REVIEW ARTICLE

A Review of Therapeutic Uses of Mirtazapine in Psychiatric and Medical Conditions

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ABSTRACT

Objective: To review the literature examining the use of mirtazapine with an emphasis on its therapeutic benefits for psychiatric patients with comorbid medical conditions.

Data Sources: MEDLINE, PsycINFO, Global Health, and AGRICOLA were searched using the terms *mirtazapine* OR *Remeron*. Limits were English language, human, year 1980–2012, treatment and prevention, and therapy.

Study Selection: Two hundred ninety-three articles were identified.

Data Extraction: Identified articles were reviewed with a focus on indications and therapeutic benefits in patients with medical comorbidities.

Results: Mirtazapine is an effective antidepressant with unique mechanisms of action. It is characterized by a relatively rapid onset of action, high response and remission rates, a favorable side-effect profile, and several unique therapeutic benefits over other antidepressants. Mirtazapine has also shown promise in treating some medical disorders, including neurologic conditions, and ameliorating some of the associated debilitating symptoms of weight loss, insomnia, and postoperative nausea and vomiting.

Conclusions: Mirtazapine offers clinicians multiple therapeutic advantages especially when treating patients with comorbid medical illness.

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Submitted: April 29, 2013; accepted July 9, 2013. Published online: October 10, 2013. Corresponding author: Abdulkader Alam, MD, 3520 5th Ave, Lower Level, Ste 1, Pittsburgh, PA 15213 (alama@upmc.edu). M irtazapine is a novel antidepressant originally known as Org 3770. It was first synthesized in The Netherlands in 1987¹ and introduced in the United States in 1996. Mirtazapine has a unique dual mode of action as a noradrenergic and specific serotonergic antidepressant.² Mirtazapine shows rapid improvement in the symptoms of depression, with minimal anticholinergic or serotoninrelated adverse effects. Comparisons of mirtazapine to the selective serotonin reuptake inhibitors (SSRIs) suggest a faster onset of action.³ Most notably, in a trial designed specifically to test onset of action of mirtazapine versus sertraline, a significant difference in favor of mirtazapine was observed as early as the fourth day of treatment.⁴ The advantages of quick onset of effects and a favorable safety profile have resulted in frequent use of mirtazapine in psychiatric patients with comorbid medical problems. This article reviews the literature examining the use of mirtazapine with an emphasis on its therapeutic benefits for patients with comorbid medical conditions.

METHOD

MEDLINE, PsycINFO, Global Health, and AGRICOLA were searched using the keywords *mirtazapine* OR *Remeron*. Limits were English language, human, years 1980–2012, treatment and prevention, and therapy. Two hundred ninetythree articles were identified. The identified articles were reviewed with a focus on indications and therapeutic benefits in patients with medical comorbidities.

PHARMACOLOGIC PROPERTIES

Mirtazapine, a noradrenergic and specific serotonergic antidepressant,^{5,6} enhances noradrenergic transmission via blockade of central α 2-adrenoceptors.^{7,8} Mirtazapine is a potent serotonin 5-HT₂ and 5-HT₃ antagonist, thereby increasing serotonergic stimulation via the 5-HT₁ receptor.⁷ Mirtazapine has no significant affinity for dopamine receptors, low affinity for muscarinic cholinergic receptors, and no effect on monoamine reuptake.^{8,9}

Mirtazapine is available in an oral tablet form and as an oral rapidly disintegrating tablet.¹⁰ It is well absorbed by the gastrointestinal tract, and its bioavailability does not appear to be affected by the presence of food.¹¹ Mirtazapine is extensively metabolized in the liver, and its metabolites are eliminated primarily in the urine (up to 75%) and in the feces.¹¹ Mirtazapine has a half-life of 20–40 hours, which may increase by 30%–40% in patients with hepatic impairment.¹¹ The drug's clearance may decrease by 30%–50% in patients with moderate-to-severe renal impairment.¹¹ Mirtazapine does not auto-induce hepatic isoenzymes. In vitro studies show that mirtazapine is not a potent inhibitor or inducer of P450 isoenzymes 1A2, 2D6, and 3A4.¹¹ The most commonly reported adverse effects are transient somnolence, hyperphagia, and weight gain, which may be attributed in part to the antihistaminic activity of mirtazapine at low doses.⁸

THERAPEUTIC BENEFITS

Depressive Disorders

As an antidepressant, mirtazapine has proven to be equally as effective as the tricyclic antidepressants and trazodone in patients with moderate-to-severe depression in both inpatient and ambulatory settings.^{12–16} Mirtazapine was found to be as effective as amitriptyline, but it causes fewer and less severe anticholinergic and cardiovascular side effects.¹⁷ When compared with the SSRIs fluoxetine,¹⁸

- Mirtazapine leads to rapid and sustained improvement in depressive symptoms and is effective in subgroups of depressed patients, particularly anxious patients and those with melancholic depression, treatment-resistant depression, geriatric depression, depression and anxiety associated with alcohol dependence, and agitated elderly patients.
- Mirtazapine's range of clinically useful applications includes improved sleep, antiemetic benefits, improved appetite, pain management, and weight gain.
- There is no conclusive evidence to support the use of mirtazapine for treatment of depression associated with dementia, treatment of depression with cocaine dependence, or treatment of obstructive sleep apnea.

citalopram,¹⁹ sertraline,⁴ and paroxetine,^{20,21} as well as the serotonin-norepinephrine reuptake inhibitor venlafaxine,⁹ mirtazapine was shown to be equally effective but with a significantly earlier onset of action, with effects seen as early as 1 and 2 weeks after treatment initiation.^{4,22} Compared to participants taking SSRIs, those taking mirtazapine had a 74% greater likelihood of achieving remission during the first 2 weeks of therapy.²³ This early improvement appears to be a specific antidepressant effect that is independent of mirtazapine's sleep-improving properties,⁹ and it has been identified as a highly sensitive predictor of later stable response or stable remission.²⁴ Early improvement was also noted in the primary care setting in depressed patients treated with mirtazapine.²⁵ Similarly, in primary care, mirtazapine (30-45 mg/d) showed a statistically significant early improvement over paroxetine (20-30 mg/d), although both were found to be efficacious.²⁶ Benefits for other subtypes of depression are listed in Table 1.

Depression and Comorbid Medical Conditions

Treating depression in patients with general medical conditions can be done safely and effectively with antidepressants, including mirtazapine, with no additional adverse effects or tolerability burden.³⁴ One study suggests that mirtazapine and venlafaxine are effective not only for the treatment of overall symptoms of depression, but may also be useful for the treatment of somatic symptoms in depressed patients.³⁵

Post-myocardial infarction depression. Depression after myocardial infarction is associated with increased cardiac morbidity and mortality, while antidepressant treatment in patients with cardiac disease and depression may result in significant therapeutic benefit.³⁶ Additionally, there is evidence that nonresponse to treatment of post-myocardial infarction depression may be associated with more cardiac events.³⁷

Honig et al³⁸ examined mirtazapine's efficacy in postmyocardial infarction depressed patients in a randomized, double-blind, placebo-controlled, 24-week trial and found that mirtazapine (15–45 mg) exhibited safety and efficacy on primary and secondary depression measures in the treatment of post-myocardial infarction depression. There were no differences between the control and treatment groups in serious adverse events, although patients reported more fatigue and appetite changes with mirtazapine.³⁸ Additionally, antidepressive response to mirtazapine (30 mg) in post-myocardial infarction patients was associated with significant decrease in inflammatory markers in contrast to placebo and nonresponder groups.³⁹

Poststroke depression. Niedermaier et al⁴⁰ found that prophylactic treatment with mirtazapine (30 mg) begun 1 day poststroke significantly reduced the rate of developing poststroke depression, with 5.7% (2/35) of treated patients becoming depressed compared to 40% (14/35) of nontreated patients. Mirtazapine was also shown to be effective in treating poststroke depression in the nontreated patients who developed depression in the first phase of the study.⁴⁰

Temporal lobe epilepsy and comorbid depression. Mirtazapine, citalopram, and reboxetine were each evaluated for the treatment of patients with temporal lobe epilepsy and depression in an inpatient setting.⁴¹ Treatment was efficacious with all 3 antidepressants. No serious adverse events, drug interactions, or increase in frequency or severity of seizures occurred. However, the endpoint dropout rate for patients treated with mirtazapine was significantly higher than for those treated with either citalopram or reboxetine.⁴¹

Substance dependence and comorbid depression. In a study of patients with alcohol dependence and comorbid depressive disorder, Altintoprak et al⁴² demonstrated significant improvement in depression and alcohol craving scores with both mirtazapine and amitriptyline, although mirtazapine was better tolerated. Another study looked at treating depressed cocaine-dependent subjects with either mirtazapine (45 mg daily) or placebo for 12 weeks.⁴³ Urine concentrations of benzoylecgonine (the main cocaine metabolite) and self-reports did not show mirtazapine to be more effective than a placebo in reducing cocaine use or improving symptoms of depression.⁴³

Geriatric depression. A 10-week, open-label trial of mirtazapine in 16 elderly patients with depression and 1 or more serious comorbid medical illnesses found that mirtazapine improves depression, insomnia, anxiety, somatic symptoms, and certain quality-of-life measures.⁴⁴ A 12-week open-label trial suggested that mirtazapine orally disintegrating tablets were effective and well tolerated in depressed nursing home residents aged 85 years or older.⁴⁵ A comparison study of depressed subjects aged 65 years or older found both mirtazapine and paroxetine to be effective during acute (8 weeks) and extension (16 weeks) phases of the trial.⁴⁶ However, mirtazapine demonstrated a faster median response time of 26 days compared to 40 days for paroxetine and was associated with greater reduction in anxiety/ somatization and sleep disturbance scores.⁴⁶ Additionally, mirtazapine (15-45 mg) was found to be similar in efficacy and safety when compared to amitriptyline (30-90 mg) in the treatment of depressed patients aged 60-85 years.⁴⁷

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Table 1. Use of Mirtazapine in Subtypes of Depression						
Indication	Reference	Study Population	Design	Outcome		
Melancholic depression	Guelfi et al, 2001 ²⁷	153 hospitalized patients	8-wk, randomized, double-blind trial comparing mirtazapine and venlafaxine	62% response rates with mirtazapine vs 52% with venlafaxine		
Relapse prevention	Thase et al, 2001 ²⁸	156 fully remitted patients	40-wk, randomized, double-blind, therapy-continuation, placebo- controlled trial	Significantly lower relapse rates vs placebo		
	Montgomery et al, 1998 ²⁹	217 patients who responded in a 6-wk double-blind trial	2-y, randomized, double-blind, placebo-controlled trial comparing mirtazapine, amitriptyline, and placebo	Significantly lower relapse rates vs placebo and amitriptyline		
Persistent and treatment-resistant depression	Carpenter et al, 2002 ³⁰	26 patients with persistent depression after monotherapy	4-wk, randomized, double-blind, placebo-controlled trial of augmentation with mirtazapine	Response rate: 64% vs 20% with placebo; higher remission rates: 45.4% vs 13.3% with placebo		
	Fava et al, 2006 ³¹ (Sequenced Treatment Alternatives to Relieve Depression trial)	235 patients who failed to respond to 2 consecutive antidepressants	14-wk, randomized, unblinded trial comparing mirtazapine and nortriptyline	Insignificantly lower response and lower remission rates with nortriptyline		
	Hirschfeld, 2002 ³²	250 patients with selective serotonin reuptake inhibitor– resistant depression	8-wk, multicenter, double-blind study comparing mirtazapine to sertraline	Equally efficacious at endpoint; remission rates at wk 1 and wk 2 significantly higher for mirtazapine		
Depression with anxiety	Kim et al, 2011 ²²	60 patients with major depressive disorder and a high level of anxiety symptoms	8-wk, randomized, open-label trial comparing orally disintegrating mirtazapine and paroxetine	Similar rates of improvement at endpoint; mirtazapine more effective in wk 1–2		
	Versiani et al, 2005 ³³	294 severely depressed patients	8-wk, randomized, double-blind study comparing mirtazapine and fluoxetine	Similar rates of improvement; mirtazapine more effective in wk 1–2		

Dementia with comorbid depression and agitation. A study assessed the use of antidepressants for depression associated with dementia in participants in England and found no difference in depression scores at 13 weeks between 111 controls and 107 participants receiving sertraline or mirtazapine or between the participants in the mirtazapine and sertraline arms.⁴⁸ For agitation, an open-label prospective pilot study of 16 patients with severe agitation associated with Alzheimer's dementia found that mirtazapine was associated with significant improvement in agitation and appetite without significant side effects or cognitive deterioration.⁴⁹

Substance Use Disorders

Alcohol dependence. Liappas et al⁵⁰ demonstrated that mirtazapine significantly improved the effects of cognitivebehavioral therapy on social anxiety symptoms in patients with alcohol dependence after a detoxification protocol. Mirtazapine also reduced anxiety and depressive symptoms more quickly when administered in combination with psychotherapy during the postwithdrawal phase.⁵¹ Compared to venlafaxine, mirtazapine significantly improved anxiety and depression scores in patients undergoing detoxification from alcohol.⁵²

Methamphetamine use disorders. A randomized controlled trial found that treatment with mirtazapine in actively using methamphetamine-dependent men who have sex with men resulted in decreased methamphetamine use and decreased sexual risk behaviors despite low-to-moderate medication adherence.⁵³ In a double-blind, randomized, placebo-controlled trial of withdrawal treatment in 31

participants,⁵⁴ mirtazapine was not associated with a significant difference in participant retention or symptom reduction. In another study of withdrawal treatment,⁵⁵ mirtazapine was associated with a less severe withdrawal than pericyazine, although modafinil resulted in the mildest withdrawal.

Anxiety and Related Disorders

Multiple studies have looked into the benefits of mirtazapine in treating anxiety disorders. Those benefits are summarized in Table 2.

Neurologic Disorders

The use of mirtazapine in contemporary neurology is based on the improved understanding of disease mechanisms and from the drug's effectiveness seen with certain movement disorders.

Progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy is a fatal demyelinating disease caused by the reactivation of latent infection with human John Cunningham polyomavirus, predominantly affecting patients infected with human immunodeficiency virus (HIV).⁷¹ In 2004, Elphick et al⁷² published a seminal article on 5-HT_{2A} receptor mediation of John Cunningham polyomavirus entry into cells, spurring the empiric use of mirtazapine in progressive multifocal leukoencephalopathy therapy on the basis of the drug's 5-HT₂ receptor antagonism. Cettomai and McArthur⁷³ reported on a case series of 4 HIV-infected patients diagnosed with progressive multifocal leukoencephalopathy treated with highly active antiretroviral

Table 2. Use of Mirtazapine in Anxiety Disorders						
Indication	Reference	Study Population	Design	Outcome		
Panic disorder						
	Boshuisen et al, 2001 ⁵⁶ Ribeiro et al, 2001 ⁵⁷	28 patients 27 patients	15-wk open-label trial 9-wk, randomized, double-blind trial comparing mirtazapine and fluoxetine	63% response rate at 6 wk Favored for phobic anxiety on the basis of global evaluation over fluoxetine		
	Sarchiapone et al, 2003 ⁵⁸	48 patients	12-wk open-label trial	42% responders after 2 wk; 91% responders after 12 wk		
Posttraumatic s	tress disorder					
	Bahk et al, 2002 ⁵⁹	15 patients	8-wk pilot study	Significant improvement in posttraumatic stress disorder and depression		
	Davidson et al, 2003 ⁶⁰	29 patients	8-wk, double-blind, placebo- controlled study	Response: 78.6% vs 16.7% for placebo		
	Chung et al, 2004 ⁶¹	100 patients	6-wk, randomized, open-label study comparing mirtazapine and sertraline	Nonsignificant higher response to mirtazapine over sertraline		
	Seo et al, 2010 ⁶²	40 patients	8-wk, randomized, open-label study comparing mirtazapine and paroxetine	Equally efficacious at endpoint		
Combat-related	l posttraumatic stress disorde	r				
	Alderman et al, 2009 ⁶³	13 males	12-wk open-label study	Significant reduction in symptoms		
Obsessive-comp	pulsive disorder					
	Koran et al, 2005 ⁶⁴	30 patients	12-wk open-label phase followed by 8-wk placebo-controlled discontinuation phase	Significant reduction in symptoms with treatment and continuation		
	Pallanti et al, 2004 ⁶⁵	49 patients	12-wk, single-blind, placebo- controlled trial of augmentation of citalopram	Increased response rate at 4 wk but not at 8 wk		
Generalized and	xiety disorder					
	Gambi et al, 2005 ⁶⁶	44 patients	12-wk open-label study	79.5% response rate		
Social anxiety d	lisorder					
	Muehlbacher et al, 2005 ⁶⁷	66 females	10-wk, randomized, double-blind, placebo-controlled study	Significant reduction in social phobia symptoms		
	Van Veen et al, 2002 ⁶⁸	12 patients	12-wk pilot study	41.7% response rate		
	Schutters et al, 2010 ⁶⁹	60 patients	12-wk, randomized, double-blind, placebo-controlled study	No significant efficacy as compared to placebo		
	Schutters et al, 2011 ⁷⁰	43 nonresponders	12-wk placebo-controlled trial of augmentation of mirtazapine or placebo with paroxetine	No significant improvement with augmentation		

therapy followed by the addition of mirtazapine (15 mg), in which 3 of the 4 patients demonstrated clinical improvement, while the patient who failed to show improvement was not fully adherent with treatment. Also, a 49-year-old man with HIV on highly active antiretroviral therapy who was diagnosed with progressive multifocal leukoencephalopathy and given mirtazapine and mefloquine hydrochloride showed subjective functional and cognitive improvement.⁷⁴ However, a 55-year-old man with hepatitis C virus treated with pegylated interferon- α and ribavirin and subsequently diagnosed with progressive multifocal leukoencephalopathy resulted in a mortal outcome despite a 5-day course of cytarabine and mirtazapine.⁷⁵

In a review of 28 cases of patients with multiple sclerosis who developed natalizumab-associated progressive multifocal leukoencephalopathy, Clifford et al⁷⁶ found that mirtazapine was used as a part of adjunctive therapy in 39% of the cases, although it is difficult to comment on mirtazapine's contribution in the setting of multidrug regimens.

Movement Disorders

The use of mirtazapine in treating tremors started with the description by Pact and Giduz⁷⁷ of the reduction

or elimination of parkinsonian tremor, action tremor, and levodopa-induced dyskinesias in 5 patients taking mirtazapine (30 mg). Tremor and dyskinesias reemerged on discontinuation of mirtazapine in 2 patients and once again abated when mirtazapine was restarted.⁷⁷ A double-blind, placebo-controlled, cross-over pilot study of mirtazapine as an add-on therapy in reducing essential tremor in 17 patients, 13 of whom were already treated with other antitremor medications, showed global improvement in 3 patients but no significant improvement compared to baseline.78 Uccellini et al⁷⁹ conducted an open-label observer-blind study of 30 patients with untreated essential tremor and found that 85% of those who remained on mirtazapine treatment therapy after 1 month demonstrated good control of essential tremor. After 1 year of treatment, 55% of patients continued to show benefit,⁷⁹ which is comparable to the estimated 50% improvement rate seen with propranolol and primidone.⁸⁰

Tension-type headache. A randomized, double-blind, placebo-controlled, crossover trial in 24 patients with chronic tension-type headache found mirtazapine to be effective in reducing headache severity⁸¹ at a rate comparable to treatment with amitriptyline.⁸² In a follow-up double-blind, placebo-controlled, parallel trial of mirtazapine,

ibuprofen, or the combination of both in 93 patients with chronic tension-type headache, low-dose mirtazapine alone was found to reduce headache severity by 20%, with a noted dose-response effect on efficacy and tolerance.⁸³

Other Possible Therapeutic Benefits

Pain in advanced cancer. Interest in the use of mirtazapine as an adjuvant treatment in the palliation of advanced cancer was originally spurred by the hope that it could offer an alternative to tricyclic antidepressants in pain management. In fact, a double-blind cross-over trial demonstrated that a single dose of mirtazapine could significantly increase the pain threshold of healthy participants.⁸⁴ A pilot open-label trial,⁸⁵ which targeted advanced cancer patients who were experiencing moderate-to-severe residual pain despite opioid maintenance, identified only a small insignificant improvement in pain and pain relief scores with mirtazapine, although there were significant dose-independent improvements in self-rated depression and functional assessment measures.

Fibromyalgia

In a 6-week open-label trial of mirtazapine,⁸⁶ 54% of the 26 fibromyalgia patients who completed the study demonstrated a clinically significant reduction in pain intensity and in mean weekly dosage of acetaminophen. Additionally, there was a significant improvement in sleep quality and somatic symptoms, including cold extremities, dry mouth, sweating, dizziness, and headache. Of note, the magnitude of reduction in major fibromyalgia symptoms was significantly correlated with the magnitude of reduction in depression.⁸⁶

Weight Loss or Appetite Stimulation

Trials of mirtazapine in the treatment of weight loss were motivated by weight gain being one of the most common side effects, which was attributed to increased appetite⁸⁷ and food craving.⁸⁸ A 6-week, open-label, crossover trial of mirtazapine in 36 advanced cancer patients with pain found a significant increase in weight at weeks 4 and 7, along with improvement in appetite.85 Another openlabel trial of mirtazapine in 17 patients with cancer-related cachexia/anorexia found weight gain in 24% of patients and weight maintenance in 6%, which was encouraging given that patients were losing weight prior to enrollment.⁸⁹ In an uncontrolled trial of mirtazapine administered over a range of 29 to 412 days in 5 patients with cystic fibrosis,⁹⁰ all demonstrated an increase in weight, body fat, and growth velocity at the end of the study. In a retrospective analysis of 6 patients with cystic fibrosis aged 10-19 years who were treated with mirtazapine over a range of 8 to 28 months,⁹¹ all patients demonstrated an increase in body mass index percentile for age. One instance of cystic fibrosis-related diabetes reported in the trial by Boas et al⁹⁰ contributed to the lack of support for the drug as an appetite stimulant in cystic fibrosis.⁹² On the other hand, in a small naturalistic study of 11 adults, Himmerich et al93 found that inpatients

with major depression actually showed improved glucose tolerance after 2 to 6 weeks of mirtazapine treatment despite the associated weight gain.

Insomnia

The high incidence of somnolence, 53.3% reported across US trials of mirtazapine,⁹⁴ spurred an interest in leveraging this side effect for the treatment of insomnia. A 2-week parallel trial of 15 mg versus 30 mg daily mirtazapine in 130 depressed patients with insomnia found persistent improvement in sleep quality and quantity, ease of getting to sleep, and daytime alertness with both doses.⁹⁵ The initial 10% incidence of somnolence decreased as the trial progressed, suggesting rapid development of tolerance to the sleep induction effect of H1 antagonism.95 In a double-blind placebo-controlled study of 20 young healthy volunteers given 1 dose of 30 mg of mirtazapine, Aslan et al⁹⁶ confirmed the findings of increased sleep continuity and efficiency in the acute setting while reporting additional benefit of prolonged slow-wave sleep attributed to 5-HT_{2A/C} antagonism. Of note, 5-HT $_{\rm 2A/C}$ antagonism has not been implicated in unwanted sedation or tolerance.96 A double-blind study of 19 depressed patients with insomnia compared mirtazapine versus fluoxetine over an 8-week period and found that the mirtazapine group alone demonstrated significant improvements in total sleep time and sleep latency without the unwanted rapid eye movement suppression that is seen with many antidepressants, including fluoxetine.97

Obstructive Sleep Apnea

Although a manufacturer-sponsored, double-blind, 3-arm, crossover trial of placebo versus mirtazapine in 12 newly diagnosed patients with uncomplicated obstructive sleep apnea showed significant reduction of apnea-hypopnea index,⁹⁸ 2 randomized, double-blind, placebo-controlled trials of mirtazapine in patients with obstructive sleep apnea found no measurement of sleep apnea improved with mirtazapine.⁹⁹

Nausea and Vomiting

Mirtazapine's blockade of 5-HT₃ receptors may help to prevent nausea and vomiting in a manner similar to ondansetron. Initial reports from the obstetrics literature demonstrated its successful use in the treatment of depression, anxiety, and hyperemesis gravidarum during pregnancy.100,101 In a double-blind randomized trial of mirtazapine plus dexamethasone versus dexamethasone alone in 80 gynecologic surgery patients with risk factors for postoperative nausea and vomiting, Chen et al¹⁰² found that 80% of the mirtazapine group did not experience postoperative nausea and vomiting or require administration of rescue antiemetic versus 50% of the placebo group. Furthermore, patients in the mirtazapine group experienced significantly lower anxiety 1 hour after mirtazapine administration without significant impact on most anesthesia parameters and recovery times.¹⁰² In a randomized, placebo-controlled trial of mirtazapine given 1 hour prior to orthopedic surgery

© 2013 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES Prim Care Companion CNS Disord 2013;15(5):doi:10.4088/PCC.13r01525 in 84 men and 16 women,¹⁰³ regardless of risk factors, the incidence of postoperative nausea and vomiting was again significantly lower in the mirtazapine group when compared to placebo.

Sexual Dysfunction

Although mirtazapine may be associated with a lower incidence of sexual side effects than other antidepressants,¹⁰⁴ a study of 148 premenopausal women with sexual dysfunction associated with fluoxetine did not find the addition of mirtazapine to be efficacious in reducing sexual dysfunction.¹⁰⁵ However, a study of augmentation in generalized anxiety disorder found that the 21 patients treated with the combination of mirtazapine and paroxetine experienced less sexual dysfunction than the 22 patients treated with paroxetine and placebo.¹⁰⁶ For lifelong early ejaculation, a double-blind fixed-dose study of 24 healthy men did not show mirtazapine to be effective in prolonging ejaculation latency time.¹⁰⁷

CONCLUSION

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that is approved for use in the treatment of major depressive disorder. Its unique pharmacologic properties are thought to be responsible for its excellent tolerability. Monotherapy with mirtazapine 15-45 mg/d leads to rapid and sustained improvements in depressive symptoms. This efficacy has been demonstrated in patients treated in the hospital, as outpatients, and in primary care. Mirtazapine was also effective in subgroups of depressed patients, particularly anxious patients and those with melancholic depression, treatment-resistant depression, geriatric depression, and depression and anxiety associated with alcohol dependence and agitated elderly patients. Mirtazapine appears to be safe and effective in the treatment of post-myocardial infarction depression, as well as in the prevention and treatment of depression after stroke and in association with temporal lobe epilepsy. A number of rather small trials have suggested the efficacy of mirtazapine in the treatment of patients with anxiety disorders including posttraumatic stress disorder (see Table 2), but larger-scale studies are needed to support these conclusions.

Our results also suggest a range of clinically useful applications including improved sleep, antiemetic benefits, improved appetite, and pain management. The results for pain management are intriguing and should encourage further trials of mirtazapine in other patient populations with pain. The weight gain associated with mirtazapine as a side effect was used in treating cancer-related cachexia as well as weight loss with cystic fibrosis.

Mirtazapine showed potential in the treatment of some medical and neurologic conditions. Treatment of progressive multifocal leukoencephalopathy was very promising, although only a randomized trial could establish the role of mirtazapine in the treatment of this disease. Mirtazapine may also present an alternate treatment for essential tremor with a different side effect profile and improved tolerability. Although studies that looked at perioperative use of mirtazapine included fairly narrow patient populations, the combination of their results suggests that mirtazapine can be useful in perioperative settings.

There is no conclusive evidence to support the use of mirtazapine in treatment of depression associated with dementia, treatment of depression with cocaine dependence, or for treatment of obstructive sleep apnea. Mirtazapine may improve sexual function in some patients taking SSRIs, but that finding was not supported in premenopausal women taking an SSRI, nor was it effective in treating males with early ejaculation sexual dysfunctions.

Drug names: citalopram (Celexa and others), cytarabine (Depocyt, Cytosar-U, and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), ondansetron (Zofran and others), paroxetine (Paxil, Pexeva, and others), propranolol (Inderal, InnoPran, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

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