Side effects of low-dose mirtazapine and amitriptyline in patients with insomnia: a randomized, double-blind, placebo-controlled trial

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Abstract

Background

A low dose of mirtazapine (7.5-15mg) and amitriptyline (10-20mg) is often prescribed off-label for the treatment of insomnia disorder. However, the knowledge of the effectiveness and the occurrence of the side effects in this treatment is limited. Therefore, we conducted the Drug REdiscovery: low-dose Amitriptyline and Mirtazapine for INsomnia disorder in General practice (DREAMING) study.

Method

This analysis is embedded in the pragmatic DREAMING study. In total, 80 patients (18-85) with insomnia disorder were included. The Antidepressant Side-Effect Checklist (ASEC-24) questionnaire was used to measure patients' self-reported side effects [18]. The generalized estimating equation (GEE) linear model and linear mixed model (LMM) were used to analyze the data.

Results

In total, 67 (84%) patients reported three or more health complaints at baseline. In week 6, 15 (55%), 18 (67%) and 16 (61%) patients on placebo (n=27), mirtazapine (n=27) and amitriptyline (n=26) reported three or more side effects, respectively.

The patients in the mirtazapine arm reported significantly more SEs attributed to the study medication than the patients in placebo arm (OR = 7.3, 95% CI 1.66-32.88) in week 6. There was no statistically significant difference, in week 12 (OR=3.5, 95% CI 0.93-13.45).

The patients in the amitriptyline arm reported no statistically significant difference in attributed SEs in comparison to patients in the placebo arm (OR=2.3, 95%CI 0.70-7.76) in week 6 and also in week 12 (OR=2.1, 95% CI, 0.61-7.33), as estimated with the GEE model.

Drowsiness in the morning, weight gain and vivid dreams were most frequently attributed SEs to the use of mirtazapine in week 6. Drowsiness in the morning, vivid dreams and dry mouth were similarly attributed SEs in the amitriptyline arm in week 6. In week 6, dry mouth, drowsiness in the afternoon and weight gain were the SEs which were most frequently attributed to the use of placebo.

The difference in the average body weight between the mirtazapine or amitriptyline arm in comparison to the placebo arm was not statistically significant in weeks 6, 12 and 20 as estimated with the linear mixed model.

Conclusion

The results of the patients' self-reported side effects in addition to the reported effectiveness based on a double-blind, randomized, placebo-controlled pragmatic trial may contribute to the decision-making in general practice concerning off label low-dose mirtazapine and amitriptyline treatment of insomnia.

Keywords

low-dose mirtazapine and amitriptyline; patients' self-reported side effects; Antidepressant Side-Effect Checklist (ASEC) questionnaires; the difference; compared to placebo

Introduction

Background

Insomnia disorders are a worldwide problem with a high prevalence, i.e., 10-30% of the population has chronic and persistent insomnia [1]. The prevalence of insomnia disorders in the Netherlands is 8.2% [2]. It can occur from the early age of 12 until 85. The most common health problems from insomnia are fatigue, concentration problems, mood changes and anxiety. Insomnia can lead to severe cardiovascular disorders, diabetes mellitus and mental disorders such as decreasing cognitive functions [3]. The criteria for insomnia disorder are described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Insomnia disorder may be diagnosed if the patient has sleeping problems three times a week for more than three months, according to DSM-5 [4].
In one American study, direct and indirect yearly costs per patient were estimated to be around 5000 dollars. The direct costs are associated with costs for health consultations and drug prescriptions. The indirect costs are mainly related to the loss of work productivity caused by insomnia [5].

Cognitive-behavioral therapy is the first-choice therapy for insomnia disorders. In the Dutch guidelines for the treatment of insomnia non-pharmacological treatment is recommended, i.e., advising and educating the patients about the cause of sleeping problems. This includes advice on stimulus control, sleep restriction, relaxation exercises and cognitive therapy [6]. Second-line treatment includes pharmacological therapy such as benzodiazepines and Z-drugs (zopiclone and zolpidem). However, the efficacy of those medicines for the quantity of sleep is limited. Only in the first three nights do patients sleep about 30 to 50 minutes longer and 15 min faster in sleep onset as compared to placebo [7-8]. After several weeks of use, the hypnotic effect is decreased [9-10]. Despite the short-term efficacy they can cause severe side effects such as sedation during the day, increased risk of falls and hip fractures in the elderly population, memory disorders and dependence [6]. In the latest meta-analyses for acute and long-term management of insomnia it was confirmed that benzodiazepines are effective for the treatment of acute insomnia. However, the long-term effects are still not available. Only eszopiclone and lemborexant were more effective than placebo for long-term treatment of insomnia, but still with a significant increase of adverse effects. In the treatment with zolpidem and zopiclon there were more patients who discontinued the treatment due to the SEs than placebo [11].

A low dose of the antidepressant mirtazapine (7.5-15mg) and amitriptyline (10-20mg) is often prescribed for the treatment of insomnia, but they are not registered for this indication (off-label medicines) [12]. Amitriptyline (tricyclic antidepressant) can improve sleeping due to the antagonizing of H1 and 5HT2A receptors and mirtazapine (tetracyclic antidepressant) improves sleeping due to the blocking of H1 and 5HT2A/C receptors [13-14-15]. In the Netherlands, the use of the antidepressant mirtazapine in patients with insomnia is gradually increasing [16].
Hypothetically, the use of those medicines in low doses for the treatment of insomnia is due to selectivity for histamine 1 receptor, i.e., the blocking effect.

There are still no medicines for the treatment of long-term insomnia problems or chronic insomnia disorder due to a lack of research in this area. Therefore, the DREAMING (the Drug REdiscovery: low-dose Amitriptyline and Mirtazapine for INsomnia disorder in General practice) study was performed to research the effectiveness of low-dose mirtazapine and amitriptyline compared to placebo as alternative medicines for the treatment of insomnia [17]. The main objective of this study was to analyze the tolerability of low-dose amitriptyline and mirtazapine. Side effects of low-dose mirtazapine and amitriptyline are also still not assessed in the treatment of insomnia especially in comparison to placebo. Therefore, it is important to study, describe and evaluate the side effects of low dose of those medicines in comparison to placebo. This research represents sub-research from the main DREAMING study.

Objectives

The main objective of this research was to assess the patients' self-reported side effects of low-dose mirtazapine (7.5-15mg) and amitriptyline (10-20mg) in patients with insomnia in comparison to placebo. Knowledge of the occurrence of side effects may contribute to the facilitation of decision-making among general practitioners (GPs) and patients regarding the use of these medicines in the treatment of insomnia.

Methods

Study Design

The DREAMING study was a randomized, double-blind, placebo-controlled, phase III trial with three treatment groups. The patients were randomized to start treatment with the study medication mirtazapine (7.5 mg), amitriptyline (10 mg) or placebo for 16 weeks. During the monitoring visit at week 3, the GP could double the dose of study medication up to week 16 in case of insufficient effectiveness. The randomization proportion was 1:1:1. The details of the study design are described in the study protocol of the DREAMING study [17].

Study population

All patients (18-85) with insomnia disorder based on the DSM-5 criteria were included in the baseline assessment and randomization. Patients who ask for sleep medication from their general practitioner in cases where the non-pharmacological treatment was insufficient were also eligible to be included in the study. The main exclusion criteria were insomnia as a result of other medical conditions and contraindications of amitriptyline or mirtazapine. All inclusion and exclusion criteria, recruitment of participants and sample size calculations are provided in the DREAMING study [17].

Study outcomes

The primary study outcome was the difference in the occurrence of the SEs attributed to the use of the study medicines in comparison to placebo. The secondary outcomes were the nature and severity of the patients' self-reported side effects of a low dose of mirtazapine (7.5-15mg) and amitriptyline (10-20mg) in patients with insomnia compared to placebo. We also assessed the difference in the average body weight between mirtazapine and amitriptyline compared to placebo.

Measurement of side effects

Side effects (SEs) were measured as self-reported side effects with a set of questionnaire Antidepressant Side-Effect Checklist (ASEC-24) at week 6 and week 12. The ASEC-21 is already validated and used to measure 21 self-reported side effects [18]. In addition to the validated list (ASEC-21), the ASEC-24 contained more three SEs such as vivid dreams, difficulty waking up and drowsiness which is divided into drowsiness in the morning and drowsiness in the afternoon. The occurrence of the health complaints scored as mild, moderate, and severe was measured in the baseline with the same set of questions. Furthermore, the occurrence of the side effects scored as mild, moderate, and severe was measured in weeks 6 and 12. At weeks 6 and 12 for each reported SEs, subjects were asked to indicate whether the side effect was attributed to the use of the study medication. In addition, subjects filled out the body weight in kg at baseline, weeks 6, 12 and 20 to calculate the differences in the average body weight.

Statistical Analyses

Intention-to-treat (ITT) analysis was performed whereby all randomized patients were included. The total number (%) of HCs and SEs from each period was calculated in two cut-off points, first from mild (summary of mild, moderate, and severe) and second from moderate (summary from moderate and severe only). Descriptive statistics were performed to evaluate the nature and severity of self-reported HCs and SEs. The descriptive statistics of n(%) frequencies of HCs and SEs, divided into cases of zero, one or two and three or more for each group: placebo, mirtazapine and amitriptyline and each period: i.e., the baseline, week 6 and week 12, respectively, was performed. The top 10 HCs and SEs were selected for baseline (T0), week 6 (T1) and week 12 (T2) from mild/moderate and for placebo, amitriptyline, and mirtazapine, respectively.

The univariate and bivariate analysis was performed. The frequency and percentages were calculated for the health complaints in the baseline and the side effects from placebo, amitriptyline, and mirtazapine per period T1 (week 6) and T2 (week 12), respectively. The bivariate analysis with the generalized estimating equation (GEE) linear model was performed to assess the dichotomy data from the total side effects attributed to the use of study medications as a dependent variable and the time (week 6 and week 12) and treatment (placebo, amitriptyline, and mirtazapine) as an independent variable. Wald Chi-Square Test was also performed to find if the binary variables in the model are significant. The odds ratio (OR) was calculated and the 95% confidence interval (CI) whereby $p<0.05$ was considered statistically significant.

The difference in the average body weight between mirtazapine and placebo or amitriptyline and placebo was analyzed with the linear mixed model (LMM) from week 20 and baseline, week 12 and baseline and week 6 and baseline, respectively.

All data were analyzed with a statistical program SPSS 26.

Results

Study population

A total of 153 patients were enrolled in this study of which 80 patients were included for further baseline assessment and randomization. 73 patients were excluded because they did not meet the inclusion criteria (such as those with chronic use of benzodiazepines), declined to participate or for other reasons. 27, 27 and 26 patients were allocated to receive placebo, mirtazapine and amitriptyline, respectively. Two patients from the placebo arm did not start the treatment, but they were included in the ITT analysis. In total 69 and 62 patients filed the questionary in weeks 6 and 12, respectively. Figure 1 shows an overview of the study population. Table 1 represents the basic characteristics of the study population. Most of the patients (57%) were between the age of 35-64 and 72% were female.

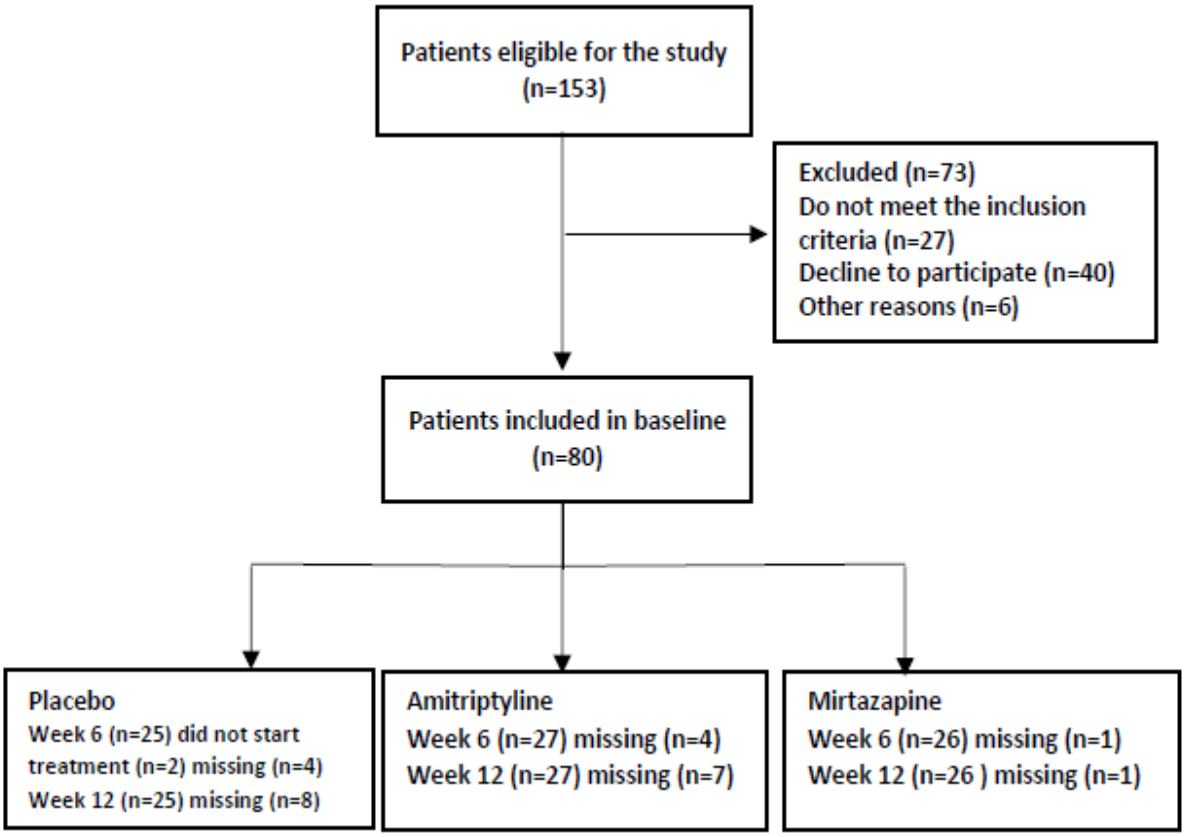

FIGURE 1. Flow chart study population

Table 1. Basic characteristics of the study population

	Total n=80	Placebo n=27	Mirtazapine n=27	Amitriptyline n=26
Age of patients in groups n(%)				
18-35	15 (19)	7 (26)	4 (15)	4 (15)
35-64	46 (57)	14 (52)	16 (59)	16 (61)
65-74	12 (15)	4 (15)	5 (18)	3 (11)
>75	7 (9)	2 (7)	2 (7)	3 (11)
Age in year (mean, SD)	53 (16)	50 (17)	54 (16)	53 (17)
Gender n(%)				
Female	58 (72)	22 (81)	19 (70)	17 (65)
Male	22 (27)	5 (18)	8 (30)	9 (35)
Body weight in kg (mean, SD)	70.7(13)	70.6 (17)	67.8 (10)	70.5 (12)

SD Standard Deviation; n(%) Frequency with the percentage of the total

Descriptive statistics of the self-reported HCs and SEs

Total frequencies n(%) calculated for each occurred self-reported HCs and SEs scored as mild, moderate and severe and attributed SEs to the use of the study medication in baseline and week 6 are shown in Table 2.

In week 6, the most frequently self-reported SEs in the mirtazapine arm were drowsiness in the morning in 14 (52%), vivid dreams in 14 (52%), dry mouth, weight gain and difficulty waking up in 9 (33%) patients. In the amitriptyline arm, the most frequently self-reported SEs were drowsiness in the morning in 13 (50%), vivid dreams and dry mouth in 10 (38%) patients. Drowsiness in the morning, drowsiness in the afternoon and restless sleep in 11 (41%) patients in the placebo group were reported, respectively.

Drowsiness in the morning in 13 (48%), weight gain in 9 (33%) and vivid dreams in 9 (33%) patients were the most attributed SEs to the use of mirtazapine and drowsiness in the morning in 8 (31%), dry mouth in 8 (31%) and vivid dreams in 7 (27%) patients to the use of amitriptyline were reported in week 6. The most attributed SEs to the use of placebo were dry mouth in 4 (15%), drowsiness in the afternoon in 4 (15%), drowsiness in the morning and weight gain in 3 (11%) patients.

Table 2. Total HCs in the baseline (T0), total SEs of placebo, amitriptyline and mirtazapine and attributed SEs to the use of the study medication in week 6 (T1) in n(%)

	Baseline (T0)	Total SEs in week 6 (T1)			Attributed SEs		
ASEC-24	Total HCs (n=80)	PLA (n=27)	MIR (n=27)	AMI (n=26)	PLA (n=27)	MIR (n=27)	AMI (n=26)
Dry mouth	22 (27)	9 (33)	9 (33)	10 (38)	4 (15)	6 (22)	8 (31)
Difficulty waking up	28 (35)	6 (22)	9 (33)	9 (35)	1 (4)	7 (26)	4 (15)
Drowsiness in the morning	49 (61)	11 (41)	14 (52)	13 (50)	3 (11)	13 (48)	8 (31)
Drowsiness in the afternoon	45 (56)	11 (41)	9 (33)	8 (31)	4 (15)	5 (18)	4 (15)
Restless sleep	64 (80)	11 (41)	6 (22)*	7 (27)*	1 (4)	4 (15)	2 (8)
Vivid dreams	33 (41)	8 (30)	14 (52)	10 (38)	2 (7)	9 (33)	7 (27)
Blurred vision	19 (24)	4 (15)	4 (15)	3 (11)	2 (7)	2 (7)	0 (0)
Headache	41 (51)	7 (26)	6 (22)	5 (19)	3 (11)	3 (11)	0 (0)
Constipation	20 (25)	6 (22)	6 (22)	2 (8)	0 (0)	6 (22)	1 (4)
Diarrhea	8 (10)	5 (18)	2 (7)	1 (4)	0 (0)	1 (4)	0 (0)
Appetite increase	15 (19)	7 (26)	8 (30)	3 (11)	2 (7)	7 (26)	3 (11)
Appetite decrease	18 (22)	4 (15)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Nausea or vomiting	12 (15)	3 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urination problems	9 (11)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sexual problems	16 (20)	3 (11)	3 (11)	0 (0)	0 (0)	3 (11)	0 (0)
Palpitations	18 (22)	4 (15)	2 (7)	0 (0)	1 (4)	2 (7)	0 (0)
Orthostatic hypotension	30 (37)	8 (30)	3 (11)*	1 (4)*	2 (7)	2 (7)	1 (4)
Vertigo	13 (16)	3 (11)	0 (0)	0 (0)	2 (7)	0 (0)	0 (0)
Sweating	19 (24)	6 (22)	5 (18)	2 (8)	2 (7)	2 (7)	0 (0)
Increased temperature	4 (5)	4 (15)	2 (7)	0 (0)	1 (4)	1 (4)	0 (0)
Tremor	12 (15)	3 (11)	1 (4)	0 (0)	1 (4)	1 (4)	1 (4)
Disorientation	11 (14)	2 (7)	3 (11)	0 (0)	1 (4)	2 (7)	0 (0)
Yawning	35 (44)	9 (33)	2 (7)*	2 (8)*	2 (7)	1 (4)	1 (4)
Weight gain	14 (17)	5 (18)	9 (33)	5 (19)	3 (11)	9 (33)	4 (15)

ASEC Antidepressant Side-Effect Checklist; HCs Health Complaints; SEs Side-effects; n(%) Frequency with the percentage of the total; Attributed SEs represents the frequency with the percentage of the total users that answered yes to the question if the SE is attributed to the use of the study medication; Total HCs/SEs are calculated from mild (summary of mild, moderate and severe).

*p<0,05, a statistically significant difference in the frequency of side effects between mirtazapine or amitriptyline and placebo (Chi-square test/X^2 test)

Total frequencies n(%) calculated for each occurred self-reported HCs and SEs scored as mild, moderate and severe and attributed SEs to the use of the study medication in baseline and week 12 are shown in Table 3.

In week 12, the most frequently self-reported SEs in the mirtazapine arm were vivid dreams in 12 (44%), weight gain in 11 (41%) and difficulty waking up in 10 (37%) patients and vivid dreams in 13 (50%), drowsiness in the morning in 12 (46%) and restless sleep in 12 (46%) patients in the amitriptyline arm. In the placebo arm, the most reported SEs were restless sleep in 9 (33%), drowsiness in the afternoon in 7 (26%) and yawning in 7 (26%) patients.

In week 12, difficulty waking up in 8 (30%), vivid dreams in 8 (30%) and weight gain in 8 (30%) patients were most attributed SEs to the use of mirtazapine and drowsiness in the morning in 9 (35%), vivid dreams in 7 (30%) and dry mouth in 6 (23%) patients were most attributed SEs to the use of amitriptyline. The most attributed SEs to the use of placebo were vivid dreams in 3 (11%), orthostatic hypotension in 2 (7%) and drowsiness in the morning and afternoon in 2 (7%) patients.

Table 3 and 7 shows that the occurrence of the weight gain and dry mouth persisted after 12-week treatment in the mirtazapine and amitriptyline group compared to the placebo group.

The most frequently self-reported health complaint in the baseline was restless sleep in 64 (80%) patients. In general, most of the total HCs and further SEs are gradually decreased from the baseline to week 6 and week 12. Total frequencies of the HCs and SEs in the baseline, week 6 and week 12 are shown in the table 1 in the appendix.

Table 3. Total HCs in the baseline (T0), total SEs of placebo, amitriptyline and mirtazapine and attributed SEs to the use of the study medication in week 12 (T2) in n(%)

	Baseline (T0)	Total SEs in week 12 (T2)			Attributed SEs		
ASEC-24	Total HCs (n=80)	PLA (n=27)	MIR (n=27)	AMI (n=26)	PLA (n=27)	MIR (n=27)	AMI (n=26)
Dry mouth	22 (27)	4 (15)	8 (30)	9 (35)	1 (4)	5 (18)	6 (23)
Difficulty waking up	28 (35)	6 (22)	10 (37)	10 (38)	1 (4)	8 (30)	6 (23)
Drowsiness in the morning	49 (61)	6 (22)	8 (30)	12 (46)	2 (7)	4 (15)	9 (35)
Drowsiness in the afternoon	45 (56)	7 (26)	6 (22)	7 (30)	2 (7)	2 (7)	4 (15)
Restless sleep	64 (80)	9 (33)	7 (26)	12 (46)	0 (0)	3 (11)	5 (19)
Vivid dreams	33 (41)	5 (18)	12 (44)	13 (50)	3 (11)	8 (30)	7 (30)
Blurred vision	19 (24)	3 (11)	7 (26)	2 (8)	0 (0)	3 (11)	2 (8)
Headache	41 (51)	5 (18)	3 (11)	6 (23)	1 (4)	0 (0)	2 (8)
Constipation	20 (25)	6 (22)	5 (18)	4 (15)	0 (0)	3 (11)	1 (4)
Diarrhea	8 (10)	3 (11)	3 (11)	1 (4)	0 (0)	1 (4)	1 (4)
Appetite increase	15 (19)	6 (22)	7 (26)	3 (11)	1 (4)	5 (18)	3 (11)
Appetite decrease	18 (22)	3 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea or vomiting	12 (15)	3 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urination problems	9 (11)	2 (7)	2 (7)	2 (8)	0 (0)	1 (3.7)	2 (8)
Sexual problems	16 (20)	3 (11)	1 (4)	0 (0)	0 (0)	1 (3.7)	0 (0)
Palpitations	18 (22)	3 (11)	3 (11)	1 (4)	0 (0)	1 (3.7)	2 (8)
Orthostatic hypotension	30 (37)	6 (22)	2 (7)*	3 (11)*	2 (7)	0 (0)	2 (8)
Vertigo	13 (16)	2 (7)	2 (7)	1 (4)	0 (0)	1 (4)	0 (0)
Sweating	19 (24)	5 (18)	1 (4)	3 (11)	0 (0)	1 (4)	2 (8)
Increased temperature	4 (5)	3 (11)	0 (0)	2 (8)	1 (4)	0 (0)	1 (4)
Tremor	12 (15)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Disorientation	11 (14)	2 (7)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Yawning	35 (44)	7 (26)	3 (11)*	5 (19)*	1 (4)	1 (4)	4 (15)
Weight gain	14 (17)	5 (18)	11 (41)	6 (23)	1 (4)	8 (30)	4 (15)

ASEC Antidepressant Side-Effect Checklist; HCs Health Complaints; SEs Side-effects; n(%) Frequency with the percentage of the total; Attributed SEs represents the frequency with the percentage of the total users that answered yes to the question if the SE is attributed to the use of the study medication; Total HCs/SEs are calculated from mild (summary of mild, moderate and severe).

*p<0,05, a statistically significant difference in the frequency of side effects between mirtazapine or amitriptyline and placebo (Chi-square test/X^2 test)

We analyzed the total SEs divided per case to study how common are the SEs in placebo, mirtazapine, and amitriptyline arms. Table 4 represents frequency with the percentage of the total of HCs and SEs divided into cases of zero, one or two, and three or more for each placebo, mirtazapine, and amitriptyline group and for each period: i.e., the baseline, week 6 and week 12, respectively. The case of three or more SEs was approximately similarly reported among the mirtazapine, amitriptyline, and placebo arms. More particularly, in week 6, 15 (55%), 18 (67%) and 16 (61%) patients reported three or more side effects in the placebo, mirtazapine and amitriptyline arm, respectively. Table 2 in the appendix shows HCs/SEs divided into the case of zero, one or four and five or more.

The top 10 HCs in the baseline n(%) scored as mild, moderate and severe and total from mild and the top 10 SEs N(%) scored as mild, moderate and severe and total from mild in weeks 6 and 12 per placebo, mirtazapine and amitriptyline are listed in table 5, 6 and 7, respectively. In table 5 and 6 in the appendix, they are shown as those from the second cut-off calculated from moderate for weeks 6 and 12, respectively.

Generalized Estimating Equations linear model for the difference in the occurrence of SEs attributed to mirtazapine and amitriptyline compared to placebo

The Generalized Estimating Equations (GEE) linear model was used to assess the difference in the occurrence of SEs attributed to the use of mirtazapine and amitriptyline compared to placebo. It was calculated in two cut-off points i.e., from mild or from moderate in week 6 and week 12.
The patients in the mirtazapine arm reported significantly more attributed side effects than patients in the placebo arm in week 6 by the first cut-off point calculated from mild (OR=7.3, 95% CI 1.66-32.88, p=0.009). The difference in the occurrence of the attributed side effects by the patients in the amitriptyline arm in comparison to the placebo arm was not statistically significant (OR=2.3, 95%CI 0.70-7.76, p=0,165). In week 12 these differences decreased and were not statistically significant for the patients in the mirtazapine and amitriptyline arm compared to the placebo arm (OR=3,5, 95% CI 0.93-13.45, p=0.064) and (OR=2,1, 95% CI, 0.61-7.33, p=0.237), respectively. All results are shown in table 3 in the appendix.

A linear mixed model for the difference in the body weight

A linear mixed model was used to analyze the difference in the average body weight between the mirtazapine or amitriptyline arm in comparison to the placebo arm in three different periods i.e., 6, 12 and 20 weeks to baseline. The model calculated the differences in average body weight between both medicines and placebo, p-value and 95% CI. The difference in average body weight was not statistically significant. The results are shown in the table 4 in appendix.

Table 4. Frequency of HCs and SEs per case, per period and placebo, mirtazapine and amitriptyline in n(%)

	Baseline (t0)	Week 6 (t1)			Week 12 (t2)		
The number of HCs/SEs per case n (%)	Total (n=80)	PLA (n=27)	MIRT (n=27)	AMI (n=26)	PLA (n=27)	MIRT (n=27)	AMI (n=26)
Zero	8 (10)	8 (30)	4 (15)	3 (11)	12 (44)	9 (33)	4 (15)
One or two	5 (6)	4 (15)	5 (18)	7 (27)	3 (11)	3 (11)	3 (11)
Three or more	67 (84)	15 (55)	18 (67)	16 (61)	12 (44)	15 (55)	19 (73)

HCs Health Complaints; SEs Side-effects; n(%) Frequency with the percentage of the total; PLA Placebo n=27; MIRT Mirtazapine n=27; AMI Amitriptyline n=26.

Table 5. Top 10 health complaints (HCs) in the baseline scored as mild, moderate, severe and total n(%)

Top 10 HCs in the baseline n (%)	Mild	Moderate	Severe	Total
Restless sleep	1 (1)	24 (30)	39 (49)	64 (80)
Drowsiness in the morning	7 (9)	22 (27)	20 (25)	49 (61)
Drowsiness in the afternoon	5 (6)	17 (21)	23 (29)	45 (56)
Headache	14 (17)	21 (26)	6 (7)	41 (51)
Yawning	7 (9)	17 (21)	11 (14)	35 (44)
Vivid dreams	9 (11)	14 (17)	10 (12)	33 (41)
Orthostatic hypotension	10 (12)	14 (17)	6 (7)	30 (37)
Difficulty waking up	6 (7)	13 (16)	9 (11)	28 (35)
Dry mouth	7 (9)	11 (14)	4 (5)	22 (27)
Constipation	5 (6)	8 (10)	7 (9)	20 (25)

HCs Health Complaints; n(%) Frequency with the percentage of the total (80); Total HCs are calculated from mild (summary of mild, moderate and severe).

Table 6. Top 10 side effects (SEs) in week 6 scored as mild, moderate, severe and total for placebo, mirtazapine and amitriptyline in n(%)

PLACEBO (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Drowsiness in the morning	3 (11)	5 (18)	3 (11)	11 (41)
Drowsiness in afternoon	0 (0)	7 (26)	4 (15)	11 (41)
Restless sleep	0 (0)	6 (22)	5 (18)	11 (41)
Dry mouth	2 (7)	6 (22)	1 (4)	9 (33)
Yawning	0 (0)	6 (22)	3 (11)	9 (33)
Vivid dreams	2 (7)	3 (11)	3 (11)	8 (30)
Orthostatic hypotension	1 (4)	3 (11)	4 (15)	8 (30)
Headache	1 (4)	6 (22)	0 (0)	7 (26)
Appetite increase	3 (11)	2 (7)	2 (7)	7 (26)
Difficulty waking up	2 (7)	3 (11)	1 (4)	6 (22)
MIRTAZAPINE (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Drowsiness in the morning	2 (7)	8 (30)	4 (15)	14 (52)
Vivid dreams	2 (7)	8 (30)	4 (15)	14 (52)
Dry mouth	2 (7)	6 (22)	1 (4)	9 (33)
Difficulty waking up	4 (15)	3 (11)	2 (7)	9 (33)
Drowsiness in the afternoon	2 (7)	6 (22)	1 (4)	9 (33)
Weight gain	2 (7)	3 (11)	4 (15)	9 (33)
Appetite increase	0 (0)	5 (18)	3 (11)	8 (30)
Restless sleep	2 (7)	1 (4)	3 (11)	6 (22)
Headache	2 (7)	3 (11)	1 (4)	6 (22)
Constipation	2 (7)	2 (7)	2 (7)	6 (22)
AMITRIPTYLINE (n=26)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Drowsiness in the morning	3 (11)	7 (20)	3 (11)	13 (50)
Dry mouth	0 (0)	8 (31)	2 (8)	10 (38)
Vivid dreams	2 (8)	4 (15)	4 (15)	10 (38)
Difficulty waking up	3 (11)	4 (15)	2 (8)	9 (35)
Drowsiness in the afternoon	6 (23)	2 (8)	0 (0)	8 (31)
Restless sleep	1 (4)	2 (8)	4 (15)	7 (30)
Headache	2 (8)	2 (8)	1 (4)	5 (19)
Weight gain	1 (4)	2 (8)	2 (8)	4 (15)
Blurred vision	1 (4)	2 (8)	0 (0)	3 (11)
Constipation	0 (0)	0 (0)	2 (8)	2 (8)

n(%) Frequency with the percentage of the total; SEs Side-effects; Total SEs are calculated from mild (summary of mild, moderate and severe).

Table 7. Top 10 side effects (SEs) in week 12 scored as mild, moderate, severe and total for placebo, mirtazapine and amitriptyline in n(%)

PLACEBO (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Restless sleep	0 (0)	5 (18)	4 (15)	9 (33)
Drowsiness in the afternoon	2(7)	4 (15)	1 (4)	7 (26)
Yawning	4 (15)	2(7)	1 (4)	7 (26)
Difficulty waking up	4 (15)	2(7)	0 (0)	6 (22)
Drowsiness in the morning	3 (11)	1 (4)	2(7)	6 (22)
Constipation	4 (15)	2(7)	0 (0)	6 (22)
Appetite increase	2(7)	3 (11)	1 (4)	6 (22)
Orthostatic hypotension	3 (11)	3 (11)	0 (0)	6 (22)
Vivid dreams	3 (11)	2(7)	0 (0)	5 (18)
Headache	0 (0)	5 (18)	0 (0)	5 (18)
MIRTAZAPINE (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Vivid dreams	4 (15)	4 (15)	4 (15)	12 (44)
Weight gain	5 (18)	5 (18)	1 (4)	11 (41)
Difficulty waking up	2 (7)	4 (15)	4 (15)	10 (37)
Dry mouth	5 (18)	2 (7)	1 (4)	8 (30)
Drowsiness in the morning	3 (11)	3 (11)	2 (7)	8 (30)
Restless sleep	2 (7)	3 (11)	2 (7)	7 (26)
Blurred vision	5 (18)	2 (7)	0 (0)	7 (26)
Appetite increase	1 (4)	4 (15)	2 (7)	7 (26)
Drowsiness in the afternoon	1 (4)	4 (15)	1 (4)	6 (22)
Constipation	0 (0)	4 (15)	1 (4)	5 (18)
AMITRIPTYLINE (n=26)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Vivid dreams	2 (8)	6 (23)	5 (19)	13 (50)
Drowsiness in the morning	6 (23)	4 (15)	2 (8)	12 (46)
Restless sleep	1 (4)	7 (27)	4 (15)	12 (46)
Difficulty waking up	6 (23)	4 (15)	0 (0)	10 (38)
Dry mouth	2 (8)	5 (19)	2 (8)	9 (35)
Drowsiness in the afternoon	3 (11)	2 (8)	2 (8)	7 (27)
Headache	0 (0)	2 (8)	4 (15)	6 (23)
Weight gain	2 (8)	3 (11)	1 (4)	6 (23)
Yawning	1 (4)	4 (15)	0 (0)	5 (19)
Constipation	2 (8)	2 (7)	0 (0)	4 (15)

n(%) Frequency with the percentage of the total; SEs Side-effects; Total SEs are calculated from mild (summary of mild, moderate and severe.

Discussion

The study objective was to assess the patients' self-reported side effects of low-dose mirtazapine (7.5-15mg) and amitriptyline (10-20mg) in patients with insomnia in comparison to placebo. Moreover, to answer our research question we have analyzed the difference in the occurrence of the SEs attributed to the use of the study medicines in comparison to placebo and the nature and severity of the patients' self-reported SEs. These were investigated using the amended ASEC-24 questionnaire over a 12-week period.

Our study indicates that the use of mirtazapine and amitriptyline was associated with significantly more side effects attributed to the use of study medicines compared to placebo. Low-dose mirtazapine for a period of six weeks was associated with a significantly higher probability of the occurrence of attributed SEs in comparison to placebo. The increased probability of occurrence of attributed SEs to the use of amitriptyline compared to placebo was not significant in week 6. These differences decreased after 12 weeks of treatment. This study confirms the known decrease of SEs after a few months of antidepressant use as found in another

research during long-term use of antidepressants [19]. Furthermore, from a pharmacological aspect and known antidepressant mechanism of action, it is assumed that decreasing of the SEs after 12 weeks of treatment was due to the downregulation of monoamine receptors. Additionally, it is assumed that increasing of the attributed SEs was related to the previously known pharmacological effect in the begin of therapy with the antidepressants i.e., increased release of neurotransmitters in the synapse due to the antagonism of the monoamine receptors [14].

At baseline, more than half of the patients experienced health complaints such as restless sleep, drowsiness in the morning and afternoon and headache, which are symptoms of insomnia. These complaints are similar to some side effects of mirtazapine and amitriptyline. It is important not to confuse side effects with preexistent symptoms of insomnia.

Drowsiness in the morning and afternoon, vivid dreams, dry mouth, difficulty waking up in week 6 and additional weight gain in week 12 were the most frequently reported side effects of low-dose mirtazapine. The most frequently side effects of higher doses of mirtazapine (30mg or 45mg) are increased appetite, weight gain, drowsiness in the morning, sedation, headache, and dry mouth [20]. Hypertension and tachycardia in lower doses than 15mg are present in fewer cases [21]. In line with this finding, our study showed that the occurrence of adrenergic SEs in the mirtazapine arm was infrequently reported compared to the placebo arm. In long-term of use of mirtazapine (5-35mg/day) was found that the occurrence of dry mouth was double more frequently reported than placebo [22]. Our results confirmed this finding, the occurrence of dry mouth of low-dose mirtazapine (7.5-15mg) after 12 weeks treatment was reported double more as compared to placebo.

Vivid dreams, drowsiness in the morning, restless sleep, difficulty waking up and dry mouth were the top 5 SEs of amitriptyline in week 12. The most frequently side effects of higher doses of amitriptyline (25mg-150mg) are anticholinergic side effects such as a dry mouth, blurred vision, urinary retention, constipation, then cardiovascular SEs such as orthostatic hypotension, palpitations, and extreme sweating and other such as weight gain [23]. Other receptors may be involved in the occurrence of anticholinergic SEs in higher doses i.e., antagonizing of M1 receptors and antagonizing of α1 receptors for cardiovascular SEs [13-23]. On the other hand, it is not unlikely that drowsiness in the morning, restless sleep and difficulty waking up as symptoms of insomnia are dominant in the side effects profile. The occurrence of dry mouth as an anticholinergic SE was found after 12 weeks of treatment with a low dose of amitriptyline as compared to placebo. Dry mouth was also commonly reported when a low dose of amitriptyline was used in the treatment of pain [24]. Orthostatic hypotension, palpitations and sweating were not reported in the top 10 SEs neither when calculated from mild nor from moderate. It was assumed that the occurrence of cardiovascular SEs was infrequently reported in the amitriptyline arm compared to the placebo arm. This finding was also confirmed when a low dose of amitriptyline was used in the treatment of pain [24].

Side effects can also occur from the use of placebo such as dry mouth, weight gain, headache, drowsiness, sedation, and constipation [22]. This was consistent with our findings i.e., drowsiness in the morning and afternoon and dry mouth were the most commonly reported side effects of placebo in week 6. As expected, there was no improvement in insomnia disorder in the placebo arm. All reported SEs in the placebo arm were associated with the symptoms of insomnia.

In the three groups, a similarity in reporting of the SEs in weeks 6 and 12 was observed. This was the case in patients with three or more SEs in particular. In a univariate analysis of the prevalence of three or more SEs among four groups of antidepressants conducted by Bet et al. was shown that there was no difference in SE prevalence among the groups [19]. This finding was in line with our results i.e., the consistency of reported SEs in the case of three or more SEs among mirtazapine, amitriptyline, and placebo groups.

Weight gain was reported by one-third of the patients in the mirtazapine arm and was attributed to the use of mirtazapine. In line with this finding, patients also reported an increased appetite. Weight gain also persisted in a low dose of amitriptyline as compared to placebo. According to the meta-analysis on antidepressants and body weight, it was found that amitriptyline was significantly associated with weight gain in short period (4-12 weeks) and longer (more than 4 months) periods of treatment [25]. An appetite increase was also found in the top 10 SEs in the placebo arm. In week 12, an increase of approximately 2 kg, 1.5 kg and 1 kg weight gain on average was found in the mirtazapine, amitriptyline, and placebo arm, respectively. Another study showed that in short-term use (4-12 weeks) of mirtazapine a weight gain of 1.7 kg and 1.5 kg from the use of amitriptyline can occur [25]. Weight gain is more prominent in females, and after a longer duration of time [19]. Additionally, weight gain is common among females in midlife due to ageing and a decrease in estrogen levels [26]. In our study, most of the patients (57%) were at the age of 35-64 and 72% were female. A recent study showed an impact of the COVID lockdown on increasing of the body weight [27]. The DREAMING study was performed during the COVID pandemic which may be an additional factor for increasing the weight gain in all groups. Finally, the occurrence of weight gain persisted in both medicines after 12 weeks of treatment based on information from the patients' self-reported SEs. Monitoring is recommended during the treatment of insomnia with mirtazapine and amitriptyline.

Strength and limitation

This study is the first research on the side effects of low-dose mirtazapine and amitriptyline in comparison to placebo used as off-label medicines in insomnia treatment. The randomized, placebo-controlled, double-blind, pragmatic design of this study provides more relevant findings. The present article shows a detailed insight into the top 10 side effects of each group scored as mild, moderate, severe, and total from mild and moderate in week 6 and week 12. The intention to treat analysis is more realistic to what happens in practice, which is also an advantage because the results

can be better extrapolated into the practice. All patients both adherent and non-adherent and the patients who discontinued the treatment due to the SEs are included.
However, this study had certain limitations. The study was performed with only 80 patients with insomnia disorder. The small sample size of this study indicates a limitation to the power of the study i.e., especially concerning to the potential rare side-effects of low-dose amitriptyline or mirtazapine. Moreover, the sample size was calculated for the primary outcomes (insomnia severity index) of the DREAMING study, whereby in total of 156 participants and 43-52 participants per group had to be included. Additionally, the wide confidence interval due to the small sample size indicates more uncertainty of estimated effect. In parallel research was found that both non-intentional and intentional medication non-adherence and early discontinuation occurred. Twenty-one of eighty participants discontinued study medication early or were lost to follow-up. Two patients from the placebo group did not start the treatment. Furthermore, the calculation of the average body weight was only performed with the present information, some of the patients did not fill out their body weight in the questionnaires. The intermediate duration of the study (12 weeks) was also a limitation of this study. We do not provide any data on the dose-SEs relationship.

Clinical implications and further research

This study reveals the frequency, nature, and severity of the self-reported side effects of a low-dose amitriptyline and mirtazapine in comparison to placebo. It is assumed that in the future these results in addition to the results of effectiveness will facilitate the selection process for the most appropriate hypnotic for patients. More specifically, the results of this study may help, support, and facilitate the decision-making in general practice for use of mirtazapine and amitriptyline as off-label treatment of insomnia. The present study did not provide answers about the dose-SEs relationship. Further research with larger sample size and longer duration may improve the present findings.

Conclusion

Our study indicates that the patients in the mirtazapine arm in week 6 reported statistically more significant attributed SEs than those in the placebo arm. Increased occurrence of attributed SEs in the amitriptyline arm was not significant compared to the placebo arm. As estimated with the GEE model these differences decreased after 12 weeks of treatment.

Ethics and registration

This trial was approved by the Medical Ethics Committee of VU Medical Centre in Amsterdam, and it was registered in the Dutch Trial Registry under the number NTR7449.

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Appendix

Table 1. Total frequencies of HCs/SEs in baseline, week 6 and week 12 in n(%)

	Baseline (t0)	Week 6 (t1)		Week 12 (t2)	
ASEC-24	Total HCs	Total SEs	Attributed SEs	Total SEs	Attributed SEs
Dry mouth	22 (27)	28 (35)	18(22)	21 (26)	12 (15)
Difficulty waking up	28 (35)	24 (30)	12 (15)	26 (32)	15 (19)
Drowsiness in the morning	49 (61)	38 (47)	24 (30)	26 (32)	14 (17)
Drowsiness in the afternoon	45 (56)	28 (35)	13 (16)	20 (25)	8 (10)
Restless sleep	64 (80)	24 (30)*	7 (9)	28 (35)	8 (10)
Vivid dreams	33 (41)	32 (40)	18 (22)	30 (37)	18 (22)
Blurred vision	19 (24)	11 (14)	4 (5)	12 (15)	5 (6)
Headache	41 (51)	18 (22)	6 (7)	14 (17)	3 (4)
Constipation	20 (25)	14 (17)	7 (9)	15 (19)	4 (5)
Diarrhea	8 (10)	8 (10)	1 (1)	7 (9)	2 (2)
Appetite increase	15 (19)	18 (22)	12 (15)	16 (20)	9 (11)
Appetite decrease	18 (22)	4 (5)	1 (1)	3 (4)	0 (0)
Nausea, vomiting	12 (15)	3 (4)	0 (0)	3 (4)	0 (0)
Urination problems	9 (11,3)	2 (2)	0 (0)	6 (7)	3 (4)
Sexual problems	16 (20)	6 (7)	3 (4)	4 (5)	1 (1)
Palpitations	18 (22)	6 (7)	3 (4)	7 (9)	3 (4)
Orthostatic hypotension	30 (37)	12 (15)*	5 (6)	11 (14)*	4 (5)
Vertigo	13 (16)	3 (4)	2 (2)	5 (6)	1 (1)
Sweating	19 (24)	13 (16)	4 (5)	9 (11)	3 (4)
Increased temperature	4 (5)	6 (7)	2 (2)	5 (6)	2 (2)
Tremor	12 (15)	4 (5)	3 (4)	2 (2)	0 (0)
Disorientation	11 (14)	5 (6)	3 (4)	3 (4)	0 (0)
Yawning	35 (44)	13 (16)*	4 (5)	15 (19)*	6 (7)
Weight gain	14 (17)	19 (24)	16 (20)	22 (27)	13 (16)

ASEC The antidepressant Side-Effect Checklist; HCs Health Complaints; SEs Side-effects; n(%) Frequency with the percentage of the total (80); Attributed SEs represents the frequency with percentage from the total users that answered yes to the question if the SE is attributed to the use of the study medication; Total HCs/SEs are calculated from mild (summary of mild, moderate and severe).
*p<0,05, a statistically significant difference in the frequency of side effects between mirtazapine or amitriptyline and placebo (Chi-square test/X^2 test)

Table 2. Frequencies of HCs and SEs per case, period and per placebo, mirtazapine and amitriptyline in n(%)

	Baseline (t0)	Week 6 (t1)			Week 12 (t2)		
The number of HCs/SEs per case	Total (n=80)	PLA (n=27)	MIRT (n=27)	AMI (n=26)	PLA (n=27)	MIRT(n=27)	AMI (n=26)
Zero	8 (10)	8 (30)	4 (15)	3 (11)	12 (44)	9 (33)	4 (15)
One or four	18 (22.5)	8 (30)	13 (48)	18 (69)	7 (26)	8 (30)	10 (38)
Five or more	54 (67.5)	11 (41)	10 (37)	5 (19)	8 (30)	10 (37)	12 (46)

HCs Health Complaints; SEs Side-effects; n(%) Frequency with the percentage of the total; PLA Placebo n=27; MIRT Mirtazapine n=27; AMI Amitriptyline n=26

Table 3. The GEE linear model for the differences in the occurrence of SEs attributed to the use of mirtazapine and amitriptyline compared to placebo for week 6 and 12

	Treatment	**Week 6**			**Week 12**		
			95% Confidence Interval			95% Confidence Interval	
		OR	lower	upper	**OR**	lower	upper
First Cut-off	Mirtazapine/placebo	**7.3***	1,66	32,38	**3,53**	0,93	13,46
	Amitriptyline/placebo	**2.3**	0,70	7,76	**2,11**	0,61	7,33
Second Cut-off	Mirtazapine/placebo	**7.3***	1.61	32.38	**3.08**	0.81	11.73
	Amitriptyline/placebo	**1.6**	0.51	5.33	**3.01**	0.82	10.96

The first cut-off point is calculated from mild (summary of mild, moderate and severe); The second cut-off is calculated form moderate (summary of moderate and severe); OR Odds ratio; Attributed SEs represents the frequency with a percentage of the total users that gave an answer yes/no to the question if the SE is attributed to the use of the study medication.
*p<0,05, a statistically significant difference in the occurrence of SEs attributed to mirtazapine compared with placebo

Table 4: Linear mixed model analyses of the differences in body weight between mirtazapine and amitriptyline versus placebo

Time	Intervention	The difference in average body weight in kg	95% Confidence Interval, p<0.05	
			Lower	Upper
T1-B	y-x	0.66	-0.94	2.25
T1-B	z-x	0.47	-1.15	2.08
T2-B	y-x	0.93	-0.69	2.55
T2-B	z-x	0.64	-0.98	2.25
T3-B	y-x	0.36	-1.29	2.01
T3-B	z-x	-0.66	-2.32	0.99

T1= 6 week; T2=12 week; T3=20 week; B=baseline; y = mirtazapine; z=amitriptyline; x=placebo.

Table 5. Top 10 side effects (SEs) in week 6 scored as mild, moderate, severe, and total for placebo, mirtazapine and amitriptyline in n(%)

PLACEBO (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Drowsiness in the afternoon	0 (0)	7 (26)	4 (15)	11 (41)
Restless sleep	0 (0)	6 (22)	5 (18)	11 (41)
Yawning	0 (0)	6 (22)	3 (11)	9 (33)
Drowsiness in the morning	3 (11)	5 (18)	3 (11)	8 (30)
Dry mouth	2 (7)	6 (22)	1 (4)	7 (26)
Orthostatic hypotension	1 (4)	3 (11)	4 (15)	7 (26)
Vivid dreams	2 (7)	3 (11)	3 (11)	6 (22)
Headache	1 (4)	6 (22)	0 (0)	6 (22)
Sweating	1 (4)	3 (11)	2 (7)	5 (18)
Difficulty waking up	2 (7)	3 (11)	1 (4)	4 (15)
MIRTAZAPINE (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Drowsiness in the morning	2 (7)	8 (30)	4 (15)	12 (44)
Vivid dreams	2 (7)	8 (30)	4 (15)	12 (44)
Appetite increase	0 (0)	5 (18)	3 (11)	8 (29)
Dry mouth	2 (7)	6 (22)	1 (4)	7 (26)
Drowsiness in the afternoon	2 (7)	6 (22)	1 (4)	7 (26)
Weight gain	2 (7)	3 (11)	4 (15)	7 (26)
Difficulty waking up	4 (15)	3 (11)	2 (7)	5 (18)
Sweating	0 (0)	3 (11)	2 (7)	5 (18)
Restless sleep	2 (7)	1 (4)	3 (11)	4 (15)
Headache	2 (7)	3 (11)	1 (4)	4 (15)
AMITRIPTYLINE (n=26)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Dry mouth	0 (0)	8 (31)	2 (8)	10 (38)
Drowsiness in the morning	3 (11)	7 (27)	3 (11)	10 (38)
Vivid dreams	2 (8)	4 (15)	4 (15)	8 (31)
Difficulty waking up	3 (11)	4 (15)	2 (8)	6 (23)
Restless sleep	1 (4)	2 (8)	4 (15)	6 (23)
Weight gain	1 (4)	2 (8)	2 (8)	4 (15)
Headache	2 (8)	2 (8)	1 (4)	3 (11)
Drowsiness in the afternoon	6 (23)	2 (8)	0 (0)	2 (8)
Blurred vision	1 (4)	2 (8)	0 (0)	2 (8)
Constipation	0 (0)	0 (0)	2 (8)	2 (8)

n(%) Frequency with the percentage of the total; SEs Side-effects; Total SEs are calculated from moderate (summary of moderate and severe).

Table 6. Top 10 side effects (SEs) in week 12 scored as mild, moderate, severe and total for placebo, mirtazapine and amitriptyline in n(%)

PLACEBO (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Restless sleep	0 (0)	5 (18)	4 (15)	9 (33)
Drowsiness in the afternoon	2(7)	4 (15)	1 (4)	5 (18)
Headache	0 (0)	5 (28)	0 (0)	5 (18)
Dry mouth	0 (0)	3 (11)	1 (4)	4 (15)
Appetite increase	2(7)	3 (11)	1 (4)	4 (15)
Drowsiness in the morning	3 (11)	1 (4)	2(7)	3 (11)
Orthostatic hypotension	3 (11)	3 (11)	0 (0)	3 (11)
Yawning	4 (15)	2(7)	1 (4)	3 (11)
Weight gain	2(7)	2(7)	1 (4)	3 (11)
Difficulty waking up	4 (15)	2(7)	0 (0)	2(7)
MIRTAZAPINE (n=27)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Difficulty of waking up	2 (7)	4 (15)	4 (15)	8 (30)
Vivid dreams	4 (15)	4 (15)	4 (15)	8 (30)
Appetite increase	1 (4)	4 (15)	2 (7)	6 (22)
Weight gain	5 (18)	5 (18)	1 (4)	6 (22)
Drowsiness in the morning	3 (11)	3 (11)	2 (7)	5 (18)
Drowsiness in the afternoon	1 (4)	4 (15)	1 (4)	5 (18)
Restless sleep	2 (7)	3 (11)	2 (7)	5 (18)
Constipation	0 (0)	4 (15)	1 (4)	4 (15)
Dry mouth	5 (18)	2 (7)	1 (4)	3 (11)
Palpitations	0 (0)	3 (11)	0 (0)	3 (11)
AMITRIPTYLINE (n=26)				
SEs	**Mild**	**Moderate**	**Severe**	**Total**
Restless sleep	1 (4)	7 (30)	4 (15)	11 (42)
Vivid dreams	2 (8)	6 (23)	5 (19)	11 (42)
Dry mouth	2 (8)	5 (19)	2 (8)	7 (30)
Drowsiness in the morning	6 (23)	4 (15)	2 (8)	6 (23)
Headache	0 (0)	2 (8)	4 (15)	6 (23)
Difficulty waking up	6 (23)	4 (15)	0 (0)	4 (15)
Drowsiness in the afternoon	3 (11)	2 (8)	2 (8)	4 (15)
Yawning	1 (4)	4 (15)	0 (0)	4 (15)
Weight gain	2 (8)	3 (11)	1 (4)	4 (15)
Sweating	0 (0)	2 (8)	1 (4)	3 (11)

n(%) Frequency with the percentage of the total; SEs Side-effects; Total SEs are calculated from moderate (summary of moderate and severe).