

Evaluation of the Efficacy of Combined Therapy with Escitalopram and Sublingual Alprazolam in Major Depression Associated with Insomnia

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Abstract

Introduction: Insomnia is usually considered a secondary manifestation of other psychiatric diseases, like major depression. This being the case, insomnia often goes untreated, with the expectation that it will be resolved with the improvement of the primary psychiatric disorder. New evidence in the field of Sleep Medicine suggests that insomnia is a risk factor in the future occurrence of depression.

Objectives: The primary objective is to assess the efficacy of a 60-day treatment plan that combines sublingual alprazolam with 10 mg of escitalopram daily to treat insomnia associated with major depression. The secondary objective is to assess the improvement of depressive symptoms in each group and to establish whether the improvement of insomnia had an impact on the improvement in depression.

Material and Methods: Prospective, comparative, multicenter, randomized, double-blind, placebo-controlled trial, involving 95 patients, 45 of which received Escitalopram/Placebo and 50 of which received Escitalopram/Alprazolam, and using the 17-item Hamilton Rating Scale for Depression (HAM-D17) and Pittsburgh Sleep Quality Index (PSQI) to evaluate depression and insomnia, respectively.

Results: At day 60, depression was effectively treated in both groups. In Escitalopram/Alprazolam group the mean values achieved remission according HAM-D17 and good sleeper's status according PSQI.

Conclusion: Simultaneous treatment of depression and insomnia with the combination of escitalopram/sublingual alprazolam may be a good option for patients with major depression disorder associated with insomnia, since the remission of depression (HAM-D17) and the status of good sleepers (PSQI) were statistically achieved only by the escitalopram group + sublingual alprazolam.

Keywords: Major depression; Insomnia; Escitalopram

Introduction

The relationship between mental disorders and sleep disorders – and insomnia, in particular—is very complex and clearly bidirectional. Many psychiatric disorders, such as Major Depression Disorder and Generalized Anxiety Disorder, are associated with insomnia, and between 40 and 80% of patients with insomnia have an associated psychiatric disorder [1,2].

In fact, both the DSM 5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) [3] and the ICD 10 (International Classification of Diseases, 10th Edition) [4], include sleep disorders among the diagnostic criteria for Major Depression.

Until just a few years ago, the belief that insomnia was a secondary symptom of other psychiatric diseases led many professionals to avoid treating it, as they expected the insomnia would resolve itself if the primary psychiatric disorder was treated.

Those concepts are currently being revised in light of new psychiatric approaches and advances in a new sub-discipline: Sleep Medicine. These new psychiatric approaches suggest that the insomnia experienced by psychiatric patients is of a different nature and constitutes a risk factor in the future occurrence of depression, alcoholism and anxiety disorders.

The clinical remission of depression can improve insomnia, but not necessarily restore sleep back to normal. In fact, insomnia is the most

commonly reported residual symptom in patients who have recovered from a depressive episode [5]. Many studies have shown that insomnia has a profoundly negative impact on the quality of life [6-8].

Major depression associated with insomnia is also a risk factor for suicide in adolescents [9] and adults [10].

Insomnia also tends to be the symptom most frequently reported by depressive patients prior to a new depressive episode, which makes insomnia an important risk factor in the symptomatic relapse in depression [11,12].

Finally, multiple clinical trials with antidepressants have

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demonstrated a wide range of responses in sleep disorders associated with depression, including the worsening of insomnia alongside an improvement in depressive symptoms [13]. This challenges the assumption that improvements to the affective disorder would automatically lead to improvements in sleep abnormalities.

Some clinical data suggests that reduced insomnia in patients with psychiatric comorbidity not only improves their sleep quality and quantity but may also improve their response to antidepressant treatment. Patients who received initial antidepressant treatment along with insomnia treatment showed significant improvements in sleep and daytime activities, compared with patients who were treated with antidepressants alone [14-18].

Insomnia, therefore, could be interpreted not only as diagnostic criteria for these disorders, a risk factor for different psychiatric diseases or a very common residual symptom of depression, but also as an independent comorbid entity.

This being the case, the relationship between sleep and depression is very complex and future studies should be conducted to determine the bidirectionality between both disorders.

It is estimated that 30% of patients that are treated with Selective Serotonin Re-uptake Inhibitors (SSRIs) are treated concomitantly with benzodiazepines [19]. However, at present, benzodiazepines are only prescribed to treat transient and short-term insomnia disorder and cases of anxiety and depression at the beginning of the treatment [20].

Considering that insomnia associated with depression is a chronic episodic process and that certain antidepressants are prescribed for long-term use, using benzodiazepines for just a few weeks does not seem to make much sense.

Even when insomnia is a manifestation of a state of anxiety, often associated with depression, the residual anxiolytic effect that is secondary to the use of benzodiazepines may be beneficial, as we saw in one of our clinical trials with sublingual alprazolam [21].

Over the last 30 years, numerous clinical trials have proven the safety and effectiveness of benzodiazepines. Nonetheless, fears about abuse and dependency have cast a shadow on these medications and raised doubts about their therapeutic strategies, despite the fact that it continues to be prescribed. These fears have spread to the patients themselves, who often seem worried when they are prescribed benzodiazepines because they fear they will grow dependent on them, and who sometimes self-prescribe insufficient dosages or stop taking the drugs before completing the prescribed treatment plan.

Using the term “habituation” as a synonym of “abuse” or “dependency” often leads to the belief that habituation is pathological when, in fact, it refers to nothing more than the organism’s physiological adaptation to exposure to a drug over prolonged periods, after which one or more biological parameters may remain at normal levels only in the presence of the inductive drug or similar agents. Physiological habituation does not develop in the large majority of individuals who take therapeutic dosages of benzodiazepines over prolonged periods of time. On the other hand, the abrupt interruption of many psychiatric medications, not only benzodiazepines, can easily provoke symptoms of abstinence or withdrawal, whether it is the doctor who triggers them by abruptly reducing the dosage or the patient who triggers them by discontinuing their use without adequate supervision.

With regard to abusive consumption, numerous studies have revealed that patients medicated with benzodiazepines usually take a lower amount of the medication than that prescribed by their doctors [22].

Nowadays, the goal of antidepressive treatment should not be the response (a 50% reduction in the Hamilton D-17 Score) but rather remission, which is defined as a score of ≤ 7 on the Hamilton D-17 Scale and is usually achieved within 4 to 8 weeks [23,24]. In order to test the hypothesis that insomnia may interfere with the achievement of remission in depression or that the resolution of the insomnia may facilitate remission, we decided to conduct a clinical trial in which we would prescribe an antidepressant, 10 mg dosage of escitalopram, to be taken daily along with a single 0.5 to 1 mg dosage of alprazolam to be taken sublingually at night for a period of 60 days, with a gradual reduction in the dosage over the following 15 days, to a group of patients diagnosed with Major Depression associated with Insomnia that would be controlled with another group of patients who would receive the same dosage of the antidepressant and sublingual placebo dosages.

Objective

Primary objective

Evaluate the efficacy of sublingual alprazolam combined with 10 mg of escitalopram daily, in patients with major depression associated with insomnia, over 60 days as part of a double-blind, placebo-controlled study.

Secondary objective

Evaluate improvements in the symptoms of depression in each group to establish whether recovery from insomnia has an impact on recovery from depression.

Material and Methods

Design

Prospective, comparative, multicenter, double-blind, placebo-controlled, randomized (1:1) trial.

Treatment allocation was randomized 1:1 ratio based on a list of random numbers obtained from the “list of random numbers EPITABLE package EPI-INFO 6.04”, one copy (in a sealed envelope) to Principal Investigator and other to Sponsor. Regarding the appearance and flavoring of placebo pill it was prepared one with similar characteristics to be absorbed sublingually and with a bitter taste similar to the active drug pill obtained with grapefruit essence.

Study population

Patients of both sexes, from 18 to 65 years old, with moderate to severe Major Depression associated with insomnia, in accordance with DSM-IV TR criteria.

The recruitment was done from April 2011 to December 2013, with outpatients referred by the physicians.

The patients taking part in the study had to be willing to sign an informed consent, and had to not be undergoing treatment with hypnotics or anxiolytics or have a personal history of schizophrenia, mental illnesses, bipolarity or addiction.

The study did not include women who were pregnant or breastfeeding, or patients affected by insomnia associated with sleep apnea, for which benzodiazepines are not recommended.

Sample size

The sample size was established based on an experimental model intended to demonstrate a difference of 30% between both groups, assuming that the efficacy on insomnia in the sublingual alprazolam

group would be 70% and estimating that the efficacy in the placebo group would be 40%, allowing for an alpha error of 5% and a test power of 80%, the number of evaluable patients to study would be around 100, that is, 50 patients per treatment group.

Study schedule and methodology

Group 1: The patients were to start with one 10 mg tablet of escitalopram daily at breakfast, combined with a 0.5 mg tablet of alprazolam to be taken sublingually before going to bed; after the fourth night, depending on the clinical response and the consent of the attending physician, contacted by phone, the patient's dosage could be doubled (1 mg of sublingual alprazolam before bed), while continuing with the same antidepressant medication until the end of the study, on day 75.

Group 2: The patients were to start with one 10 mg tablet of escitalopram daily at breakfast, combined with a 0.5 mg sublingual placebo tablet before going to bed; after the fourth night, depending on the clinical response and the consent of the attending physician, contacted by phone, the patient's dosage could be doubled (1 mg of sublingual placebo before bed), while continuing with the same antidepressant medication until the end of the study, on day 75.

The appointment schedule consisted of an initial appointment and appointments on days 15, 30 and 60, with a final appointment on day 75. Every researcher was required to establish contact with the patient during the course of the trial, either in person or over the phone, in order to modify the initial dosage of placebo or alprazolam, if necessary.

The participants from both groups were given appointments on day 60 so that the researchers could begin the procedure of tapering the dosage of alprazolam or placebo to 50%, in order to finish the study on day 75 with the final evaluation.

Evaluation methodology

On entering the study (day 0), the participating patients completed the "Pittsburgh Sleep Quality Index", which supplemented a Visual Analog Scale for Insomnia. They also completed the 17-item Hamilton Rating Scale for Depression (HAM-D17). At the other appointments, held on days 15, 30, 60 and 75, the participants completed the Patient General Impression (PGI) scale, the PSQI, the Visual Analog Scale for Insomnia and the HAM-D17. The final appointment was held on day 75, at which point the assigned treatment plan had been completed, and included the same evaluations that were conducted on day 60. Tolerability was also evaluated during the appointments on days 15, 30 and 60.

Statistical analysis

First, the researchers prepared a descriptive analysis (statistical description) of the group studied. The qualitative nominal variables: age, sex, etc., were calculated as absolute and relative frequencies, that is, percentages and proportions; the ordinal qualitative variables were also expressed as absolute or relative frequencies.

The continuous qualitative variables were expressed as the mean \pm the standard deviation. The discreet quantitative variables that emerged from recounts were whole numbers and were expressed as absolute frequencies. For the quantitative variables, the researchers used the Shapiro Wilk test or Kolmogorov-Smirn of test to determine whether the distribution of the variables was normal or not.

Bar graphs were used to represent qualitative variables and box plots were used to represent quantitative variables. The CHI-squared test

and Fischer's exact test were used to compare proportions (qualitative variables).

Quantitative variables were compared using the Student's t-test if they followed a normal distribution and the Mann Whitney test if they were not normally distributed.

To compare the averages of more than 2 independent samples, researchers used ANOVA followed by a post-hoc such as Bonferroni or Newman Keuls.

Ethical criteria

1. The study was conducted in accordance with the principles stated in the declarations of Helsinki (Seoul 2008), Nuremberg, Tokyo and the International Conference on Harmonization (ICH).
2. The patients signed an informed consent, which was offered to them without any pressure, after they were informed of the scope and the risks of the study, as well as their right to withdraw from the protocol.
3. The protocol was approved by the Ethics Committees of the participating Institution and by independent Ethics Committees.
4. Confidentiality: The records that identify the participants will remain confidential and will not be made public knowledge to the fullest extent permissible pursuant to applicable laws and/or regulations.
5. Justification for using a placebo: The use of the placebo in this study is justified, since the omission of an intervention that has proven to be effective (benzodiazepines) would expose the subjects, at the most, to temporary discomfort or delay in the relief of their symptoms (insomnia).
6. The health authorities (ANMAT) were notified of the protocol before the study began.
7. Conflicts of Interest: None of the researchers participating in this study have conflicts of interest with the sponsor.

Results

One hundred ten patients, 95 of which were evaluable, participated in the study between April 2011 and February 2014. The patients were recruited from 6 centers by 7 lead researchers. There were 15 no evaluable patients for not fulfilling the inclusion criteria, or did not pass the screening or did not attend the second visit.

Seven patients who were assessed only for tolerability, discontinued treatment before Day 15 due to adverse events. Of the evaluable patients, 65 were women and 30 were men, with an average age of 44. The Baseline value of the Hamilton D-17 test was 24.1 ± 4.3 (Major Depression 18-29), the PSQI Baseline was 13.8 ± 3.2 (0 to 18, the higher the value, the lower the quality of sleep, with a cutoff point of ± 5 =poor sleepers). The Visual Analog Scale (VAS) Baseline for insomnia was 2 ± 1.3 (0=worst sleep and 10=best sleep).

The distribution of the demographic variables and baseline values for efficacy between both treatments groups (Table 1), using the Shapiro-Wilk test, revealed a normal distribution, which was the reason for using parametric tests for the corresponding evaluations.

As determined by the randomization, the escitalopram + placebo treatment was administered to 45.26% of the evaluable patients and the

	Evaluable patients (n=95)	Escitalopram/Alprazolam (n=52)	Escitalopram/Placebo (n=43)	p
Age	44.20 ± 12.70 (21 to 67)	44.20 ± 12.24 (21 to 66)	44.51 ± 12.81 (23 to 67)	0.97
Sex	F: 65 (68.42%) M: 30 (31.58%)	F: 36 (69.23%) M: 16 (30.77%)	F: 29 (67.44%) M: 14 (32.56%)	0.85
Weight	68.91 ± 13.17	69.23 ± 13.31	68.53 ± 13.14	0.80
Height	1.68 ± 0.08	1.67 ± 0.08	1.68 ± 0.09	0.80
Hamilton d-17 baseline	24.10 ± 4.30	24.14 ± 4.21	24.05 ± 4.47	0.92
Baseline psqi	13.87 ± 3.20	14.22 ± 3.18	13.43 ± 3.19	0.24
Baseline vas	2.05 ± 1.33	1.91 ± 1.15	2.22 ± 1.51	0.28

Table 1: Distribution of demographic variables and Baseline Efficacy Values.

	Escitalopram/Alprazolam (N=48)	Escitalopram/Placebo (N=40)
Baseline	23.96 ± 4.05	24.05 ± 4.47
Day 15 *	16.77 ± 5.97	19.55 ± 6.47
Day 30 **	9.33 ± 5.03	12.88 ± 6.41
Day 60 ***	4.94 ± 4.40	8.03 ± 5.28
ANOVA Test for repeated measurements	p<0.01	p<0.01
Newman Keuls	*p<0.01 vs. Baseline	*p<0.01 vs. Baseline
	**p<0.01 vs. Baseline	**p<0.01 vs. Baseline
	***p<0.01 vs. Baseline	***p<0.01 vs. Baseline
Post-Hoc Test	*p<0.01 vs. **	*p<0.01 vs. **
	*p<0.01 vs. ***	*p<0.01 vs. ***
	p<0.01 vs. *	**p<0.01 vs. ***

ANOVA GLOBAL for paired data “between treatments” p=0.01

Newman Keuls Post-Hoc Test: Baseline: p=0.94; Day 15: p=0.05; Day 30: p=0.01; Day 60: p=0.01

Table 2: Hamilton-D 17 Rating Scale for Depression.

	Escitalopram/Alprazolam (n=48)	Escitalopram/Placebo (n=40)
Remission (values below 7 in Hamilton D-17.)	By day 15: 4 pts. (8.33%)	By day 15: 2 pts. (5%)
	By day 30: 14 pts. (29.17%)	By day 30: 8 pts. (20%)
	By day 60: 39 pts. (81.25%)	By day 60: 19 pts. (47.5%)

Table 3: Number of patients who achieved remission of their depression.

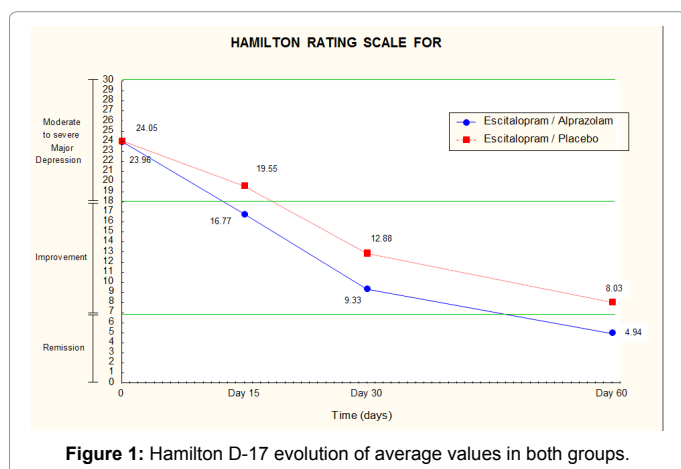


Figure 1: Hamilton D-17 evolution of average values in both groups.

escitalopram + sublingual alprazolam treatment was administered to the remaining 54.74%.

Of the 95 evaluable patients, 88 patients were evaluated for efficacy and tolerability and 7 patients were evaluated for tolerability alone.

Results of efficacy in depression

As seen in Table 2, both groups experienced statistically significant improvements in their symptoms of depression as compared to the baseline values. However, the improvement observed in the escitalopram/alprazolam group was significantly higher than that achieved by the escitalopram/placebo group (p=0.03), particularly after day 30.

On the other hand, if the goal in treating depression is remission and not just the response, combined treatment seems to be the better option. Table 3 shows that by day 60, 81% of the patients who were treated with escitalopram/alprazolam achieved remission, whereas only 47% of the patients in the escitalopram/placebo group achieved remission.

As seen in Figure 1, by day 60, only the escitalopram/alprazolam group reached Remission values on the Hamilton D-17 Scale.

Figure 2 displays patients’ perception of their depression. Percentages were calculated based on their responses: much better + somewhat better.

Bech and Maier established subscales within the Hamilton D-17 known as the:

- Melancholy Index- items (1: depressed mood, 2: feeling of guilt, 7: work and activities, 8: inhibition, 10: psychic anxiety-, 3: general somatic symptoms-)
- Anxiety Index- items (9: agitation-, 10: psychic anxiety, 11: somatic anxiety)
- Sleep Alterations Index- items (4, 5, 6: related to insomnia)

The results are displayed in Table 4.

Results of efficacy in insomnia

As seen in Table 5, the difference in the efficacy of the treatments offered to both groups was statistically significant as of day 15.

In both treatment plans, insomnia improved with regard to the PSQI baseline values, but as seen in Figure 3, only those patients who received the escitalopram + alprazolam combination, achieved “good sleeper” levels.

The Visual Analog Scale for insomnia reaffirms the results of the PSQI, as seen in Figure 4, where on a scale from 0 to 10, 0 is the worst sleep and 10 is the best sleep.

Figure 5 displays patients’ subjective evaluations with regard to the improvement of insomnia, using data gathered from the PGI (Patient

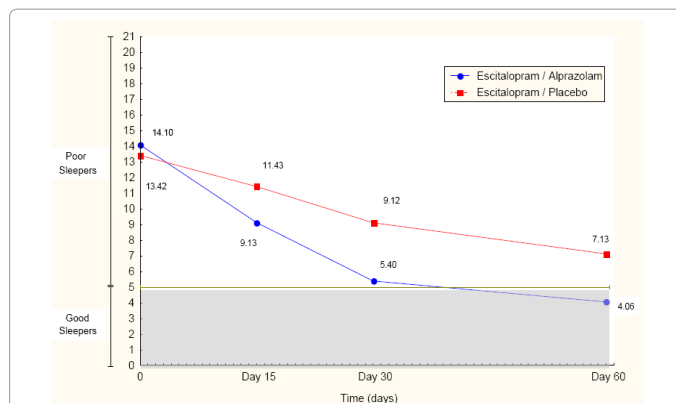


Figure 3: Sleep Quality (PSQI) evolution of average values in both groups.

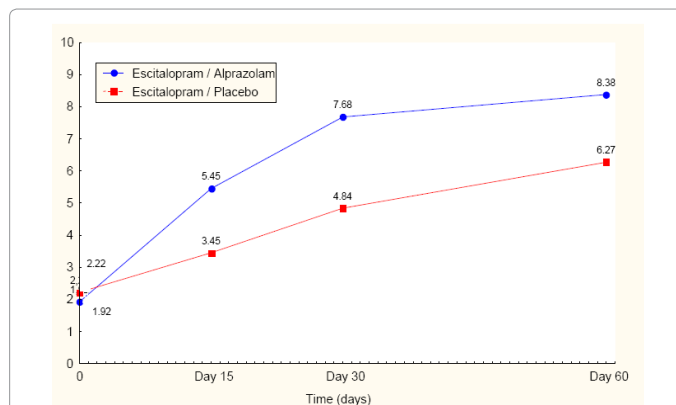


Figure 4: Visual Analog Scale for Insomnia: evolution of average values in both groups.

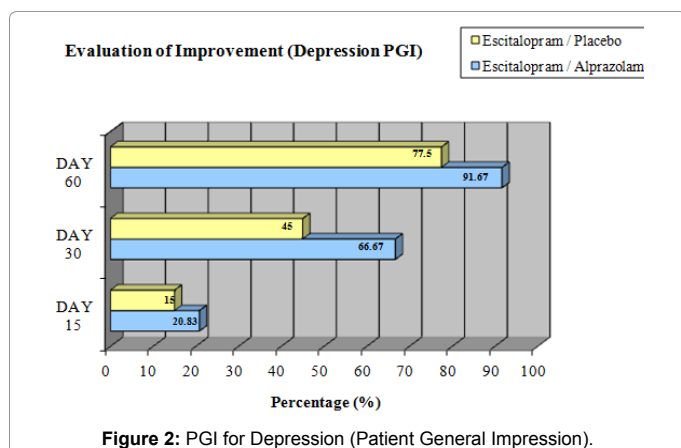


Figure 2: PGI for Depression (Patient General Impression).

	Melancholy		Anxiety		Insomnia	
	ALP.	PLAC.	ALP.	PLAC.	ALP.	PLAC.
Baseline	11.77 ± 2.50	11.58 ± 2.75	4.25 ± 1.44	4.28 ± 1.26	4.92 ± 1.06	4.63 ± 1.36
DAY 15	8.58 ± 3.46	9.19 ± 3.95	3.08 ± 1.62	3.30 ± 1.61	2.75 ± 1.80	3.56 ± 1.88
DAY 30	4.90 ± 3.00	6.02 ± 3.73	1.96 ± 1.22	2.05 ± 1.41	1.19 ± 1.39	2.74 ± 2.13
DAY 60	2.71 ± 3.06	2.91 ± 2.70	1.21 ± 1.29	1.33 ± 1.36	0.71 ± 1.07	2 ± 1.94

Table 4: Bech and Maier subscales within Hamilton D-17.

	Escitalopram/Alprazolam (n=48)	Escitalopram/Placebo (n=40)
Baseline	14.10 ± 3.10	13.42 ± 3.19
Day 15 *	9.13 ± 3.93	11.43 ± 3.65
Day 30 **	5.40 ± 2.64	9.12 ± 4.49
Day 60 ***	4.06 ± 2.58	7.13 ± 4.13
ANOVA Test For repeated measurements	p<0.01	p<0.01

ANOVA GLOBAL for paired data “between treatments” p<0.01
Newman Keuls Post-Hoc Test: Baseline: p=0.22; Day 15: p=0.01; Day 30: p=0.01; Day 60: p=0.01

Table 5: PSQI (Pittsburgh Sleep Quality Index).

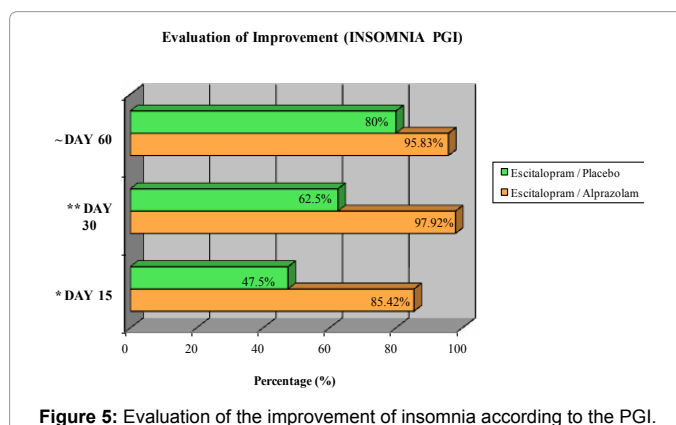


Figure 5: Evaluation of the improvement of insomnia according to the PGI.

General Impression). This graph illustrates the responses “a little better”, “somewhat better” and “much better”.

Tolerability results

Table 6 displays the tolerability results. Around 90% of the patients, both from the escitalopram + alprazolam group and the escitalopram + placebo group tolerated the treatment very well. Table 7 displays the percentage of adverse events recorded in both groups.

*3 patients presented nausea of moderate intensity and probably related to the medication. It did not require treatment or discontinuation.

	Escitalopram/Alprazolam (N=52)			Escitalopram/Placebo (N=43)		
	Day 15	Day 30	Day 60	Day 15	Day 30	Day 60
Very Good	42 (80.77%)	50 (96.15%)	48 (92.31%)	37 (86.05%)	39 (90.70%)	38 (88.37%)
Good	9 (17.31%)	1 (1.92%)	-	5 (11.63%)	3 (6.98%)	2 (4.65%)
Average	1 (1.92%)	-	1 (1.92%)	-	-	-
Poor	-	-	-	1 (2.33%)	-	-

Table 6: Tolerability in both treatment groups.

Escitalopram/Alprazolam	7 (13.46%)*
Escitalopram/Placebo	6 (13.95%)**

Table 7: Adverse events recorded.

Sublingual Alprazolam	
•	19% stopped taking it
•	40% stopped taking regular dosages but continued taking it as needed
•	41% went back to taking previous dosages

Table 8: Required dosage of alprazolam by day 75.

2 patients presented drowsiness, 1 of low intensity and the other of moderate intensity and possibly/probably related to the medication. It did not require treatment or discontinuation.

1 patient presented trembling in the upper limbs of low intensity and possibly related to the medication. It did not require treatment or discontinuation.

1 patient presented headaches and nausea of moderate intensity and possibly related to the medication. It did not require treatment or discontinuation.

** 1 patient presented headaches of moderate intensity and not related to the medication. It did not require treatment or discontinuation.

1 patient presented nausea of moderate intensity and probably related to the medication. It did not require treatment or discontinuation.

1 patient presented diarrhea of low intensity and not related to the medication. It did not require treatment or discontinuation.

1 patient presented persistent depression of moderate intensity and not related to the medication. It required treatment and the patient had to withdraw from the protocol.

1 patient presented vomiting and nausea of severe intensity and definitely related to the medication. It did not require treatment but the patient did have to withdraw from the protocol.

1 patient presented sexual dysfunction of moderate intensity and possibly related to the medication.

Withdrawals

3 patients who received Escitalopram/Placebo abandoned the treatment at day 60, because of the lack of efficacy.

Required dosages of alprazolam

Table 8 shows the required dosage of alprazolam at the end of the clinical trial.

The dosage of Escitalopram was held at 10 mg for all of the patients except 7, for whom the dosage was increased due to a failure to respond (between days 15 and 60), and who were later removed from the study, evaluating only the Tolerability item.

Discussion

The main objective of this randomized, double-blind, placebo-controlled clinical trial was to demonstrate that the combined treatment of an antidepressant with a benzodiazepine approved for treating short-term insomnia would be more effective in treating major depression combined with insomnia than using an antidepressant without combinations.

If the goal of the antidepressant treatment was to go beyond the response (a 50% reduction in the HAM-D17) and aim for the remission of the symptoms of depression (≤ 7 on the HAM-D17) it is clear that this objective was only achieved with the Escitalopram / Alprazolam combination. Considering that recent studies have set the cutoff point for remission at ≤ 5 on the HAM-D17, in an effort to guarantee psychosocial functionality, the escitalopram + alprazolam combination has also proven to achieve this objective. The escitalopram + placebo group's symptoms of depression improved without achieving remission.

All of this suggests that improving the insomnia these patients experience would substantially help them to achieve the remission of their depressive symptoms.

On the other hand, although the insomnia of the escitalopram + placebo group also improved, this group never became "good sleepers" as conceptually established in the PSQI, while the escitalopram + alprazolam group did.

Although the bidirectionality between depression and insomnia is a topic of debate, it is important to consider that insomnia is regularly reported as a risk factor preceding a relapse in depressive symptoms [11,12], which is why treating insomnia is of such relevance.

There is a lot of debate about whether insomnia is a manifestation of depression or whether it is an independent comorbidity. In this clinical trial, the patients who participated in the escitalopram + placebo group did not manage to become good sleepers after 60 days of treatment and this clearly interfered with the remission of the depression, since in the subscales of the Hamilton D-17 Scale, the index associated with sleep disorders was the only one for which the differences were statistically significant.

In Bech and Maier12bis subscales, the sleep alterations index is the only index in which significant statistical differences were observed.

The combined treatment was very well tolerated and at the end of the clinical trial (day 75), 58% of the patients who took alprazolam were able to stop using it and, in some cases, keep some extras to use when needed.

Although withdrawal symptoms of benzodiazepines can be severe, clinical experience has shown that it is much more likely to be mild and can easily be treated by tapering the dosages of the medication.

The limitations of this clinical trial included the fact that it did not evaluate scales for performance at work or driving vehicles during the day, or records of daytime fatigue, although some studies have brought light to these points [14-18].

It is clear that the objective of the treatment for Major Depressive Disorder is not only to achieve clinical remission but also to restore the level of functionality patients had before the depression began, which can be impeded by residual or subclinical symptoms, whose true nature continues to be controversial and certainly multi-faceted (inadequate treatment, comorbidity with other somatic processes or mental disorders, greater initial severity, longer duration of the episode, etc).

Another limitation of this clinical trial was the failure to evaluate the residual symptoms and grade of social and work-related functionality of the patients who achieved clinical remission.

One aspect that would be left up to the good judgment of the specialist is how to continue treating insomnia after achieving the remission of the signs and symptoms of depression. The gradual reduction of benzodiazepines seems to be the most universally accepted concept, but on-demand therapies are an alternative to keep in mind, as long as they are supervised by specialist.

In terms of the amount of time the combined therapy should last, it is estimated that 60 days is the ideal period, since that is the point at which the patients in this clinical trial achieved remission values for depression and were deemed “good sleepers” in accordance with the PSQI.

Another noteworthy detail of this clinical trial was the use of a visual analog scale for insomnia. It proved to be useful and reliable, demonstrating a very high statistical correlation (Spearman Test) with the data obtained by the PSQI [25].

Conclusion

The simultaneous treatment of depression and insomnia with the combination of escitalopram and sublingual alprazolam may be a good option for patients with Major Depressive Disorder associated with Insomnia, since the remission of the depression (HAM-D17) and the range of good sleepers (PSQI) were only achieved in the escitalopram + sublingual alprazolam group.

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