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Subjective hypnotic efficacy of Trazodone and Mirtazapine in patients with chronic insomnia: a retrospective, comparative study

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ABSTRACT

Objective. To compare the efficacy of two sedating antidepressants, trazodone and mirtazapine, for the treatment of chronic insomnia.

Design. Retrospective cross-sectional study. Patients received trazodone or mirtazapine for at least three months at the dosage that was effective in the titration period.

Material and Methods. 150 patients with chronic insomnia, referred to the Sleep Disorder Center of Bari, diagnosed as chronic insomniacs according to ICSD-3 diagnostic criteria, with or without dysthymic disorder according to DSM V diagnostic criteria, and treated with trazodone or mirtazapine were retrospectively chart-reviewed. 79 patients satisfying inclusion criteria were enrolled: 33 had been treated with trazodone (12 males and 21 females aged 36 to 77 years, mean age 63.57±10.38 years; 18 with psychophysiological insomnia and 15 with insomnia associated with dysthymic disorder) and 46 with mirtazapine (26 males and 20 females aged 25 to 86 years, mean age 60.04±16.67 years; 25 with psychophysiological insomnia and 21 with insomnia comorbid with dysthymic disorder). The patients were considered responsive to the treatment when they no longer met the criteria for insomnia at the end of the maintenance period.

Results. Both drugs were efficacious in more than 60% without any difference in the proportion of responders between the two medication groups (87.87% in the trazodone group versus 86.95% in the mirtazapine group; p=0.26) and regardless of sex, age and possible association of insomnia with depression. The minimum dosages used for both drugs (25 mg for trazodone and 7.5 mg for mirtazapine) corresponded to the highest percentage of responders in the groups treated successfully with either trazodone (37.93%) or mirtazapine (52.5%). For each medication group, subgroup analysis revealed higher statistically significant rates of responders in patients with lower final dosage (25 to 75 mg for trazodone and 7.5 to 15 mg for mirtazapine) than in those with higher final dosage (100 to 150 mg for trazodone and 15 to 30 mg for mirtazapine) (100% versus 42.85%; p<0.001 in the trazodone group and 100% versus 53.84%; p<0.001 in mirtazapine group)

Conclusion. On a long term basis trazodone administration appeared as effective and well tolerated as mirtazapine in the treatment of chronic insomnia regardless of its association with dysthymia. Both medications resulted efficacious at very low doses and had a sustained efficacy, likely without problems of tolerance.

Key words

Insonnia • Trazodone • Mirtazapine

Introduction

The ICSD-3 (2014) defines insomnia as a "reported difficulty with sleep initiation, duration, consolidation that occurs despite adequate opportunity and circumstances for sleep, and results in some forms of daytime impairment".

Two observational insomnia studies, Morfeo 1 (Terzano et al, 2004) and Morfeo 2 (Terzano et al, 2004), con-

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ducted in Italy in conjunction with general practitioners showed an elevated incidence of insomnia, when actively investigated (44% according to the ICSD-3 criteria in Morfeo 1 and 41% in Morfeo 2), with significant health and socioeconomic consequences.

Mental health disorders are frequently associated with insomnia; the epidemiological study Morfeo 1 found concomitant mood disorders in 70% of patients receiving diagnosis of insomnia according to the current diagnostic criteria. A Consensus Report produced by sleep specialists and primary-care physicians in Italy outlined the mandatory importance of recognizing and treating insomnia especially in the presence of mood disorders, since the persistence of insomnia could be considered a bad prognostic factor for depression outcome (Terzano et al, 2005).

Antidepressants represent the first line drugs in the management of patient with chronic insomnia with comorbid depression (Schutte-Rodin et al, 2008).

Some triciclic antidepressants (TCAs), such as amitriptyline, on top of blocking the presynaptic reuptake of norepinephrine and serotonin (5HT), have also effects on other neurotransmitter systems, including antagonism of hystaminergic H1 and muscarinic cholinergic receptors, that results in sleepiness. Stimulating 5HT2A and 5HT2C receptors is known to be linked to the side effects of some antidepressants, including insomnia, anxiety and sexual dysfunction; consequently 5HT2A and 5HT2C antagonism has begun to be seen as a novel sleep-promoting mechanism. Trazodone is a "multifunctional" drug approved as a high dose antidepressant but is commonly used "off label" as a low dose hypnotic; hypnotic efficacy is due to cumulative antagonist action at 5HT2A /5HT2C, hystaminergic H1 and alfa1 receptors. Mirtazapine is a tetracyclic antidepressant FDA approved for the treatment of major depressive disorder; it also provides sedation, mainly resulting from selective blockade of hystaminergic H1 receptors, and from antagonism of postsynaptic 5HT2A and 5HT2C receptors (Vande Griend and Anderson, 2012).

On the other hand, antidepressants are also "off label" commonly and successfully used in the treatment of primary insomnia.

To date, in the general population, data supporting the use of mirtazapine for insomnia in the absence of a coexisting mood disorder are lacking and only a few trials evaluated trazodone in patients with primary insomnia. Across the class of sedative antidepressants there is also concern about the next day effects including psychomotor slowing and sedation. Moreover, to the best of our knowledge, no study compared chronic insomnia patients treated with trazodone to insomniacs receiving mirtazapine, nor data about the sustained efficacy of both drugs are available in the literature.

In the present study the effects of trazodone and mirtazapine were investigated in patients affected by insomnia with or without associated symptoms of depression and a comparison of efficaciousness and safety was performed.

Study Design

This was a retrospective cross-sectional study. Subjects were given mirtazapine or trazodone for 3 to 6-month and were seen on 2 to 4 scheduled visits. The treatment period could be divided in two parts: the titration period over 3 to 16 weeks and the maintenance period over 3 months.

Patients and methods

The last one hundred and fifty patients referred to the Sleep Disorders Center of Bari (Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari) who had received a diagnosis of chronic insomnia with or without depressive disorder and a treatment with trazodone or mirtazapine were retrospectively chart-reviewed. Chronic insomnia disorder was diagnosed when ICSD-3 diagnostic criteria for chronic insomnia were met.

Eligible patients were included in the study if they:

1) Aged between 18 and 90 years
2) Had psychophysiological insomnia or insomnia associated with depressive disorder consisting of dysthymic disorder diagnosed according to DSM V diagnostic criteria (2013).
3) Were not on antidepressant or psychotropic medication, except for a short half-life hypnotic to be taken sporadically
4) Received at least one medical check after the maintenance period

Exclusion criteria were as follows:

Table I. - Demographic and clinical characteristics of the sample.

	Trazodone (N = 33)	Mirtazapine (N = 46)	P-value
Sex			
Male (%)	12 (36.6%)	26 (56.52%)	0.1235
Female (%)	21 (63.64%)	20 (43.48%)	(χ^2 with Yates correction)
Age			
Range	36-77	25-86	
Mean (SD)	63.57±10.38	60.04±16.67	0.14
	17 (51.51%)	24 (52.17%)	(t test for unpaired data)
Adult patients (%)	17 (51.51%)	24 (52.17%)	0.86
Elderly patients (%)	16 (48.48%)	22 (47.82%)	(χ^2 with Yates correction)
Characteristics of insomnia			
Psychophysiological Insomnia (%)	18 (54.55%)	25 (54.35%)	0.83
Insomnia + Dysthymia (%)	15 (45.45%)	21 (45.65%)	(χ^2 with Yates correction)

1) Insomnia associated with severe psychiatric disorders, such as major depressive disorder
2) Coexistence of other sleep disorder such as sleep apnea syndrome or sleep-related movement disorders or sleep-wake rhythm disorders

All patients had signed the consent to the processing of sensitive data with the express intention of treating their data anonymously in order to conduct investigations for research purposes.
Trazodone extended release formulation was used and the starting dose was 25 mg once daily, about 2-4 hours before bedtime. At the first visit, the patients in the trazodone group were instructed to increase by one third the dose of trazodone every 3-4 weeks until they obtained a reduction of sleepless nights to 2 or less than 2 per week or in any case up to a maximum dose of 75 mg before the scheduled medical check. During the medical check, in case of still not satisfactory improvement, they were proposed increments of a third of the dose every 3-4 weeks to a maximum of 150 mg. The starting dose of mirtazapine was 7,5 mg, once daily about 2 hours before bedtime. Similarly, patients taking mirtazapine were instructed to increase the starting dose of mirtazapine by 7.5 mg every 3-4 weeks until obtained a decrease in the number of weekly nights of insomnia to 2 or less than 2.
The maintenance period was for both drugs of at least 3 months with the final dosage found to be effective.
The patients were considered responsive to the treatment when no longer met the criteria for insomnia at the end of the maintenance period. If the patient did not respond even with the dose of trazodone 150 mg or mirtazapine 30 mg, the administration of the medication was tapered and then discontinuated.

Statistical analysis

Mean and standard deviations were used to express the central tendency and dispersion of continuous variables in normal distribution. In case of ordinal variables, medians and ranges were evaluated. Discrete variables were described as numbers and percentages.
The differences between patient groups were tested using student's independent t-test for continuous variables. Mann-Whitney U test was used to compare the medians for ordinal variables. Categorical data were compared with the use of Pearson's chi-square test or Fisher exact test when the sample size of the examined subgroups was not too large.
Statistical significance was set at $p < 0.05$.

Results

35 patients were not eligible for the study due to concomitant treatment with other psychotropic medications (5 patients) or to comorbidity with: Depressive Major Disorder or other severe psychiatric disorders (8 subjects), sleep apnea syndrome (14 cases), sleep-related movement disorder (7 patients), sleep-wake rhythm disorder (3 subjects). 36 patients dropped out: 6 (2 patients receiving trazodone 75 mg, 6 patients taking mirtazapine, 5 at 7,5 mg and 1 at 15 mg, were unable

Table II. - Trazodone versus Mirtazapine: comparison between the percentages of responders in the total groups and in different subgroups depending on sex, age and characteristics of insomnia.

	Trazodone	Mirtazapine	P value
Total group Responders (%) Non responders(%)	N= 33 29 (87.7%) 4 (12.12%)	N= 46 40 (86.95%) 6 (13.4%)	0.26 (Fisher Exact Test)
Males Responders (%) Non responders (%)	N= 12 11 (91.66%) 1 (8.33%)	N= 26 22 (84.61%) 4 (15.39%)	0.30 (Fisher Exact Test)
Females Responders (%) Non responders (%)	N= 21 18 (85.71%) 3 (14.28%)	N= 20 18 (90%) 2 (10%)	0.33 (Fisher Exact Test)
Adult patients Responders (%) Non responders (%)	N= 17 15 (88.23%) 2 (11.76%)	N=24 22 (91.66%) 2 (8.33%)	0.37 (Fisher Exact Test)
Elderly patients Responders (%) Non responders (%)	N=16 14 (87.5%) 2 (12.5%)	N= 22 18 (81.81%) 4 (18.18%)	0.31 (Fisher Exact Test)
Psychophysiological Insomnia Responders (%) Non responders (%)	N= 18 16 (88.88%) 2 (11.11%)	N=25 24 (96%) 1 (4%)	0.30 (Fisher Exact Test)
Insomnia+Dysthymia Responders (%) Non responders (%)	N=15 13 (86.66%) 2 (13,34%)	N=21 16 (76.19%) 5 (23.80%)	0.25 (Fisher Exact Test)

to continue treatment because of side effects (excessive daytime sleepiness), 28 did not show up at the scheduled checkup after the first visit (5 in the trazodone and 10 in the mirtazapine group) or the maintenance period (8 in the trazodone and 5 in the mirtazapine group).

Thus 79 patients satisfying inclusion and exclusion criteria were enrolled: 33 had been treated with trazodone and 46 with mirtazapine.

The group of patients treated with trazodone was composed of 12 males (36.36%) and 21 females (63.64%), aged 36 to 77 years (mean age 63.57±10.38 years). 17 were adult (≤ 65 yrs) and 16 were elderly (>65 yrs) patients. 18 subjects suffered from psychophysiological insomnia and 15 were affected by insomnia associated with dysthymic disorder.

The group of patients receiving mirtazapine consisted of 26 males (56.52%) and 20 females (43.48%) aged 25 to 86 years (mean age 60.04±16.67 years). 24 patients were ≤65 years and 22 > 65 years aged. 25 patients were diagnosed as psychophysiological insomniacs and 25 received a diagnosis of insomnia comorbid with dysthymic disorder.

The two groups of patients resulted homogeneous for sex distribution (χ^2 with Yates correction = 0.1235) and age (Student's t test for unpaired data = 0.14).

Demographic and clinical characteristics of the sample are listed in Table I.

Trazodone resulted effective in 29 patients (87.87%): 11 males (37.93%) and 18 females (62.06%), 15 adult patients (51.72%) and 14 elderly patients (48.28%), 16 patients with psychophysiological insomnia (55.17%) and 13 with insomnia coexisting with dysthymic disorder (44.83%).

Mirtazapine resulted effective in 40 patients (86.95%): 22 males (55%) and 18 females (45%), 22 adult patients (55%) and 18 elderly patients (45%), 24 patients with psychophysiological insomnia (60%) and 16 with insomnia coexisting with dysthymic disorder (40%).

No difference was found in the proportion of responders among patients treated with trazodone compared to those treated with mirtazapine. Additionally, subgroup analysis was performed after dividing each group of medications into subgroups according to sex, age and characteristics of insomnia; we failed in demonstrating any difference even comparing with each other the percentage of responders to the drug in the obtained subgroups: males and females, younger and older than 65 years, psychophysiological insomniacs and insomniacs with dysthymia. The proportion of responders in the two medication groups and in the different subgroups for both medications, together with results of statistical analysis, are summarized in Table II.

Table III. - Sex distribution, range of age, characteristics of insomnia and final dose of medication in the successful group of patients treated with **trazodone** compared to the unsuccessful group.

	Successful group (N=29)	Unsuccessful group (N=4)	P value
Sex distribution Males (%) Females (%)	 11 (91,66%) 18 (85,71%)	 1 (8,33%) 3 (14,28%)	0.39 (Fisher Exact Test)
Age Adult patients (%) Elderly patients (%)	 15 (88,23%) 14 (87,5%)	 2 (11,77%) 2 (12,5%)	0.39 (Fisher Exact Test)
Characteristics of insomnia Psychophysiological Insomnia (%) Insomnia + Dysthymia (%)	 16 (88,88%) 13 (86,66%)	 2 (11,11%) 2 (13,33%)	0.39 (Fisher Exact Test)
Final dose of medication 25-50-75 mg (%) 100-125-150 mg (%)	 26 (100%) 3 (42.85%)	 0 4 (57.14%)	0.00086 **(<0.001)** (Fisher Exact Test)

The median doses used were 50 mg (10-150) for trazodone and 15 mg (3.75-30) for mirtazapine, without any difference depending on sex, age ≤ 65 or >65 yrs and characteristics of insomnia (psychophysiological or associated with dysthymia).

As far as the effective dosage, the minimum dosage, 25 mg, corresponded to the highest percentage of responders in the successful group treated with trazodone (11 patients= 37.93%) followed by gradually increasing doses of 50 mg (9 patients= 31.03%), 75 mg (6 patients=20.68%) and 100 mg (3 patients= 10.34%); no responder had to reach the final dose of 150 mg (Figure 1A). Similarly, the minimum dosage of mirtazapine, 7.5 mg, corresponded to the highest percentage of responders (21 patients=52.5%), followed by doses of 15 mg (12 patients=30%), 30 mg (4 patients= 10%) and 22.5 mg (3 patients=7.5%) (Figure 1B).

Both groups of patients were divided into two groups depending on whether they had taken a final dosage lower (25-50-75 mg for trazodone and 7.5-15 mg for mirtazapine) or higher (100-125-150 mg for trazodone and 15-30 mg for mirtazapine): the subgroups with the lower dose included 26 patients, all responders, in the trazodone group, and 33 patients, all responders, in the mirtazapine group, whereas the subgroups with the higher dose comprised 7 patients in the trazodone group (3 responders and 4 non responders) and 13 in the mirtazapine group (7 responders and 3 non responders).

The comparison of insomnia characteristics, age ranges, sex distribution between the unsuccessful and successful groups did not reveal any difference in the trazodone group as well as in the mirtazapine group. On the contrary, subgroup analysis revealed higher statistically significant rates of responders in patients with lower final dosage than in those with higher final dosage in each group of medications (100% versus 42.85%; $p<0.001$ in trazodone group and 100% versus 53.84%; $p<0.001$ in mirtazapine group). These results are summarized in Tables III and IV.

With regard to tolerability, only two patient treated with mirtazapine reported side effects: the first complained about weight gain whereas the second reported a very short episode of poorly defined palpitations; however, in neither case the occurrence of adverse effects prevented continuation of treatment.

Discussion

The results of the present study show the efficacy of mirtazapine and trazodone on chronic insomnia in more than 60% of patients treated, without any difference between the two drugs in the percentage of responders.

Both drugs induced similar improvement, regardless of sex, age range (more or less than 65 years) and presence or absence of depression associated with chronic insomnia.

For each medication, the proportion of responders appeared higher in the subgroup treated with lower final dosage; in other words, for both groups of patients, it was more likely to find responders in the subgroups treated with a lower rather than in those receiving a higher dose. This result seems to suggest that if the sedative antidepressant works, it works even at low dosage; therefore, if the improvement does not occur at lower doses, it might be better to change the drug rather than increasing the dose.

Table IV. - Sex distribution, range of age, characteristics of insomnia and final dose of medication in the successful group of patients treated with **mirtazapine** compared to the unsuccessful group

	Successful group (N=40)	Unsuccessful group (N=6)	P value
Sex distribution Males (%) Females (%)	 22 (84.615%) 18 (90%)	 4 (15.38%) 2 (10%)	0.30 (Fisher Exact Test)
Age Adult patients (%) Elderly patients (%)	 22 (91.66%) 18 (81.81%)	 2 (8.33%) 4 (18.18%)	0.21 (Fisher Exact Test)
Characteristics of insomnia Psychophysiological Insomnia (%) Insomnia + Dysthymia (%)	 24 (96%) 16 (76.19%)	 1 (4%) 5 (23.80%)	0.05 (Fisher Exact Test)
Final dose of medication 7.5-15 mg (%) 22.5-30 mg (%)	 33 (100%) 7 (53.84%)	 0 6 (46.15%)	0.00018 **(<0.001)** (Fisher Exact Test)

The sedative effect of trazodone and mirtazapine is well known. In depressed patients, trazodone (50-100 mg) has been demonstrated to be associated with significantly better scores in subjective sleep ratings than placebo, with better effect in lower doses (Mayers and Baldwin, 2005). Trazodone can improve sleep continuity both in short and in long therapy, while inducing only slight decrease of REM sleep in short term and no change in long term administration (Wilson and Argyropoulos, 2005). Several trials with mirtazapine showed significant improvements in sleep quality and quantity of patients with depression with comorbid insomnia; also sleep physiology measures showed an improvement with increase of total sleep time and decrease of sleep onset latency in patients with major depression and insomnia (Alam et al, 2013), as well as an increase of continuity both in short (5-10 days) and long term (more than 21 days) treatment without an undesirable REM sleep suppression (Wilson and Argyropoulos, 2005).

The American Academy of Sleep Medicine (AASM) recommends the administration of a low-dose, sedating antidepressant, if not contra-indicated, in insomnia with comorbid depression or in the case of other treatment failure". The AASM recommendations list trazodone and mirtazapine among the examples of these drugs, though "evidence for efficacy when used alone is relatively weak". Certainly, low-dose sedating antidepressants do not warrant appropriate treatment of major depression; however low-dose trazodone, in addition to another full-dose antidepressant, has shown moderate efficacy in improving sleep quality and quantity in patients with depressive disorders (Schutte-Rodin et al, 2008). According to AASM recommendations, it is unclear whether the findings on the effectiveness of sedating antidepressants can be extended to other form of insomnia.

It's noteworthy that our results are in agreement with previous studies demonstrating the improving effect of trazodone and mirtazapine on subjective sleep ratings in depressed patients when compared to placebo, SSRIs (Serotonin Selective Reuptake Inhibitors), or TCAs (Wilson and Argyropulos, 2005).

Of note, this study shows the efficaciousness of both mirtazapine and trazodone not only in insomniacs with depression but also in patients with psychophysiological insomnia, that is a chronic primary insomnia. To date, trials evaluating the efficacy of mirtazapine in primary insomnia are lacking; three studies investigated the effect of trazodone on primary insomnia. The first one dates back to 1983 and showed only a reduction of wake after sleep-onset with trazodone 150 mg (Montgomery et al., 1983); the second one was performed on more than 300 participants at a threefold lower dose of trazodone (50 mg) and found an improvement of sleep latency, total sleep time, number of awakenings and wake after sleep onset only at week 1(Walsh et al, 1998); the third and more recent one (Roth et al, 2011) used the same dosage (50 mg), had a small sample size and only demonstrated a significant decrease of awakenings number. However these studies were of short duration, 21 days in the first, 14 days in the second and only 7 days in the third one, so, in our opinion, it can be risky to draw conclusions on the effectiveness of trazodone or the possibility that a rapid tolerance has been established.

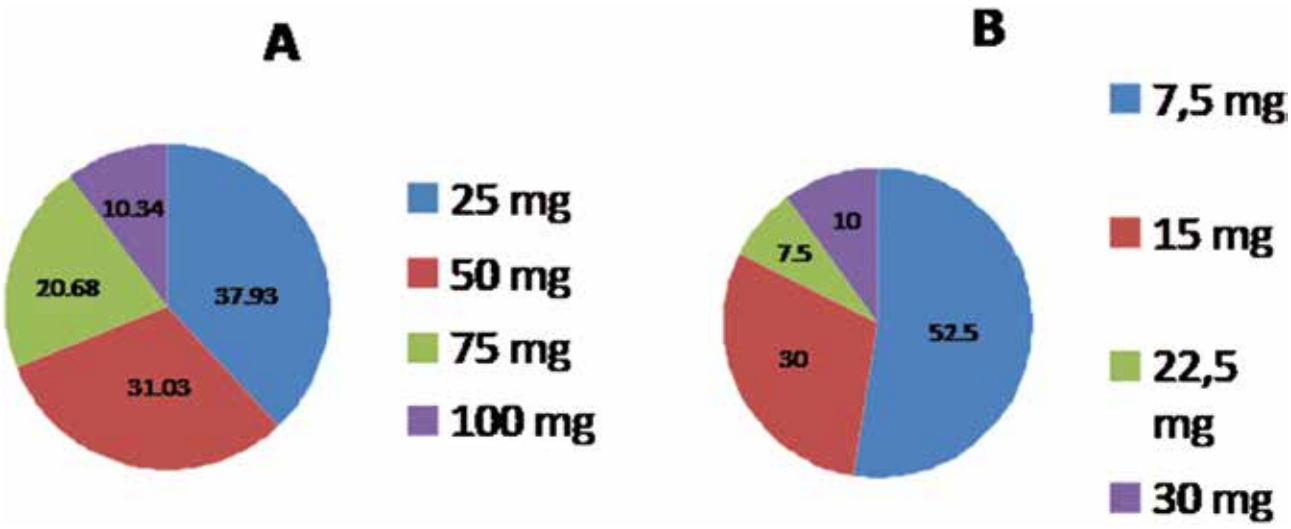

Fig. 1. - Percentage of responders to different doses in patients receiving trazodone (A) and mirtazapine (B).

The present study highlights that both mirtazapine and trazodone can result efficacious at very low doses and have a sustained efficacy, likely without problems of tolerance; in fact no patient in the study had increased on his own his medication dose.

Mashiko (1999) showed in depressed patients a better improvement of sleep scores on HAMD with lower rather than higher doses of trazodone (50-100 mg). According to Stahl (2009), the clinical effective hypnotic doses of trazodone are in the 25-100 mg range: actually, although all 5-HT2A receptors are saturated at 10 mg, due to the most powerful affinity for these receptors, higher doses recruiting additional blocking actions on other receptors, such as alfa1 adrenergic and H1 histamine receptors, are necessary for the hypnotic action of trazodone. Indeed, the majority of our patients obtained a sleep subjective improvement with only 25 mg that is less than the lowest dose generally indicated in previous studies.

With regard to mirtazapine, it's well known that lower doses (e.g., 7.5-15 mg) may provide more sedation when compared with higher doses, as higher doses result in noradrenergic stimulation, blunting the drug's sedative effect. In a previous study comparing effectiveness and safety of mirtazapine in chronic insomniacs at three different doses (7,5-15-30 mg), we found that the most adequate dose was 7,5, since it had comparable efficacy with higher doses, but with fewer side effects (Cardinali et al, 2008). The results of the present study confirm the data, since most of the patients responded to the lowest dose of mirtazapine.

The patients of our study reported side effects in only two cases, and only a few participants had been excluded due to a drop out induced by side effects.

Rohers and Roth (2012) stated that "the major problem with using antidepressants as hypnotics is that there is limited information regarding the dose range along which they improve sleep and their safety at low doses". The results of the present study seem to allow a reduction of concerns regarding the dose-related effects of trazodone and mirtazapine and their safety at low doses. In fact, our data on the one hand confirm the hypnotic efficacy of low doses of both drugs, as previously reported in the literature, on the other hand show a satisfactory tolerability for both medications.

Our study has some methodological limitations: retrospective design, small sample size, lack of a placebo arm, and subjective measure of sleep quality. Actually, differences between objective and subjective sleep measures in patients receiving antidepressants have long been known (Ware, 1983).

Nevertheless this is the first study that investigated the effectiveness of sedative antidepressants in primary insomnia for a sufficiently long period, not less than three month, thus verifying a continuity of drug efficacy. It is also the first study comparing the two most commonly used antidepressants in the treatment of insomnia and confirming their efficacy.

In conclusion, the results of the present study point out that trazodone, as well as mirtazapine, are suitable drugs for first line management of chronic insomnia regardless of the association with a depressive disorder. Moreover, our data suggest to start the treatment at the lowest dose.

However, more large, well designed, randomized controlled trials evaluating trazodone and mirtazapine for the treatment of insomnia are necessary to confirm the adequacy of low doses in insomniacs.

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