Mirtazapine: only for depression?

San L, Arranz B. Mirtazapine: only for depression?

Background: Mirtazapine is an antidepressant first approved in the Netherlands in 1994 for the treatment of major depressive disorder. However, evidence suggests its effectiveness in a variety of other psychiatric disorders and non-psychiatric medical conditions.

Objective: The present paper reviews the published literature on the off-label indications of Mirtazapine.

Methods: A search of the relevant literature from MEDLINE, PsycLIT and EMBASE databases, included in the Science Citation Index and available up to March 2006, was conducted using the terms mirtazapine, case-reports, open-label trials and randomized controlled trials. Only articles referring to conditions other than major depression were included in this present review.

Results: Off-label use of mirtazapine has been reported in panic disorder, post-traumatic stress disorder, generalized anxiety disorder, social phobia, obsessive-compulsive disorder, dysthymia, menopausal depression, poststroke depression, depression as a result of infection with human immunodeficiency virus, elderly depression, Methylendioxymethamphetamine (MDMA)-induced depression, hot flashes, alcohol and other substance use disorders, sleep disorders, sexual disorders, tension-type headaches, cancer pain, fibromyalgia, schizophrenia and other less frequent conditions.

Conclusions: So far, data on the off-label usefulness of mirtazapine are limited and mainly based on observations from case reports or open-label studies. However, positive cues suggest that confirmation of these preliminary data with randomized controlled trials may give sufficient evidence to warrant the use of mirtazapine in a broad range of disorders.

Keywords: case reports; controlled trials; mirtazapine; open-label trials; randomized

Correspondence: Luis San, Department of Psychiatry, Hospital de San Rafael, Barcelona, Spain. Tel: 34 629 736 820; Fax: 34 932 541 117; E-mail: 12636LSM@COMB.ES

Introduction

In the recent years, it has become evident that several antidepressants initially approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD) are also likely to be useful in a variety of other seemingly diverse psychiatric disorders and non-psychiatric medical conditions (1), with up to one third of initial antidepressant prescriptions for an intended treatment period of less than 6 months being used off-label and for non-psychiatric conditions (2).

Mirtazapine is an antidepressant first approved in the Netherlands in 1994 for the treatment of MDD. However, several case reports, open-label trial and randomized controlled trial have evaluated the efficacy of mirtazapine in a number of psychiatric and non-psychiatric conditions. A search of the relevant literature from MEDLINE, PsycLIT and EMBASE databases, included in the Science Citation Index and available up to March 2006, was conducted using the terms mirtazapine, case-reports, open-label trials and randomized controlled trials. Only articles referring to conditions other than major depression were included in this study. Abstracts of presentations to specialist meetings and conferences were not considered in this present review.

Anxiety disorders

For clinicians, recognition of anxiety and depressive disorders is considered to be of extreme importance, and both require adequate management (3).
This comorbidity of anxiety disorders with major depression suggests the use of antidepressants as first-line treatment, with dual-action antidepressants having an advantage in providing a greater likelihood of remission and the achievement of wellness (4).

Mirtazapine has been found to be superior to placebo and comparable with amitriptyline for the treatment of patients with major depression having symptoms of anxiety/agitation or anxiety/somatization in a meta-analysis of eight, randomized, double-blind, placebo-controlled clinical trials (5) including 161 mirtazapine-treated, 92 amitriptyline-treated and 132 placebo-treated patients, with a DSM-III diagnosis of major depression. In these studies, mirtazapine-treated patients showed a statistically significant ($p \leq 0.05$) reduction in the sum of Hamilton Depression Rating Scale (HDRS) items 9, 10 and 11 (anxiety/agitation) compared with placebo-treated patients at weeks 1, 2, 4 and 6 and at the endpoint. However, no statistically significant difference between the mirtazapine- and amitriptyline-treated patients was noted.

Panic disorder

Many clinicians consider selective serotonin reuptake inhibitors (SSRIs), either alone or in combination with high-potency benzodiazepines, to be the first-line therapy for the management of panic disorder (1), but benzodiazepines have an abuse/dependency liability that prevents their chronic use. The possibility that both serotonergic and noradrenergic activities are involved in the pathophysiology of panic disorder raise the issue of the possible efficacy of dual serotonin/noradrenaline reuptake inhibitors, which affect both systems (6).

In several open studies (Table 1), mirtazapine has shown promising results in reducing depressive and anxiety symptoms in patients with panic disorder (7–10). In an open study designed to evaluate changes induced by mirtazapine or paroxetine in 62 patients with panic disorder (11), statistically significant reductions from baseline to week 3 and from weeks 3 to 8 were noted in mirtazapine and paroxetine groups for number of panic attacks, Beck Anxiety Inventory (BAI) or Beck Depression Inventory (BDI), Clinical Global Impression (CGI) of panic disorder severity and CGI of panic disorder response. Significant differences between mirtazapine and paroxetine were found for the number of panic attacks at weeks 3 and 8 and for BAI at week 3, suggesting a faster response for mirtazapine.

So far, only one randomized, double-blind trial investigating the efficacy of mirtazapine in panic disorder has been published (12). After a 1-week placebo, 27 out-patients were randomized to an 8-week treatment with either fluoxetine or mirtazapine in a flexible dose design. Although patients from both groups showed statistically significant improvements at study endpoint, no significant differences between the two treatment groups were noted.

In summary, mirtazapine seems to be at least as effective as SSRIs in diminishing panic attacks. However, concomitant treatment of methodological problems, such as comorbidity with depression, substance abuse or other anxiety disorders, with either benzodiazepines or SSRIs and the lack of placebo group as comparator prevent from drawing definite conclusions until studies overcoming these biases are performed.

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder, with a high lifetime prevalence rate of 7.8% (13). PTSD is associated with increased rates of other psychiatric complaints, and approximately 80% of patients with PTSD have or develop comorbid psychiatric illnesses (14).

Mirtazapine has shown substantial improvement rates in three open-label studies (15–17) (Table 1). In the study by Connor et al. (15), six out-patients with severe, chronic PTSD were treated with mirtazapine up to 45 mg/day. After 8 weeks of treatment, 50% of the patients experienced a significant improvement in PTSD and depression scores. In the second study (16), mirtazapine was found to be effective and well tolerated in 15 patients with PTSD treated during 8 weeks. In a recent open-label trial (17), the potential use of mirtazapine in PTSD was compared with that of sertraline. Efficacy was evaluated by the PTSD scale (CAPS-2), the Hamilton Rating Scale for Depression (HRSD-17) and the CGI scale, at baseline and at weeks 1, 2 and 6. In all the assessments, mirtazapine appeared to be an effective and well-tolerated treatment for PTSD. In the only randomized, placebo-controlled, double-blind trial (18) published so far, 29 patients with PTSD received mirtazapine up to 45 mg/day or placebo on a 2:1 ratio for 8 weeks, with data being available for analysis for 26 subjects. Primary outcome measure included the Short Post-traumatic Stress Disorder Rating Interview and the Global Improvement item. Response rates were significantly higher for mirtazapine (64.7%) than for placebo (20%), suggesting the efficacy of mirtazapine in this disorder.
Table 1. Effectiveness of mirtazapine in anxiety disorders

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<tbody>
<tr>
<td>Panic disorder</td>
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<td>70% of patients with acute response by weeks 5–7 and 60% with positive long-term response at the 18th-week endpoint</td>
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<tr>
<td>Carpenter et al. (7)</td>
<td>16-week open-label trial</td>
<td>10</td>
<td>74% responders. Significant improvement in the number of full-symptom panic attacks and in the number of patients completely free of panic attacks from the second week</td>
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<td>Boshuisen et al. (8)</td>
<td>12-week open-label trial, with 3-week, single-blind, placebo run-in period</td>
<td>28 (19 completers)</td>
<td>Reduction in anxiety, severity of panic attacks and phobic symptoms</td>
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<tr>
<td>Carli and Sarchiapone (9)</td>
<td>12-week open-label trial</td>
<td>15 (11 with agoraphobia and 4 without agoraphobia)</td>
<td>Reduction in number and intensity of panic attacks and anticipatory anxiety. Improvement in depressive (HDRS) and anxiety (HARS) symptoms</td>
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<td>Sarchiapone et al. (10)</td>
<td>12-week open-label trial</td>
<td>45</td>
<td>No significant differences in number of panic attacks, anxiety or phobic symptoms between the two treatment groups. Patient global evaluation of phobic anxiety favors mirtazapine</td>
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<td>Montalies-Rada et al. (11)</td>
<td>8-week open-label trial, with mirtazapine vs. paroxetine</td>
<td>62</td>
<td>Significant differences between mirtazapine and paroxetine in the number of panic attacks at weeks 3 and 8 and in the BAI at week 3</td>
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<td>Ribeiro et al. (12)</td>
<td>8-week, randomized, double-blind, flexible dose of mirtazapine vs. fluoxetine</td>
<td>27 out-patients</td>
<td>Significant improvement on the clinician and self-rated scales and in depression scores in 50% of the patients</td>
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<tr>
<td>PTSD</td>
<td></td>
<td></td>
<td>Significant improvement on the clinician and self-rated scales and in depression scores in 50% of the patients</td>
</tr>
<tr>
<td>Connor et al. (15)</td>
<td>8-week open-label trial</td>
<td>Six out-patients</td>
<td>Clinical response in 88% of patients on mirtazapine and 69% of patients on sertraline at week 6. No difference between both groups in HDRS and CGI at all time-points</td>
</tr>
<tr>
<td>Bahk et al. (16)</td>
<td>8-week open-label trial</td>
<td>15 patients</td>
<td>Significant improvement in both depression and anxiety scores after the first week. Reduction of at least 50% in the HDRS total score achieved by 80% of the patients and remission achieved by 36% of the patients</td>
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<tr>
<td>Chung et al. (17)</td>
<td>6-week open-label trial, with mirtazapine vs. sertraline</td>
<td>51 patients on mirtazapine and 49 on sertraline</td>
<td>Significant improvement in both depression and anxiety scores after the first week. Reduction of at least 50% in the HDRS total score achieved by 80% of the patients and remission achieved by 36% of the patients</td>
</tr>
<tr>
<td>Davidson et al. (18)</td>
<td>8-week, randomized, placebo-controlled, (2:1 ratio) double-blind trial</td>
<td>26 patients</td>
<td>No significant differences in number of panic attacks, anxiety or phobic symptoms between the two treatment groups. Patient global evaluation of phobic anxiety favors mirtazapine</td>
</tr>
<tr>
<td>GAD</td>
<td></td>
<td></td>
<td>Significant improvement in both depression and anxiety scores after the first week. Reduction of at least 50% in the HDRS total score achieved by 80% of the patients and remission achieved by 36% of the patients</td>
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<tr>
<td>Goodnick et al. (19)</td>
<td>8-week open-label trial</td>
<td>10 patients</td>
<td>Significant differences in the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and Health Survey (SF-36) in the mirtazapine-treated subjects</td>
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<tr>
<td>Gambi et al. (20)</td>
<td>12-week, open-label, fixed-dose trial</td>
<td>44 out-patients</td>
<td>Five (41.7%) of the 12 patients completing the study classified as responders (CGI)</td>
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<tr>
<td>SAD</td>
<td></td>
<td></td>
<td>Significant differences in the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and Health Survey (SF-36) in the mirtazapine-treated subjects</td>
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<tr>
<td>Van Veen et al. (21)</td>
<td>12-week open-label trial</td>
<td>14</td>
<td>No significant differences in the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and Health Survey (SF-36) in the mirtazapine-treated subjects</td>
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<tr>
<td>Muehlbacher et al. (22)</td>
<td>10-week, randomized, double-blind placebo-controlled trial</td>
<td>66 women</td>
<td>No significant differences in the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and Health Survey (SF-36) in the mirtazapine-treated subjects</td>
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<td>OCD</td>
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<td>Significant differences in the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and Health Survey (SF-36) in the mirtazapine-treated subjects</td>
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<td>Koran et al. (23)</td>
<td>10-week open-label trial</td>
<td>10</td>
<td>20% response rate</td>
</tr>
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<td>Koran et al. (24)</td>
<td>12-week open-label phase and a 8-week, double-blind, placebo-controlled, discontinuation phase</td>
<td>30 subjects, 15 treatment naive and 15 treatment experienced. OCD of &gt;1-year duration. YBOCS scores &gt;20</td>
<td>53% response rate. Outcome measures in the discontinuation phase consistent with superiority of mirtazapine vs. placebo</td>
</tr>
<tr>
<td>Pallanti et al. (25)</td>
<td>12-week, two-tailed, single-blind trial with citalopram plus placebo or citalopram plus mirtazapine</td>
<td>49 patients with OCD without comorbid depression</td>
<td>The citalopram plus mirtazapine group achieved a reduction of at least 35% in the YBOCS score and a “much improved” or “very much improved” rating on the CGI Improvement scale from the fourth week. No difference in response rate between the two groups at weeks 9 and 12</td>
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</table>

SPRINT, Short Post-traumatic Stress Disorder Rating Interview; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale.
Generalized anxiety disorder

A high proportion of patients with generalized anxiety disorder (GAD) have comorbid depressive illness. Several antidepressants, including mirtazapine, have been found to be effective for GAD, although data for mirtazapine are limited to two open-label studies (Table 1). In an 8-week, open, pilot study, mirtazapine was administered to 10 patients with major depression and comorbid GAD (19). Patients were found to have significant reductions in the HDRS, Hamilton Anxiety Rating Scale (HARS) and BDI scores, with improvement even after the first week of therapy, and continuing improvement in both depression and anxiety scores over the study period. In a more recent open-label, fixed-dose study (20) performed during 12 weeks in 44 out-patients with GAD, a reduction of 50% or more in the HARS total score was achieved by 80% of the patients and remission was achieved by 36% of the patients.

Social anxiety disorder

One open-label study and one randomized, double-blind, placebo-controlled study suggest the efficacy of mirtazapine in patients suffering from social anxiety disorder (SAD) (Table 1). In the open study (21), 14 patients with SAD were treated with mirtazapine 30 mg/day for 12 weeks, with 5 (41.7%) of the 12 patients completing the study being classified as responders, based on a CGI scale. In the only randomized, double-blind, placebo-controlled study performed to date (22), 66 female patients suffering from social phobia were randomly assigned to mirtazapine (n = 33) or placebo (n = 33) during 10 weeks. In comparison with the placebo group, significant differences on the Social Phobia Inventory, the Liebowitz Social Anxiety Scale scores and the Health Survey (SF-36) were observed in the mirtazapine-treated subjects.

Obsessive-compulsive disorder

SSRIs are the only drugs approved by the US FDA for the treatment of obsessive-compulsive disorder (OCD). However, many patients experience little response to standard treatment with these drugs, suggesting that the pathophysiology of OCD often involves more than a deficient serotonergic neurotransmission. Although mirtazapine only achieved a 20% response rate in a 10-week, open-label, pilot study (23) (Table 1) performed in 10 patients with OCD, in a two-phase study by the same authors (24), response rate improved up to 53%. In the 12-week, open-label phase, subjects received mirtazapine starting at 30 mg/day and titrated for more than 2 weeks as tolerated to 60 mg/day. At week 12, responders were randomly assigned, doubleblind, to continue mirtazapine or to switch to placebo for 8 weeks, including a 1-week, double-blind taper week for subjects treated with placebo. Sixteen subjects (53.3%) were responders, and 15 agreed to randomization. Response was independent of comorbid mood disorders. In the 8-week, double-blind, placebo-controlled, discontinuation phase, the mean Yale-Brown Obsessive Compulsive Scale (YBOCS) score for mirtazapine group fell to a value of 2.6 ± 8.7 points (mean ± SD), while for the placebo group, the mean score rose to a value of 9.1 ± 7.5 points (mean ± SD) (p = 0.005). All other outcome measures were consistent with the superiority of mirtazapine vs. placebo for OCD.

In another study (25), 49 patients with OCD without comorbid depression were randomly assigned to a two-tailed, single-blind, 12-week clinical trial with citalopram (20–80 mg/day) plus placebo or with citalopram plus mirtazapine (15–30 mg/day). The citalopram plus mirtazapine group achieved a reduction of at least 35% in the YBOCS score and a ‘much improved’ or ‘very much improved’ rating on the CGI Improvement scale from the fourth week, while the citalopram plus placebo group obtained these results only from the eighth week. The number of responders was higher in the citalopram plus mirtazapine group at the fourth week of treatment, while no difference in the response rate between groups was noted at 8 and 12 weeks of treatment. When mirtazapine was added to citalopram, an earlier onset of response in OCD symptoms and reduced undesired side-effects were noted.

Depressive disorders other than major depression

Brief recurrent depression

Studies on brief recurrent depression have not shown any superiority of the SSRIs over placebo, and it is possible that the dual mechanism of action shared by some antidepressants, such as mirtazapine, may be required to effectively treat this condition (26). In two patients with brief recurrent depression treated with mirtazapine for 4 months, there were marked reductions in the severity, duration and frequency of the depressive episodes (27) (Table 2). These promising results need to be replicated in controlled studies.
Dysthymia

Although no randomized controlled trials investigating the efficacy of mirtazapine in dysthymia have been published, an open-label study (28) performed during 10 weeks in 15 patients with dysthymia showed significant improvements according to the HRSD and the BDI scores. While four patients discontinued treatment because of sedation, mirtazapine was effective and well tolerated in the remaining patients (Table 2).

Menopausal depression

Treatment of major depression in menopausal women is controversial. Estrogen replacement therapy (ERT) treats mild depression but may not treat more severe depression in this population. Mirtazapine seems to be effective in the treatment of major depression in perimenopausal and postmenopausal women whose depression precedes ERT use and does not respond to ERT or whose depression develops after ERT is initiated. This is evidenced in an open-label clinical trial (29) including 22 perimenopausal and postmenopausal women with major depression taking stable doses of ERT. While four patients discontinued treatment because of sedation, mirtazapine was effective and well tolerated in the remaining patients (Table 2).

Poststroke depression

Poststroke depression is one of the most frequent neuropsychiatric complications of ischemic stroke. Various studies have reported that depressive syndromes occur in approximately 20–40% of patients with poststroke depression, but they remain underdiagnosed and undertreated. A variety of antidepressants have been shown to effectively lessen depressive symptoms after stroke. Although there is consensus that it should be treated as soon as possible, little attention has been given to its possible prevention. For this reason, prophylactic treatment with mirtazapine was assessed in patients with acute stroke (30). Seventy patients with ischemic stroke received either 30 mg mirtazapine or no antidepressant medication from day 1 after the stroke in an open, randomized study design. Patients developing depression after stroke but randomly assigned to the nontreatment group were given mirtazapine after the diagnosis of depression had been established. Forty percent (14/35) of the nontreated patients and only 5.7% (2/35) of the patients treated with mirtazapine developed poststroke depression.

### Table 2. Effectiveness of mirtazapine in depressive disorders

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<td>Brief recurrent depression</td>
<td>Stamenkovic et al. (27) Case report. Mirtazapine during 4 months</td>
<td>Two patients</td>
<td>Marked reductions in the severity, duration and frequency of the depressive episodes</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>Dunner et al. (28) 10-week open-label trial</td>
<td>15 patients</td>
<td>Significant improvements according to the HRSD and the BDI scores</td>
</tr>
<tr>
<td>Menopausal depression</td>
<td>Joffe et al. (29) 8-week open-label trial</td>
<td>22 perimenopausal and postmenopausal women with major depression taking stable doses of ERT</td>
<td>Remission of depression achieved by 14 of the 16 (87.5%) completer patients</td>
</tr>
<tr>
<td>Poststroke depression</td>
<td>Niedermaier et al. (30) 12-month open-label trial. Randomization to prophylactic mirtazapine vs. no antidepressant</td>
<td>70 patients with an ischemic stroke</td>
<td>Forty percent (14/35) of the nontreated patients and only 5.7% (2/35) of the patients treated with mirtazapine develop poststroke depression</td>
</tr>
<tr>
<td>Depression due to human immunodeficiency virus infection</td>
<td>Elliot et al. (31) 12-week open-label trial</td>
<td>12 patients with HIV having recurrent MDD</td>
<td>66% full and a 100% partial response rate. Overall effectiveness similar to other antidepressants</td>
</tr>
<tr>
<td>Serra et al. (32)</td>
<td>16-week, prospective, longitudinal, open-label, observational trial</td>
<td>27 HIV-1-infected out-patients with major depression</td>
<td>Significant improvements in HADS, BDI, CGI and HIV-MOS from completing patients (41%)</td>
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HADS, Hospital Anxiety and Depression Scale.
developed poststroke depression. Altogether, 16 patients developed poststroke depression, of whom 15 remitted after initiation of treatment with mirtazapine. These results suggest the efficacy of mirtazapine in reducing the rate of poststroke depression and in treating poststroke depression.

Depression due to human immunodeficiency virus

In the past decade, it has been well established that MDD has a higher prevalence in both human immunodeficiency virus (HIV)-positive group and at-risk group, compared with lifetime and current rates in community samples. The effectiveness of mirtazapine in HIV depression has been shown in two open studies. In the first study, 12 patients with HIV having recurrent MDD were included in a nonblinded, 12-week trial with mirtazapine (31) (Table 2). Patients completing the study period showed a 66% full and a 100% partial response rates. Mirtazapine-treated patients had a low number of total adverse effects and a low rate of drop-out due to adverse effects, resulting in a high overall effectiveness similar to that seen with other antidepressants. In a prospective, longitudinal, open-label, observational study (32), 27 HIV-1-infected out-patients with major depression were assessed at baseline and after 1, 2, 4, 8 and 16 weeks of treatment with mirtazapine using the Hospital Anxiety and Depression Scale and the BDI and CGI scales. Sixteen patients dropped out of the study before reaching the last visit because of side-effects and medical complications as a result of HIV infection, but completing patients (41%) showed a statistically significant improvement in all measures.

Elderly depression

Depression is a common, treatable disorder among elderly people. In a retrospective chart review performed by Gardner et al. (33), medication use and cost in nursing facility residents treated with mirtazapine was compared with that in patients taking other antidepressants. Patients on mirtazapine were less likely to be taking a sedative/hypnotic ($p = 0.006$) as fewer patients in the mirtazapine group were taking lorazepam ($p = 0.03$). There was no difference between the two groups regarding the use of other psychotropic medications, including multiple antidepressants, antipsychotics, anticonvulsants, acetylcholinesterase inhibitors or appetite stimulants. Monthly medication costs were lower for patients receiving mirtazapine than for those receiving other antidepressants. The results of this study suggest that patients receiving mirtazapine are less likely to be on anxiolytic/hypnotic agents, with medication costs being lower when mirtazapine is used.

Anxiety and depression in patients undergoing transplantation

Depressive and anxiety disorders are of common appearance during the transplant process due to psychological stressors, medications and physiological disturbances and are associated with a reduced quality of life and negative outcomes. Studies regarding the treatment of anxiety and depressive disorders in the patients undergoing transplantation are limited in number, but recommendations are possible by review of clinical and pharmacokinetic data (34). Advantages of mirtazapine use in this population are the lack of sexual side-effects and gastrointestinal complaints and its low potential for drug interaction, particularly with immunosuppressive agents. Furthermore, the sedative and weight gain effect often associated with mirtazapine can be used advantageously in patients undergoing transplantation having decreased appetite or sleep disturbances. However, several authors have indicated the need to avoid mirtazapine as first-line agent in these patients due to exacerbation of immunosuppressant-induced metabolic changes, ie corticosteroid-induced weight gain and hyperlipidemia (35).

MDMA-induced depression

In a case report of a 28-year-old woman with a MDMA-induced depression, mirtazapine has shown its efficacy either by augmentation of serotonergic tone or by norepinephrine release, which in turn promotes serotonergic axon regrowth (36).

Pain disorders

Chronic pain

The analgesic action of tricyclic antidepressants has been extensively studied and proven, but these drugs are associated with a number of adverse effects that prevents their use in some patients. In several review articles (37,38) concerning the efficacy of the newer antidepressants in the treatment of chronic pain, data regarding SSRIs are conflicting, with no placebo-controlled studies available for mirtazapine. Results from a 6-week, open, prospective study performed in 594 patients with at least one chronic pain syndrome and concomitant depression showed a significant reduction in pain from baseline to endpoint,
together with improvement in sleep disturbance and irritability (39).

Tension-type headaches

After some preliminary positive results with the use of mirtazapine in treatment of migraine (40–42), the qualitative and quantitative efficiency of mirtazapine in the prophylaxis of chronic tension-type headaches (CTTHs) was compared with that of amitryptiline in a double-blind study (43) (Table 3). A sample of 60 patients with CTTH criteria was divided into two groups, and subjects were administered one of the drugs at 50% random for 6 months. Group I was administered 25 mg of amitryptiline, and group II received 30 mg of mirtazapine. Depression scores improved in both groups without any objective differences between them, although the subjective feeling of improvement was greater with mirtazapine. A significant reduction in the usual consumption of analgesics was noted with both treatments. Side-effects were relatively frequent and significantly fewer in the group of patients treated with mirtazapine, the most common being dry mouth and drowsiness. These results suggest that mirtazapine is as efficient as amitryptiline in the treatment of CTTH but has significantly fewer side-effects, probably because of its more selective action on the brain receptors.

In a randomized, double-blind, placebo-controlled, crossover study, the efficacy of mirtazapine was evaluated in 24 nondepressed patients with CTTH (44). Mirtazapine 15–30 mg/day or placebo was given for 8 weeks separated by a 2-week washout period. Twenty-two patients completed the study. The primary efficacy variable, area under the curve (AUC; duration × intensity), was lower during treatment with mirtazapine than during treatment with placebo. Mirtazapine also reduced the secondary efficacy variables such as headache frequency, headache duration and headache intensity. Mirtazapine reduced the AUC 34% more than placebo in difficult-to-treat patients. These findings are clinically relevant and may stimulate the development of prophylactic treatments with increased efficacy and fewer side-effects for tension-type headache and other types of chronic pain.

Cancer pain

Thirty to fifty percent of patients with cancer manifest significant affective disorders in the form

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<th>Main findings</th>
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<td>6-month double-blind trial, with amitryptiline vs. mirtazapine</td>
<td>60 depressed patients with CTTH</td>
<td>Significant reduction in the usual consumption of analgesics with both treatments. Significantly fewer side-effects in the mirtazapine-treated patients</td>
</tr>
<tr>
<td>8-week, randomized, double-blind, placebo-controlled, crossover trial</td>
<td>24 nondepressed patients</td>
<td>Lower AUC (duration × intensity) in the mirtazapine group. Mirtazapine also reduce headache frequency, headache duration and headache intensity. Mirtazapine reduces the AUC 34% more than placebo in difficult-to-treat patients</td>
</tr>
<tr>
<td>6-week, open, prospective trial</td>
<td>594 patients with at least one chronic pain syndrome and concomitant depression</td>
<td>Significant reduction of pain from baseline to endpoint, together with improvement in sleep disturbance and irritability</td>
</tr>
<tr>
<td>7-week, open-label, crossover trial</td>
<td>36 patients with cancer having pain</td>
<td>Depression scores, several somatic symptoms and quality-of-life assessments significantly improved at the end of the study</td>
</tr>
<tr>
<td>8-week open-label trial</td>
<td>30 patients with cancer having depressive disorder</td>
<td>Mirtazapine appears safe and effective</td>
</tr>
<tr>
<td>6-week open-label trial</td>
<td>29 patients with fibromyalgia and depression</td>
<td>38% responders on account of the reduction of &gt;40% in pain, fatigue and sleep disturbances and remission of depressive symptoms</td>
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</tbody>
</table>
of adjustment disorders or major depression, and they often suffer from multiple distressing symptoms. When choosing interventions for depression, targeting multiple symptoms with a single drug can potentially improve quality of life, avoid polypharmacy and drug interactions and not overly burden patients with complex regimens. In addition to their potential usefulness in treating depression, antidepressant medications have been used extensively as adjuvant treatments for cancer pain. In a pilot, open-label, crossover trial with mirtazapine (15 and 30 mg) during 7 weeks in 36 patients with advanced cancer having pain and other distressing symptoms, depression scores, several somatic symptoms and quality-of-life assessments were significantly improved at the end of the study and were not dependent on mirtazapine dosage (45) (Table 3). In another open-label study in 30 patients with cancer having depressive disorders, mirtazapine appeared safe and effective after 8 weeks of treatment (46).

In summary, mirtazapine may be an excellent choice for patients with chronic pain, anxiety, depression and weight loss and may treat multiple symptoms with once a day administration. It has an excellent drug safety and patient acceptance, a reduced risk for drug-drug interactions and fewer side-effects compared with standard palliative medications (47).

Fibromyalgia syndrome (FS) is a musculoskeletal disease of unknown etiology, for which pharmacological therapy with analgesic agents and nonsteroidal anti-inflammatory drugs is mostly unsatisfactory. Mirtazapine, 15–30 mg/day, has been used in 29 patients with FS in an open trial (48). Twenty-six patients completed the 6-week study period. Ten patients (38%) were considered responders on account of the reduction of ≥40% in pain, fatigue and sleep disturbances and remission of depressive symptoms at the end of the study. The percentage of responders was similar in high- and low-depression groups, suggesting that mirtazapine may be a promising method of FS treatment.

Substance use disorders

Alcohol dependence

Social anxiety symptoms and alcoholism are closely interrelated, but there are no systematic studies dealing with the immediate impact of alcohol detoxification on anxiety. Liappas et al. (49) showed the existence of a high incidence of social anxiety symptoms in in-patient alcoholics, which diminished following alcohol detoxification. A total of 54 alcoholic in-patients were randomly assigned to either a 4- to 5-week period of cognitive behavioural therapy during the postdetoxification phase (n = 21) or a combination of mirtazapine and psychotherapy (n = 33). A marked reduction in social anxiety symptoms was evidenced in both groups. However, patients on mirtazapine improved significantly more compared with controls, suggesting that a combined psychotherapeutic/mirtazapine treatment has a greater impact on the aforementioned symptoms than nonpharmacological treatment alone (Table 4). In a more recent study performed by the same authors (50), the collateral anxiety and depressive symptomatology were assessed during the postwithdrawal (4 weeks) phase of alcoholism. Thirty-three patients were included following a standard short-term psychotherapy, and mirtazapine was assigned to a second group of 35 patients in addition to standard treatment. As in the previous study, a marked reduction in anxiety and depressive symptoms was shown in both groups, with patients on mirtazapine improving more and at a faster rate compared with controls. Thus, mirtazapine, used adjunctively to short-term psychotherapy, may help the detoxification process by minimizing physical and subjective discomfort. Consequently, it may improve patient compliance in alcohol detoxification programmes and facilitate the initial treatment phase of alcohol dependence. Mirtazapine has also been shown to aid in the treatment of a depressed alcoholic patient (51), speculating that its 5-HT3 antagonism may have contributed to its beneficial effect, as antagonism of potentially up-regulated 5-HT3 receptors may ameliorate serotonergic dysfunction, decrease reward and regulated alcohol intake.

The impact of a combined psychotherapeutic and psychopharmacological (either with mirtazapine or with venlafaxine) treatment on the anxiety and depression symptoms during the early withdrawal phase of alcohol compared with a group treated with only psychotherapy was studied (52). A total of 60 alcohol-dependent patients were randomly assigned to three groups (psychotherapy, psychotherapy plus mirtazapine and psychotherapy plus venlafaxine). A marked improvement in anxiety and depressive symptoms was evidenced in all groups by the end of the detoxification period. However, patients on mirtazapine improved significantly more compared with the other two groups. These results suggest that addition of mirtazapine, but not venlafaxine, to a standard psychotherapy-oriented alcohol detoxification treatment may
facilitate the detoxification process by minimizing psychological discomfort. Consequently, mirtazapine may prove to be a facilitator for the long-term abstinence from alcohol.

Amphetamine dependence

The safety and efficacy of mirtazapine in amphetamine detoxification were assessed in a 14-day, randomized, placebo-controlled, pilot trial (53) performed in 20 patients with amphetamine dependence. Significant improvements in favor of mirtazapine in the total Amphetamine Withdrawal Questionnaire were noted both at days 3 and 14. No significant differences were observed in the Montgomery Asberg Depression Rating Scale (MADRS) score changes within or between groups.

Other disorders

Schizophrenia

Negative symptoms have long been recognized as a central schizophrenic feature, and they include blunted affect, poverty of thought content and speech, avolition or apathy and social withdrawal. Systematic studies have shown that negative symptoms respond poorly to conventional antipsychotic therapies (54). Some similarities between negative and depressive symptoms tend to suggest that a serotonergic dysfunction might be involved in the pathogenesis of negative symptoms of schizophrenia. For these reasons, the tendency is to suggest the use of antidepressants as augmentation strategy for the treatment of negative symptoms. The potential use of mirtazapine as augmentation strategy for the treatment of negative symptoms of schizophrenia has been emphasized in a 6-week, double-blind, randomized, placebo-controlled study performed in 30 patients with schizophrenia (55), who showed a significant decrease in negative symptoms when mirtazapine was added to haloperidol (Table 5).

In an 8-week, double-blind, randomized, placebo-controlled trial with 30 mg adjunctive mirtazapine to clozapine therapy in 24 patients with schizophrenia (56), a significant reduction in the Scale for the Assessment of Negative Symptom (SANS) total scores in the mirtazapine group was noted compared with placebo group, with a significant improvement on the SANS avolition/apathy and anhedonia/asociality subscales. These results suggest a potential role for mirtazapine as an augmentation strategy in the treatment of negative symptoms of schizophrenia without negative effects on the metabolism of different antipsychotics (57). In addition, the putative antiakathisic activity of short-term mirtazapine was explored in one case report (58) and in five patients with olanzapine- or risperidone-induced akathisia (59), while a double-blind, randomized, placebo-controlled study showed the therapeutic effect of low-dose mirtazapine during 5 days in the treatment of neuroleptic-induced akathisia in 26 patients with schizophrenia (60).

Hot flashes

Mirtazapine has been reported to reduce hot flashes in hormone-deficient, nondepressed women through blockade of 5-HT2 receptors.

### Table 4. Effectiveness of mirtazapine in substance use disorders

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>Sample</th>
<th>Main findings</th>
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</thead>
<tbody>
<tr>
<td>Alcohol dependence</td>
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<tr>
<td>Liappas et al. (49)</td>
<td>Double-blind randomization to either a 4- to 5-week period of cognitive</td>
<td>54 alcoholic in-patients</td>
<td>Patients on mirtazapine show higher improvement in depressive and anxiety</td>
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<td></td>
<td>behavioural therapy during the postdetoxification phase (n = 21) or a</td>
<td></td>
<td>symptoms</td>
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<td></td>
<td>combination of mirtazapine and psychotherapy (n = 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liappas et al. (50)</td>
<td>Double-blind randomization to a 4- to 5-week standard short-term psychotherapy</td>
<td>68 alcoholic patients</td>
<td>Reduction of anxiety and depression. Patients on mirtazapine improve more and</td>
</tr>
<tr>
<td></td>
<td>with (n = 35) or without (n = 33) mirtazapine addition</td>
<td></td>
<td>at a faster rate compared with controls</td>
</tr>
<tr>
<td>Crockford and White (51)</td>
<td>Case report</td>
<td>One depressed alcoholic patient</td>
<td>Reduction of depressive symptoms and alcohol intake</td>
</tr>
<tr>
<td>Liappas et al. (52)</td>
<td>Single-blind randomization to psychotherapy, psychotherapy plus mirtazapine</td>
<td>60 alcohol-dependent patients</td>
<td>Patients on mirtazapine show higher improvement in depressive and anxiety</td>
</tr>
<tr>
<td></td>
<td>and psychotherapy plus venlafaxine during 4-5 weeks</td>
<td></td>
<td>symptoms compared with the other two groups</td>
</tr>
<tr>
<td>Amphetamine dependence</td>
<td>Kongakon et al. (53)</td>
<td>20 male patients with amphetamine dependence</td>
<td>Significant improvements in favor of mirtazapine in the total Amphetamine</td>
</tr>
<tr>
<td></td>
<td>14-day, randomized, placebo-controlled trial</td>
<td></td>
<td>Withdrawal Questionnaire both at days 3 and 14</td>
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</table>
In a prospective 5-week, single-arm, pilot, clinical trial (62), the efficacy and tolerability of mirtazapine for alleviating hot flashes were evaluated. For the 16 patients who completed the study, the median reductions in total daily hot flashes and weekly hot flash scores were 52.5 and 59.5%, respectively. This available data suggest that mirtazapine is a reasonable treatment to consider in patients with hot flashes, particularly in those with anxiety and sleep disturbances.

Sleep disorders

Sleep patterns in depressed patients are markedly different from those in nondepressed subjects and may involve disturbances in any stage of the sleep cycle. Mirtazapine appears to have significantly different effects on electroencephalogram (EEG) sleep pattern when compared with other antidepressants. At low doses, like 15 mg/day, the prominent antihistaminergic properties of mirtazapine may result in a nonspecific sedative effect (63,64), although this sedative effect seems to be mainly mediated by 5-HT2 receptor blockade (65).

In a study on a single dose of mirtazapine given to six human volunteers with normal sleep patterns, mirtazapine significantly shortened the time to onset of sleep, and stage 1 sleep was reduced, while the amount of deep sleep was significantly increased (66). In addition, mirtazapine significantly

Table 5. Effectiveness of mirtazapine in other psychiatric and non-psychiatric disorders

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>Sample</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
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<tr>
<td>Berk et al. (55)</td>
<td>6-week, double-blind, randomized, placebo-controlled trial</td>
<td>30 patients with schizophrenia</td>
<td>Significant decrease in negative symptoms when mirtazapine is added to haloperidol</td>
</tr>
<tr>
<td>Zoccali et al. (56)</td>
<td>8-week, double-blind, placebo-controlled trial of adjunctive mirtazapine to olanzapine</td>
<td>24 patients with schizophrenia</td>
<td>Significant reduction in the SANS total scores in the mirtazapine group, with a significant improvement on the SANS avolition/apathy and anhedonia/asociality subscales</td>
</tr>
<tr>
<td>Poyurovsky et al. (58)</td>
<td>5-day, double-blind, randomized, placebo-controlled trial</td>
<td>26 patients with schizophrenia</td>
<td>Therapeutic effect of low-dose mirtazapine in the treatment of neuroleptic-induced akathisia</td>
</tr>
<tr>
<td>Hot flashes</td>
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</tr>
<tr>
<td>Waldinger et al. (61)</td>
<td>Case report</td>
<td>Four hormone-deficient, nondepressed women</td>
<td>Reduction of hot flashes</td>
</tr>
<tr>
<td>Perez et al. (62)</td>
<td>5-week open-label trial</td>
<td>16 patients</td>
<td>Reductions in total daily and weekly hot flash scores of 52.5 and 59.5%, respectively</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Guelfi et al. (73)</td>
<td>8-week, randomized, double-blind mirtazapine vs. venlafaxine</td>
<td>157 depressed patients with melancholic features</td>
<td>From first week, larger changes from baseline sleep disturbance by treatment with mirtazapine than with venlafaxine</td>
</tr>
<tr>
<td>Schittecatte et al. (72)</td>
<td>5-week open-label trial</td>
<td>17 patients with MDD</td>
<td>Improvement in the speed and ease of getting off to sleep and in the subjective periods of wakefulness</td>
</tr>
<tr>
<td>Winokur et al. (74)</td>
<td>8-week, double-blind double-dummy mirtazapine vs. fluoxetine</td>
<td>19 patients with MDD</td>
<td>Improvements in sleep latency, sleep efficiency and wake after sleep onset after 2 weeks. Significant improvement in objective sleep physiology measures at week 8</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Farah (81, 82)</td>
<td>Case reports</td>
<td>Four</td>
<td>Addition of mirtazapine to SSRI treatment improves sexual dysfunction</td>
</tr>
<tr>
<td>Koutouvidis et al. (79)</td>
<td>6-week open-label trial</td>
<td>11</td>
<td>No symptoms of sexual dysfunction</td>
</tr>
<tr>
<td>Boyarsky et al. (83)</td>
<td>12-week, flexible dosing, open-label trial</td>
<td>25 patients with major depressive episode</td>
<td>Desire, arousal/lubrication and ease/satisfaction of orgasm improve (41, 52 and 48%, respectively) in the depressed women. In men, desire, arousal/erection and ease/satisfaction of orgasm also improve (10, 23 and 14%, respectively), but much more modestly</td>
</tr>
<tr>
<td>Gelenberg et al. (80)</td>
<td>6-week open-label trial</td>
<td>19 patients in remission from a MDD and experiencing SSRI-induced sexual dysfunction</td>
<td>58% patients return to normal sexual functioning and maintain antidepressant response after switching to mirtazapine</td>
</tr>
<tr>
<td>Clayton et al. (84)</td>
<td>Observational, cross-sectional trial</td>
<td>4534 women and 1763 men</td>
<td>Patients treated with mirtazapine (n = 64) experience sexual dysfunction at a frequency similar (36–43%) to that of patients treated with SSRIs</td>
</tr>
<tr>
<td>Montejo et al. (85)</td>
<td>Multicentre, prospective, open-label trial</td>
<td>1022</td>
<td>58.1% overall incidence of sexual dysfunction when all antidepressants are considered as a whole, with relevant differences among different drugs</td>
</tr>
</tbody>
</table>
increased the latency of rapid eye movement stage 2 sleep and reduced night-time wakening. In placebo-controlled studies with depressed patients, mirtazapine has been reported to improve subjective complaints of sleep disturbance (67–71).

One open-label and two double-blind randomized studies have shown the efficacy of mirtazapine in sleep disorders. In the open-label study (72), 17 patients meeting criteria for MDD and treated with mirtazapine for 5 weeks showed substantial improvement in the speed and ease of getting off to sleep and in the subjective periods of wakefulness. In a multicentre, randomized, double-blind study, mirtazapine was also compared with venlafaxine over an 8-week treatment period of 157 severely depressed patients with melancholic features. On the sleep disturbance items of the HDRS, treatment with mirtazapine resulted from first week onward in statistically significantly larger changes from baseline than treatment with venlafaxine, and this was maintained at all assessment times throughout the study (73).

In 19 patients with MDD having insomnia, sleep continuity with mirtazapine was compared with fluoxetine using polysomnographic evaluations for more than two consecutive nights (74). Subjects were randomly assigned to either fluoxetine or mirtazapine treatment for an 8-week, double-blind, double-dummy treatment trial. Patients receiving mirtazapine (n = 8) showed significant improvement in objective sleep physiology measures at week 8. Improvements in sleep latency, sleep efficiency and wake after sleep onset were significant only after 2 weeks of mirtazapine treatment. No significant changes in sleep continuity measures were observed in the fluoxetine group (n = 11). Both groups improved clinically in mood and subjective sleep measures from baseline, with no differences between groups. These data show the differential effects of mirtazapine and fluoxetine on objective sleep parameters in patients with MDD having insomnia, with significant improvement in favor of mirtazapine. Sleep continuity seems to be enhanced by mirtazapine due to a significant shortening of the latency of onset of sleep efficiency.

Sexual disorders

Sexual dysfunction is frequent in both the general and the depressed population. There are several possible causes of sexual dysfunction in depressed patients, the main cause being related to the side-effects of medication (75). Antidepressant-induced sexual dysfunction poses a substantial problem that needs to be addressed using the antidepressants, such as mirtazapine, that causes a minimal sexual dysfunction (76–78).

Studies on switch therapy are limited to four small, uncontrolled, open-label studies (79–82) in which patients experiencing SSRI-induced sexual dysfunction, mostly loss of libido or anorgasmia, were switched to mirtazapine, titrated up to 45 mg/day for up to 6 weeks. All the studies showed that mirtazapine successfully controls depressive symptoms and improves sexual functioning in many patients but is associated with emergent adverse reactions of weight gain, irritability and sedation.

In a pilot study (83), sexual functioning and antidepressant activity in depressed patients taking mirtazapine were investigated. Twenty-five (seven men and 18 women) sexually active outpatients with a diagnosis of major depressive episode were included in a 12-week, flexible dosing, open-label, pilot study (Table 5). Desire, arousal/lubrication and ease/satisfaction of orgasm improved (41, 52 and 48%, respectively) in the depressed women. In men, desire, arousal/ejection and ease/satisfaction of orgasm also improved (10, 23 and 14%, respectively), but much more modestly. HDRS, CGI, Sheehan Disability Scale and Symptom Checklist-90 scores improved in both groups. There was a 50% drop-out rate among women before 6 weeks of treatment. However, the Arizona Sexual Experiences Scale and the HDRS scores of the groups terminating before and after 6 weeks of treatment showed similar rates of improvement. These results show that mirtazapine has a beneficial effect on sexual functioning in both depressed men and women, although longer term, double-blind research assessing sexual function during the administration of mirtazapine and other antidepressants is recommended.

Data from a large observational, cross-sectional study have shown that patients treated with mirtazapine (n = 64) experience sexual dysfunction at a frequency similar (36–43%) to that of patients treated with SSRIs (84). However, in another multicentre, prospective, open-label study (85) carried out in 1022 patients with previously normal sexual function and treated with antidepressants alone or in combination with benzodiazepines, the overall incidence of sexual dysfunction was 59.1% when all antidepressants were considered as a whole. Relevant differences were noted among the different drugs: citalopram 72%, paroxetine 70%, venlafaxine 67%, sertraline 62.9%, fluvoxamine 62%, fluoxetine 57% and mirtazapine 24%. The absence of placebo-controlled studies assessing sexual function, with specific measurements taken before and after
treatment, makes it impossible to determine the absolute or relative incidence of sexual dysfunction with mirtazapine.

Other conditions
While no significant effect of mirtazapine has been found in essential tremor patients (86), beneficial effects have been reported in patients with pruritus (87), chronic urticaria (88) and in two patients with poststroke pathological laughing who failed to respond to SSRIs or bupropion (89). The effectiveness of 30 mg/day mirtazapine has also been shown in three case reports of hyperemesis gravidarum resistant to conventional antiemesis treatment (90).

Conclusions
The current review gives evidence on the usefulness of mirtazapine in a variety of psychiatric and non-psychiatric conditions, for which an off-label use is considered. The generalization of these observations may be invalid because data on the off-label usefulness of mirtazapine are limited and mainly based on observations from case reports or data from open-label studies. However, positive cues suggest that confirmation of these preliminary data with randomized controlled trials may give sufficient evidence to warrant the use of mirtazapine in a broad range of disorders.

Disclosure
During the last two years, L. S. has received grant/research support, received honoraria and participated in speakers/advisory boards from AstraZeneca, Eli Lilly, Pfizer, Janssen and Wyeth. B. A. has received grant/research support from AstraZeneca, Eli Lilly, Pfizer and Janssen, received honoraria from Eli Lilly and Janssen and participated in speakers/advisory boards from Janssen. No conflict of interest is associated with the present review.

References


