal in 15 percent of persons and increase triglycerides to 500 mg/dL or more in 6 percent of persons. Elevations of alanine transaminase levels to more than three times the upper limit of normal were seen in 2 percent of mirtazapine-treated persons as opposed to 0.3 percent of placebo control subjects. In limited premarketing experience, the absolute neutrophil count dropped to 500/mm3 or less within 2 months of the onset of use in 0.3 percent of persons, some of whom developed symptomatic infections. This hematologic condition was reversible in all cases and was more likely to occur when

other risk factors for neutropenia were present. Increases in the frequency of neutropenia have not, however, been reported during the extensive postmarketing period. Persons who develop fever, chills, sore throat, mucous membrane ulceration, or other signs of infection should nevertheless be evaluated medically. If a low white blood cell count is found, mirtazapine should be immediately discontinued, and the infectious disease status should be followed closely. A small number of persons experience orthostatic hypotension while taking mirtazapine. Although no data exist regarding the effects on fetal development, mirtazapine should be used with caution during pregnancy. Mirtazapine use by pregnant women has not been studied, but because the drug may be excreted in breast milk, it should not be taken by nursing mothers. Because of the risk of agranulocytosis associated with mirtazapine use, persons should be attuned to signs of infection. Because of the sedating effects of mirtazapine, persons should determine the degree to which they are affected before engaging in driving or other potentially dangerous activities. DRUG INTERACTIONS Mirtazapine can potentiate the sedation of alcohol and benzodiazepines. Mirtazapine

should not be used within 14 days of use of an MAOI. LABORATORY INTERFERENCES No laboratory interferences have yet been described for mirtazapine. DOSAGE AND ADMINISTRATION Mirtazapine is available in 15-, 30-, and 45-mg scored tablets. Mirtazapine is also available in 15-, 30-, and 45-mg orally disintegrating tablets for persons who have difficulty swallowing pills. If persons fail to respond to the initial dose of 15 mg of mirtazapine before sleep, the dose may be increased in 15-mg increments every 5 days to a maximum of 45 mg before sleep. Lower dosages may be necessary in elderly persons or persons with renal or hepatic insufficiency. REFERENCES Banerjee S, Hellier J, Romeo R, et al. Study of the use of antidepressants for depression in dementia: the HTA-SADD trial— a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health Technol Assess. 2013;17(7):1–166. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. Arch Neurol. 2009;66(2):255. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry. 2006;67(Suppl 6):33. Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: A STAR*D report. Am J Psychiatry. 2006;163(7):1161. Kim SW, Shin IS, Kim JM, Park KH, Youn T, Yoon JS. Factors potentiating the risk of mirtazapine-associated restless legs syndrome. Hum Psychopharmocol. 2008;(7):615. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: A STAR*D report. Am J Psychiatry. 2006;163(9):1531. Papakostas GI, Homberger CH, Fava M. A meta-analysis of clinical trials comparing mirtazapine with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. J Psychopharmacol. 2008;22(8):843. Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry. 2007;62(11):1217. Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM Jr. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry. 2002;10:541. Schittecatte M, Dumont F, Machowski R, Fontaine E, Cornil C. Mirtazapine, but not fluvoxamine, normalizes the blunted REM sleep response to clonidine in depressed patients: Implications for subsensitivity of alpha(2)-adrenergic receptors in depression. Psychiatry Res. 2002;109:1. Stenberg JH, Terevnikov V, Joffe M, et al. Predictors and mediators of add-on

mirtazapine-induced cognitive enhancement in schizophrenia—a path model investigation. Neuropharmacology. 2013;64:248–253. Thase ME. Mirtazapine. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry.

Revision #1
Created 2026-01-04 19:51:48 UTC by Omar Ayman
Updated 2026-01-04 19:51:48 UTC by Omar Ayman