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NEW DRUGS

A Review of the Pharmacological and Clinical Profile of Mirtazapine

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ABSTRACT

The novel antidepressant mirtazapine has a dual mode of action. It is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by antagonizing the adrenergic α_2-autoreceptors and α_2-heteroreceptors as well as by blocking 5-HT_2 and 5-HT_3 receptors. It enhances, therefore, the release of norepinephrine and 5-HT_{1A}–mediated serotonergic transmission. This dual mode of action may conceivably be responsible for mirtazapine's rapid onset of action.

Mirtazapine is extensively metabolized in the liver. The cytochrome (CYP) P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4 are mainly responsible for its metabolism. Using once daily dosing, steady-state concentrations are reached after 4 days in adults and 6 days in the elderly. *In vitro* studies suggest that mirtazapine is unlikely to cause clinically significant drug-drug interactions. Dry mouth, sedation, and increases in appetite and body weight are the most common adverse effects. In contrast to selective serotonin reuptake inhibitors (SSRIs), mirtazapine has no sexual side effects.

The antidepressant efficacy of mirtazapine was established in several placebo-controlled trials. In major depression, its efficacy is comparable to that of amitriptyline, clomipramine, doxepin, fluoxetine, paroxetine, citalopram, or venlafaxine. Mirtazapine also appears to be useful in patients suffering from depression comorbid with anxiety symptoms and sleep disturbance. It seems to be safe and effective during long-term use.

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INTRODUCTION

After the discovery of the tricyclic antidepressants (TCAs) about 40 years ago, they remained first-line treatment in the drug therapy of depression for decades. In addition to TCAs, the so-called second-generation antidepressants, such as mianserin and maprotiline, were widely used in Europe during the 1980s. In comparison with TCAs, they provided a different side effect profile and some additional problems (e.g., convulsions with maprotiline, agranulocytosis with mianserin). Selective serotonin reuptake inhibitors (SSRIs) were introduced during the late 1980s and early 1990s. They were soon considered to be safer and easier to use than the older drugs and, therefore, partially replaced the older antidepressants in the drug therapy of depression. In clinical practice, as well as in some clinical trials, however, the efficacy of SSRIs was somewhat less than that of the conventional antidepressants (3). Thus, the current goal in the development of antidepressant drugs is to develop agents with efficacy equal to that of the TCAs without their inherent shortcomings. A broader biochemical spectrum rather than narrow effect on serotonin (as is the case with SSRIs) has been suggested to be the key for better antidepressant efficacy. The newest antidepressants, such as mirtazapine and venlafaxine, as well as TCAs, affect both the serotonin and norepinephrine systems in the central nervous system (CNS), but they lack the anticholinergic and cardiovascular effects of the TCAs.

Mirtazapine has a unique mode of biochemical CNS action. It is a NaSSA, which enhances noradrenergic and 5-HT_{1A}–mediated serotonergic neurotransmission by acting as an antagonist at the central α_2-adrenergic autoreceptors and heteroreceptors as well as by postsynaptic blockade of 5-HT_2 and 5-HT_3 receptors. Mirtazapine is a 6-aza derivative of mianserin, a tetracyclic antidepressant that acts mainly presynaptically at α_2-adrenoceptors.

PHARMACOLOGY

The chemical name of mirtazapine is 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-α]pyrido[2,3-c]benzazepine. Its chemical structure is shown in Fig. 1. Mirtazapine belongs to the chemical class of piperazinoazepines (33). Its molecular weight is 265.36 (18).

Mirtazapine is a racemic mixture (20) of two enantiomers. Both, the *S* (+) and *R* (–) enantiomers are pharmacologically active. The parent compound is responsible for most of the pharmacological activity of mirtazapine. Desmethylmirtazapine, its only pharmacologically active metabolite, contributes only 3–10% to the activity of mirtazapine (25,50,90).

The antidepressant activity of mirtazapine is associated with the enhancement of the serotonergic and noradrenergic systems in the CNS (50). The noradrenergic effect is attributed to the blockade of inhibitory presynaptic α_2-autoreceptors, which is also true for mianserin. This blockade leads to the enhanced release of norepinephrine to the synaptic cleft and the enhanced postsynaptic availability of this neurotransmitter. Mirtazapine does not, however, inhibit norepinephrine reuptake. In addition, mirtazapine antagonizes α_2-heteroreceptors in the serotonergic nerve terminals, thereby increasing serotonin release. Because it also blocks 5-HT_2 and 5-HT_3 receptors, only 5-HT_{1A}–mediated serotonergic transmission is enhanced (23). Mirtazapine has a high affinity for histamine H_1 receptors

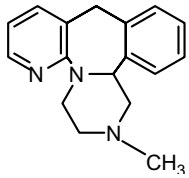

Fig. 1. The chemical structure of mirtazapine.

and a low affinity for dopaminergic and muscarinic-cholinergic receptors (42). It also has a low affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors (23). The *S*(+) enantiomer is responsible for 5-HT_2 and α_2-receptor antagonism, while the *R*(–) enantiomer blocks 5-HT_3 receptors (46). The affinity of mirtazapine for neurotransmitter receptors is presented in Table 1.

TABLE 1. Affinity of mirtazapine for neurotransmitter receptors (23,50)

Receptor	Affinity (pA_2 or pK_i)
α_2-Adrenergic autoreceptor	7.7
α_2-Adrenergic heteroreceptor	8.0
Postsynaptic α_2-adrenoceptor	7.3
Presynaptic α_2-adrenoceptor	6.8
α_1-Adrenoceptor	6.5
Serotonin 5-HT_{1A}	5.3
Serotonin 5-HT_{1B}	4.9
Serotonin 5-HT_{1D}	5.3
Serotonin 5-HT_{2A}	8.2
Serotonin 5-HT_{2B}	6.7
Serotonin 5-HT_{2C}	7.9
Serotonin 5-HT_3	8.1
Histamine H_1	9.3
Muscarinic	6.2
Dopamine D_1	5.8
Dopamine D_2	5.6

PHARMACOKINETICS

In healthy volunteers (90), mirtazapine is rapidly absorbed after a single dose and its peak plasma concentration (C_{max}) is reached within 1 to 2.1 h. With multiple doses, the C_{max} of mirtazapine is reached within 1.1 to 2.9 h. Mirtazapine binds to plasma proteins (85%) in a nonspecific and reversible manner. Its absolute bioavailability is approximately 50%, mainly due to gut wall and hepatic first-pass metabolism (90). The presence of fatty food has a minor effect on absorption (18). Mirtazapine is extensively metabolized in the liver, its elimination half-life ranges between 20 and 40 h, and steady state is reached after 4 days in adults and 6 days in the elderly (90). Mirtazapine displays linear pharmacokinetics over a dose range of 15 to 80 mg/day (90). The cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2D6, and CYP3A4 are mainly responsible for its metabolism (42). Recently, the isoenzymes CYP2D6 and CYP3A4 have been suggested to be more significant than CYP1A2 in this process (90). Moreover, CYP2D6 has been proposed to be the most active enzyme in the metabolism of mirtazapine (26). The results of a recent study (83), indicate, however, that CYP1A2, CYP2D6, and CYP3A4 each contribute 25 to 45% to the net clearance of mirtazapine at low liver concentrations. As mirtazapine concentrations increase, CYP3A4 contribution increases to about 70%, while CYP2D6, CYP2C8, CYP2C9, and CYP1A2 account for less than 15% each. The authors suggest (83) that even the complete inhibition or deficiency of one isoform is unlikely to result in a clinically significant increase in mirtazapine plasma concentration. This is sup-

ported by a study (20) that indicates that the CYP2D6 phenotype does not influence mirtazapine clearance *in vivo*.

There is no clear relationship between plasma concentrations of mirtazapine and its antidepressant efficacy, nor is there a dose-effect relationship. For the usually effective doses (15–45 mg/day), plasma concentrations of mirtazapine range between 5 and 100 μg/L (90).

In vitro studies suggest that mirtazapine is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by CYP1A2, CYP2D6, and CYP3A4 (20,83). Mirtazapine probably does not inhibit CYP2C9, CYP2C19, or CYP2E1 isoenzymes (83). However, no *in vivo* data are available (83).

When mirtazapine concentrations were measured by an achiral method, there were no differences between the extensive (EM) and poor (PM) metabolizers of debrisoquine (90). However, the area under the time-concentration curve (AUC) for the *S*(+) enantiomer was 79% larger in PMs than in EMs. There were no differences between EMs and PMs of the *R* (–) enantiomer.

SAFETY

The incidence of the most common side effects of mirtazapine was reviewed in a meta-analysis by Fawcett and Barkin (33) and is listed in Table 2. The side effects are

TABLE 2. Percentage of patients with adverse clinical experiences: mirtazapine (n = 359) vs. placebo (n = 328) (33)

	Mirtazapine	Placebo
Overall incidence rate of adverse clinical experiences	65	76
Nervous system (central, peripheral and autonomical)		
Drowsiness	23.4*	14.2
Excessive sedation	18.7	5.2
Insomnia	9.5	7.3
Agitation	8.6	7.3
Restlessness	5.0	7.3
Headache	5.4	10.4**
Vertigo	6.1	4.3
Appetite decreased	12.8	12.2
Appetite increased	10.6*	2.1
Gastrointestinal and metabolic/nutritional		
Dry mouth	25.3*	15.9
Constipation	13.1	11.9
Body weight decrease	1.9	6.1**
Body weight increase	10.3*	1.2
Others		
Fatigue	16.2	11.9

* $p < 0.05$ vs. placebo. ** $p < 0.05$ vs. mirtazapine.

mostly mild and transient. When mirtazapine is used in small doses, side effects associated with its histamine H_1 receptor blocking effect, such as excessive sedation and increase in body weight, are prominent (33). In some clinical trials (10,63,68) drowsiness diminished, even when the dose of the drug was increased. A similar phenomenon was noted in one trial for dry mouth (74).

Therapy with mirtazapine is associated with weight gain, both acutely and over the long-term (32); however, mirtazapine appears to be less likely to cause weight gain than TCAs. A meta-analysis (36) of four studies conducted in the United States showed that most weight gain took place during the first 4 weeks of treatment. In one case report (1), mirtazapine caused hyperphagia and the patient's weight increased 22 pounds over 4 weeks. The manufacturer has reported another case of hyperphagia. In one study (56) of 10 patients suffering from major depression, weight gain was associated with an increase in plasma levels of cytokines and leptin. This phenomenon has been observed also with clozapine, but not with amitriptyline.

In contrast to SSRIs, mirtazapine has no sexual side effects. In the study by Sitsen and Zivkov (77) the incidence of sexual side effects in patients treated with mirtazapine was 0.6% while it was 1.7% in the placebo group. Among various SSRIs the incidence of sexual dysfunction varies greatly. The package inserts report a range from 2% with fluoxetine to up to 20% with sertraline or paroxetine (31). In one study (5), the incidence of orgasmic dysfunction was lower with mirtazapine than with paroxetine (3.1 vs. 13.5%). There is some evidence that mirtazapine may even improve sexual functions in some patients, especially in women (8). In some cases and pilot studies (31,35) sexual dysfunction was alleviated when mirtazapine was combined with SSRIs, such as fluoxetine, paroxetine, or sertraline.

Mirtazapine therapy is associated with a very low incidence of seizures (0.04%) compared with TCAs (up to 4%) or maprotiline (up to 16%) (50). There are only two reports of seizures attributed to mirtazapine treatment (66,74). No seizures have been described with mirtazapine intoxication, even though mirtazapine doses were as high as 1,500 mg and the age of patients ranged from 3 to 90 years (42). No clinically significant alterations in heart rate or blood pressure have been reported in clinical trials with mirtazapine (10,11,63,74,94,102).

Hematologic side effects of mirtazapine have been reported (50). However, of the two patients with hematological disorders, one was treated concomitantly with ibuprofen and acetylsalicylic acid and the other had Sjögren's syndrome. Both of these conditions have been associated with hematological disorders. Thus, hematologic side effects in these cases cannot be definitively attributed to mirtazapine. There are over 4 million patients worldwide treated with mirtazapine (75) and agranulocytosis has been reported only in a few cases. In addition, no symptomatic neutropenia has been reported in one million mirtazapine-treated patients (22,50). Until September 2000, the reporting rate of agranulocytosis per one million treatment courses was about 3.1 (data on file, NV Organon). One treatment course is defined as 30 mg/day for 3 months. It has been recommended, however, that mirtazapine should be discontinued if the patient develops signs of infection with a low white blood cell count (52).

Mirtazapine rarely causes changes in clinical chemistry. According to some reports mirtazapine has been associated with an increase in alanine aminotransferase (2% of pa-

tients), cholesterol (3–4% of patients), and triglycerides (52,82). In one placebo-controlled study (57) in which hormone levels were monitored, mirtazapine 15 mg/day had no effect on the secretion of growth hormone or prolactin, but it clearly decreased the levels of cortisol in all subjects. It has been speculated that this effect could be, at least partially, due to the blockade of $5HT_{2A}$ and $5HT_{2C}$ receptors (57). It remains unclear whether these endocrine effects persist after the administration of higher doses or during repeated administration of mirtazapine (58).

Mirtazapine has usually been well tolerated in the elderly. The most common side effects have been dry mouth and drowsiness (40,43). Cardiovascular side effects have also been rare in the elderly patients with cardiovascular disease (100).

In placebo-controlled studies of mirtazapine, edema has been reported in 1% of patients. In one case report (59), two female patients suffering from major depression developed facial edema when the dose of mirtazapine was raised to 30 or 45 mg/day. In both patients, edema subsided when the dose was increased to 60 mg/day.

In one double-blind study involving 18 healthy young volunteers (73) the effect of mirtazapine on the ability to drive a car was evaluated. Mirtazapine 15 mg/day caused mild but statistically significant deterioration in driving on the second day of the treatment. A daily dose of 15 mg impaired driving even on day 16, but no extra impairment was seen in those volunteers whose dose was increased from 15 to 30 mg/day. In another study (72), the influence of different doses of mirtazapine on sleep and alertness was investigated. One group of patients was treated with mirtazapine 15 mg/day, which was later increased to 30 mg/day, while another group received mirtazapine 30 mg/day regularly during the entire study. There was no difference in the effect of mirtazapine in the two groups, with the exception that the patients who received the 30-mg dose fell asleep faster and slept better than patients who started with a 15-mg dose of the drug. In two clinical trials (74,94) the incidence of suicide attempts with mirtazapine was not different from that with other drugs. Somnolence and tachycardia were the most common toxicological symptoms during attempted suicide with mirtazapine (42).

To date, 45 cases of intoxication involving mirtazapine have been reported; five were fatal (75). In each of the fatal cases, other drugs such as benzodiazepines, and antidepressants, or alcohol beverages had been taken concomitantly. In one case (12), mirtazapine 30–45 mg/day, in addition to unknown doses of amitriptyline and chlorprothixene, caused death. Amitriptyline was considered to be the main cause of mortality.

Withdrawal effects have been reported in some cases when mirtazapine was discontinued abruptly. In one patient mirtazapine 60 mg/day was suddenly discontinued because no benefit was achieved after 1 month of treatment (4). Although the patient continued taking clomipramine, nortriptyline, and alprazolam, he suffered from dizziness, nausea, anxiety, insomnia, and paresthesias on the day after discontinuing mirtazapine. When mirtazapine was restarted two days later, the withdrawal effects disappeared. There is another case report (54) in which the discontinuation of mirtazapine caused panic attacks. This patient had also taken other drugs and was known to have drug abuse problems. However, his panic attacks disappeared when mirtazapine treatment was reintroduced.

In one case report (76), the use of mirtazapine during the first month of pregnancy did not cause any complications or any harm to the infant.

CLINICAL STUDIES

Mirtazapine has been shown to be more effective than placebo and as effective as active control drugs in most clinical trials (10,17,40,53,80). The majority of the studies have been short-term trials in patients with moderate-to-severe major depressive episodes (33). Long-term studies with continued treatment for as long as 72 weeks have been also reported. Altogether more than 4500 patients have participated in clinical trials with mirtazapine (33). The clinical trials included dose-range titration as well as fixed dose studies. The daily doses of mirtazapine in clinical trials ranged from 5 to 60 mg (33).

Pivotal Studies

Mirtazapine has been compared to placebo in 11 pivotal studies, but only six of them have been published (10,17,40,53,80,96). In one of these studies (96), no effect of mirtazapine was detected, probably due to methodological flaws. This study attempted to combine dose finding and efficacy evaluation. Moreover, the patients in this study were highly depressed and the number of dropouts was high.

In three of the placebo-controlled studies mirtazapine was effective during the first week of therapy (10,17,80). Altogether, placebo-controlled studies involved approximately 250 patients treated with either mirtazapine or placebo. The meta-analysis revealed significant difference in the efficacy of mirtazapine compared with placebo at every time point (weeks 1 to 6). At endpoint mirtazapine was significantly ($P < 0.0001$) superior to placebo in several Hamilton Rating Scale for Depression (HAM-D) parameters: melancholia, anxiety/somatization, sleep disturbance, and retardation depression (49).

Comparative Studies with other Antidepressants

Mirtazapine has been compared to many other active antidepressants in the treatment of major depressive disorder (Table 3). All studies were prospective, randomized, double-blind trials of 4 to 8 weeks' duration. Mirtazapine was compared to amitriptyline in five trials. In the meta-analysis (103) of these trials, there was no significant difference in the efficacy of the two drugs: 70% of patients responded to mirtazapine at week 6 and 73% responded to amitriptyline. Mirtazapine has also been compared with SSRIs, such as fluoxetine, paroxetine or citalopram. In two of the trials (5,60) the onset of action was faster in the mirtazapine group than in the control group. At the end of the second week of treatment, mirtazapine was significantly more effective than any of the other drugs (60). At the end of the 6- to 8-week long trials, however, there was no difference in the efficacy of the drugs studied (42). In one study (38) mirtazapine and venlafaxine were compared in severely depressed patients. Dose increase was faster than usual due to the severity of the illness. Both drugs were equally efficacious, but significantly more patients in the venlafaxine (15.2%) than in the mirtazapine group (5.1%) discontinued therapy because of the adverse events. In a more recent study (91), mirtazapine was as effective as amitriptyline in major depression. To date, one 2-year long study (67) of mirtazapine in major depressive disorder has been published. In this study mirtazapine was compared with placebo and amitriptyline. In the first analysis, at week 20, both mirtazapine and amitriptyline were equally effective and more effective than placebo. At the end of the trial, however, mirtazapine was even more effective than the active comparator. In the long-term trials

TABLE 3. Summary of clinical trials comparing mirtazapine (MIR) with amitriptyline (AMI), clomipramine (CLO), doxepin (DOX), trazodone (TRA), imipramine (IMI), fluoxetine (FLX), paroxetine (PAR), citalopram (CIT) and venlafaxine (VEN), with or without placebo (PLA) in patients with a moderate to severe major depression episode. Responders — patients with a 50% reduction in HAM-D score at end-point (last observed carried forward) (5,21,38,42,60)

Patient type (reference)	Dosage mg/day (mean)	Overall efficacy
Amitriptyline		
Outpatient (10)	MIR 5-35 (22)	MIR ≡ AMI
	AMI 40-280 (133)	MIR > PLA
	PLA	AMI > PLA
Outpatient (80)	MIR 5-35 (18)	MIR ≡ AMI
	AMI 40-280 (111)	MIR > PLA
	PLA	AMI > PLA
Inpatients (102)	MIR 20-60 (53)	MIR ≡ AMI
	AMI 75-225 (197)	
Inpatients and outpatients (43)	MIR 15-45	MIR ≡ AMI
	AMI 30-90	
Inpatients and outpatients (68)	MIR 20-60	MIR ≡ AMI
	AMI 75-225	
Clomipramine		
Inpatients (74)	MIR 2080 (47)	MIR ≡ CLO
	CLO 50-200 (114)	
Doxepin		
Inpatients and outpatients (63)	MIR 20-60 (37)	MIR ≡ DOX
	DOX 75-300 (189)	
Trazodone		
Outpatients > 55 years (40)	MIR 5-35 (20)	MIR ≡ TRA
	TRA 40-280 (151)	MIR > PLA
	PLA	TRA > PLA
Inpatients (94)	MIR 24-72	MIR ≥ TRA*
	TRA 150-450	
Imipramine		
Inpatients (13)	MIR 40-100 (76)	IMI > MIR
	IMI 38-450 (236)	
Fluoxetine		
Inpatients and outpatients (99)	MIR 15-60 (40)	MIR ≥ FLX
	FLX 20-40 (24)	
Paroxetine		
Outpatients (5)	MIR 15-45 (33)	MIR ≥ PAR
	PAR 20-40 (23)	
Citalopram		
Inpatients and outpatients (60)	MIR 15-60 (36)	MIR ≡ CIT
	CIT 20-60 (37)	
Venlafaxine		
Inpatients (38)	MIR 15-60 (50)	MIR ≡ VEN
	VEN 75-375 (255)	

* Statistically significant differences in favor of mirtazapine on all rating scales except MADRS.

Abbreviations and symbols: MADRS, Montgomery and Åsberg Depression Rating Scale; ≡, indicates no statistically significant difference in responder rates between comparators; >, indicates a statistically significant difference in responder rates ($p < 0.05$) between comparators; ≥, indicates that the first agent tended to be more effective.

comparing mirtazapine with an SSRI (citalopram or paroxetine), mirtazapine demonstrated a strong and sustained efficacy that was at least equal to that of the SSRIs (data on file, NV Organon). The proportions of long-term responders and remitters were high for all of these agents (51).

Only one open-label pilot study (27) has been found, in which 15 patients with a dysthymic disorder significantly improved after 10 weeks of treatment with mirtazapine. In another small pilot study (41), patients with a seasonal affective disorder were treated with mirtazapine. From the original group of eight patients, two discontinued the treatment; the remaining six completed the trial and adequately responded to mirtazapine therapy. Mirtazapine was also effective in 20 patients suffering from postmenopausal depression (45). In this trial mirtazapine substantially improved appetite and sleep and slightly improved anxiety and sweating.

Use of Mirtazapine in Combinations with other Antidepressants

In one study involving 20 patients (15), mirtazapine 15–30 mg/day was added to other antidepressants that were not sufficiently effective. Five of these patients used a combination of two or more antidepressants, while the others received only one antidepressant drug. The antidepressants used were SSRIs, venlafaxine, desipramine, trazodone, lithium, levothyroxine, and bupropion. Eleven patients were on clonazepam or lorazepam and two patients were on perphenazine. The addition of mirtazapine had a beneficial effect in more than 50% of these patients.

In another augmentation study (14), patients received first either mirtazapine or imipramine. Nonresponders in either group received lithium to augment the effects of antidepressants. Lithium augmentation was more efficacious in patients treated with imipramine than with mirtazapine; however, the combination treatment had to be discontinued in more patients receiving imipramine than mirtazapine.

In one double-blind study (24), the efficacy of mirtazapine, paroxetine, and their combination was compared. Each group was comprised of 20 patients suffering from diagnosed major depression. Mirtazapine and paroxetine were equally effective, but the combination had a more robust antidepressant effect and could, therefore, be useful in the treatment of refractory depression.

Use of Mirtazapine in Special Populations

A preliminary, open-label study (47) in menopausal women who were depressed but refractory to estrogen replacement treatment suggested that mirtazapine is an effective antidepressant in this patient group. Two women with depression reported hot flashes during treatment with mirtazapine 15–30 mg/day. Two other women reported that initial hot flashes and associated perspiration disappeared within a week, despite continuous treatment with mirtazapine (98).

Some preliminary studies of mirtazapine in anxiety disorders have been published. One single dose study (85) compared diazepam 10 mg and mirtazapine 5, 15, or 30 mg with placebo in female patients due for gynecological surgery on the following day. Both diazepam and mirtazapine reduced presurgery anxiety and insomnia more than placebo; the

optimal dose of mirtazapine was 15 mg. Mirtazapine has also been reported to reduce anxiety, sleeping difficulties, and nausea caused by chemotherapy in patients with breast or gynecological cancer (89). The antinausea effect of mirtazapine has been attributed to blockade of 5-HT_3 receptors (89).

The effectiveness of mirtazapine in patients with anxiety and depression was evaluated with a meta-analysis of eight randomized, double-blind, placebo-controlled studies (34). The patients had major depression and a baseline score of 6 or more for the sum of HAM-D items 9, 10, and 11 (anxiety/agitation). The anxiolytic effect of mirtazapine in those patients began during the first week of treatment and was considered to be significantly greater than that of placebo (34). In one study (37), in 10 patients with DSM-IV major depression and comorbid generalized anxiety disorder mirtazapine was active during the first week of therapy. In a small, open-label pilot study (16) mirtazapine had a beneficial effect in seven of 10 patients with a panic disorder. Preliminary data from another study (6) also suggested that mirtazapine has efficacy in the treatment of panic disorder. In an unpublished data from Organon files, mirtazapine reduced the number and intensity of panic attacks in a 12-week, open-label trial in patients with panic disorder (30). In a double-blind, randomized study ($n = 27$) of 8 weeks duration, mirtazapine was as effective as fluoxetine in panic disorder (48). A single-blind study (97) of 19 patients showed a remarkable reduction in the number of panic attacks. Three out of six patients with severe, chronic post-traumatic stress disorder also benefited from mirtazapine (19). In an open-label pilot study (95), half of 17 patients suffering from social anxiety disorder responded after 12 weeks of therapy with mirtazapine. A preliminary study (55) showed that mirtazapine may be an effective alternative in the treatment of obsessive-compulsive disorder.

Thirty haloperidol (5 mg/day)-treated patients with DSM-IV schizophrenia received additionally either mirtazapine or placebo for 6 weeks (44). Mirtazapine significantly reduced negative symptoms (as determined by the Positive and Negative Syndrome Scale [PANSS]). Moreover, Clinical Global Impression (CGI) Severity and Improvement Scale scores demonstrated superiority of mirtazapine over placebo.

In an open-label study (70), 26 patients (aged 4–23 years) suffering from autism and related disorders were treated with mirtazapine (7.5–45 mg/day) for at least 4 weeks. Seven out of 26 patients responded favorably ("much improved" or "very much improved" on the CGI).

Mirtazapine has been reported to affect certain symptoms of somatic disorders. Increased appetite and weight gain induced by mirtazapine in patients positive for human immunodeficiency virus (HIV), may be useful (29). On the other hand, mirtazapine may be of some help in the treatment of bulimia nervosa and binge eating (91). Some patients with parkinsonian tremor, action tremor, and levodopa-induced dyskinesias have benefited from mirtazapine (69). One patient has been reported to experience relief from the symptoms of irritable bowel syndrome (87) and another from the symptoms of migraine headache (9). The latter effect can be attributed to the antagonistic effect of mirtazapine at 5-HT_3 receptors and an agonistic effect at the 5-HT_{1A} receptors. In one pilot study (86), seven out of 10 patients suffering from irritable bowel syndrome were classified as responders within 6 days after the start of mirtazapine treatment. When mirtazapine was tapered off, a major relapse was seen in half of the responders.

The Economic Impact of Mirtazapine Therapy

The economic impact of using mirtazapine has been studied in Austria (39). The direct and indirect costs of therapy with mirtazapine (30 mg/day), amitriptyline (100 mg/day) or fluoxetine (20 mg/day) were compared in patients with moderate or severe depression. The final conclusion was that mirtazapine is more cost effective than comparators when the direct and indirect costs of the drugs were estimated. The cost per patient successfully treated with mirtazapine was estimated to be ATS 15,000 to ATS 18,000 less than with either amitriptyline or fluoxetine. The cost effectiveness of mirtazapine has also been studied in the United Kingdom (7); the conclusions resemble those from Austria.

DRUG INTERACTIONS

Mirtazapine seems not to have any significant inhibiting effect on cytochrome (CYP) P450 enzymes *in vitro*. Data from humans are, however, not available.

Fluoxetine (71) and paroxetine (93) slightly increase the plasma levels of concomitantly administered mirtazapine. These interactions do not seem to be clinically relevant. On the contrary, we have seen psychiatric patients whose steady-state serum mirtazapine levels increased about 200–300% when fluvoxamine was added to the treatment (Anttila and Leinonen, unpublished data).

In 12 healthy men receiving amitriptyline and mirtazapine concomitantly the blood levels of either drug were found to be higher than at the same dose of the drug when administered alone (65). This effect was not seen in women. The difference between genders was assumed to be due to differences in the absorption of the drugs; however, this pharmacokinetic interaction may not have any clinical significance (90).

One case report (81) describes a patient becoming hypomanic when mirtazapine 15 mg/day was added to a sertraline 250 mg/day regimen. Increases in blood pressure have been reported in one case when mirtazapine and amitriptyline were used concomitantly (101). This interaction was considered to be of pharmacodynamic origin. Similarly, adding mirtazapine to clonidine treatment caused hypertensive emergency. Mirtazapine is thought to antagonize the antihypertensive effect of clonidine, since mirtazapine, as an antagonist of central α_2-adrenoceptors, may increase norepinephrine release (2).

The interactions between mirtazapine and lithium were studied in 12 healthy male volunteers (78). The combination therapy was well tolerated and neither drug affected the pharmacokinetic parameters of the other. Carbamazepine, however, induced CYP enzymes, especially CYP3A4, and thereby reduced the plasma mirtazapine concentrations by 60% in young men (28).

Some data exist on the interactions between mirtazapine and benzodiazepines and mirtazapine and neuroleptics. Diazepam had no effect on the blood concentrations of mirtazapine (62). Risperidone also had no effect on serum concentrations of mirtazapine. In 16 psychiatric patients treated concomitantly with mirtazapine and risperidone, dose- and weight-corrected serum mirtazapine concentrations were not higher than those in control patients treated with mirtazapine alone (Anttila and Leinonen, unpublished data). Likewise, mirtazapine 30 mg/day had no effect on pharmacokinetics of risperidone

1–3 mg/day in six psychiatric patients (61). This combination had, however, less effect on salivation and produced, possibly, less extrapyramidal side effects than risperidone alone.

The effects of cimetidine on mirtazapine metabolism were studied in twelve healthy male volunteers (79). Cimetidine 1600 mg/day increased peak concentrations of mirtazapine 30 mg/day by 22% and the AUC by 64%. These effects were not considered to be clinically significant.

A single dose (60 g) of alcohol did not influence blood levels of mirtazapine (64). In spite of this, mirtazapine increased alcohol-induced drowsiness, probably due to a pharmacodynamic interaction. Smoking has not been found to affect mirtazapine blood levels (Anttila and Leinonen, unpublished data).

Some antidepressants, lithium, and benzodiazepines have to be discontinued during ECT (electroconvulsive therapy). According to one study on 19 patients mirtazapine can be safely administered to patients receiving ECT (84).

CONCLUSIONS

Mirtazapine is a novel, dual-acting antidepressant. It enhances both noradrenergic and serotonergic neurotransmission, but it is not a reuptake inhibitor. It is metabolized by CYP1A2, CYP2D6, and CYP3A4 isoenzymes. However, as a weak inhibitor of CYP-isoenzymes, mirtazapine is unlikely to cause clinically significant drug-drug interactions.

The antidepressant efficacy of mirtazapine has been established in several placebo-controlled trials. In these trials mirtazapine has been more effective than either placebo or trazodone. Its efficacy was comparable with that of amitriptyline, clomipramine, doxepin, fluoxetine, paroxetine, citalopram, or venlafaxine. In one study, mirtazapine was less effective than imipramine. In some studies, the onset of action of mirtazapine was more rapid than that of other antidepressants.

There are some preliminary studies on the efficacy of mirtazapine in depression-related anxiety and anxiety disorders. Moreover, mirtazapine may improve sexual function in some patients, especially those using SSRIs. Mirtazapine seems to be safe and effective in long-term treatment.

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