Received: 23 June 2022 | Revised: 15 September 2022 | Accepted: 26 October 2022

DOI: 10.1002/pds.5561

WILEY

ORIGINAL ARTICLE

Off-label low dose amitriptyline for insomnia disorder: Patient-reported outcomes

Mette H. Bakker[1,2] | Jacqueline G. Hugtenburg[2,3] | Marcel G. Smits[4] | Henriëtte E. van der Horst[1,2] | Pauline Slottje[1,2]

[1]Department of General Practice, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

[2]Research programme Quality of Care, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

[3]Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

[4]Multidisciplinary Expertise Centre for Sleep-Wake Disorders and Chronobiology, Gelderse Vallei Hospital, Ede, Netherlands

Correspondence
Mette H. Bakker, Department of General Practice, Location VUmc, Van der Boechorststraat 7, Room MF C-378 1081 BT, Amsterdam, The Netherlands.
Email: mh.bakker@amsterdamumc.nl

Abstract

Purpose: Low dose amitriptyline is prescribed off-label to improve sleep maintenance in patients with insomnia disorder. Data on treatment outcomes are limited. We aimed to assess patient-reported treatment effect and side effects of low dose amitriptyline for insomnia in routine care data.

Methods: Cross-sectional study: Seven hundred fifty-two consecutive patients with insomnia disorder having sleep maintenance problems were treated in an outpatient sleep clinic with low dose amitriptyline (10–20 mg based on self-titration). Treatment was intended to improve sleep maintenance. Before the planned follow-up consultation (approximately 6 weeks after start treatment) patients completed an online treatment evaluation questionnaire. Treatment (dose, adherence), sleep, fatigue, satisfaction and side effects were assessed by multiple-choice questions with room for free-text elaboration.

Results: 53.7% of the patients reported to use amitriptyline up to 10 mg/day, 42.9% used a self-increased dose of mostly 20 mg/day, while 3.5% had discontinued treatment. 73.9% of the total study population reported improvement of sleep maintenance, 31.3% improved sleep onset, 35.2% improved daytime fatigue, and 45.8% reported to be (very) satisfied with treatment results. 66.1% reported at least one side effect. The reported side effects were generally the already known side effects of amitriptyline.

Conclusion: These patient-reported outcomes support the clinical observations that low dose amitriptyline improves sleep maintenance on the short term and that it is generally well tolerated. This further justifies randomized controlled trials in patients with insomnia disorder and sleep maintenance problems to assess the effectiveness and safety of low dose amitriptyline on the short and long term.

KEYWORDS
insomnia disorder, low dose amitriptyline, off-label treatment, patient-reported outcomes, sleep maintenance

Key Points

- Low dose amitriptyline is prescribed off-label to treat insomnia disorder; data on treatment outcomes are limited.
- Routine care data of 752 consecutive patients with insomnia disorder treated with low dose amitriptyline (10–20 mg/day based on self-titration) can give insight in patient-reported treatment effect and side effects.
- This study shows that the majority of patients reported improvement in sleep maintenance during treatment and that treatment was generally well tolerated.
- Randomized placebo-controlled trials are needed to assess the effectiveness of low dose amitriptyline in patients with insomnia disorder both on the short and long term.

Plain Language Summary

Physicians regularly prescribe the antidepressant amitriptyline in low doses to patients with sleeping problems to improve sleeping trough. However, it is not licenced as sleep medication and there is insufficient scientific evidence that it is effective. In this study, we aim to describe how patients with insomnia disorder with sleep maintenance problems evaluate this treatment. We assessed the answers of an online treatment evaluation questionnaire of 752 subsequent patients who were treated with low dose amitriptyline (dosage 10–20 mg/day, self-adjustable by the patients after 3 weeks) in an outpatient Sleep Clinic. At the time of questionnaire (around 6 weeks) roughly half of the patients reported to use single dose and half of the patients reported to use double dose, while less than 5% had stopped taking amitriptyline. The majority (74%) of the patients reported that sleeping trough had improved. Improvement in falling asleep, daytime fatigue and treatment satisfaction were less often reported. Known side effects of amitriptyline were reported by two third of the patients. Patient experiences with amitriptyline are thus mainly positive on sleeping trough on the short term. Trials are needed to scientifically proof its effectiveness on both the short and long term.

1 | INTRODUCTION

Insomnia disorder is characterized by persisting difficulties with initiating or maintaining sleep leading to a significant impairment in daytime functioning.[1] It affects about 6% of the population[2] and is associated with chronic physical and mental health problems, reduced work performance and higher absenteeism.[3,4]

Insomnia disorder guidelines recommend non-pharmacological treatments such as cognitive behavioral therapy for insomnia (CBT-I) as first choice treatment.[5–8] However, CBT-I is not available, suitable or sufficient for all patients[6,9,10] and (concomitant) sleep medication is often requested. Benzodiazepine receptor agonist (BZRA) sleep medication, however, has serious disadvantages including the rapid development of tolerance and dependence.[8,11]

For decades the tricyclic antidepressant amitriptyline is prescribed in low dose (i.e., dosages lower than needed to treat major depression) to treat insomnia disorder, although it is not licensed for this indication.[12–14] This off-label prescription practice is probably based on the fact that clinicians are experienced with amitriptyline and its sedative effects in patients with major depression[15] and (neuropathic) pain.[16] Furthermore, amitriptyline is generic and thus relatively cheap and that its side effects in low dose are presumed to be mild.[17] Current knowledge on its pharmacological mechanism of action; that is, in low dose it antagonizes awakening mediated by histamine H1-receptors in the central nervous system,[18,19] supports the clinical observations of potential improvement in sleep maintenance. Based on consensus recommendations, some international guidelines mention amitriptyline or other sedating antidepressants as alternative short-term treatment, when insomnia is accompanied with depression or when other treatments have failed.[5,8]

However, off-label prescription exposes patients to risks without evidence of the benefit[13] and placebo-controlled trials on the effectiveness of low dose amitriptyline in treating insomnia disorder have not yet been published.[20] Given this paucity in evidence, analysis of routine care data will shed light on patient-reported treatment effect and side effects of low dose amitriptyline in patients with insomnia disorder and will help to answer the question whether further controlled trials with low-dose amitriptyline for insomnia disorder indeed are worth doing.

We aimed (a) to assess the proportion of patients with insomnia disorder and sleep maintenance problems treated with low dose amitriptyline that reported sleep maintenance improvement on the short term (intended treatment effect), (b) to assess the proportion of

patients reporting improvement in sleep onset, improvement in daytime fatigue, satisfaction with treatment and the occurrence of side effects; (c) to explore the nature of self-reported side effects of low dose amitriptyline in insomnia disorder patients in relation to the known side effects of amitriptyline and (d) to explore patient's dose preferences.

2 | METHODS

2.1 | Design

Cross-sectional study: descriptive analysis of patient reported outcomes routinely collected in clinical practice (single center).

2.2 | Study population

The target population consisted of adult patients referred to secondary care for insomnia disorder and sleep maintenance problems who were treated with low dose amitriptyline. Between October 2013 and January 2019, patients referred the outpatient Sleep Clinic of a General Hospital in the center of the Netherlands, and who were diagnosed with insomnia disorder and sleep maintenance problems, were offered insomnia treatment options including CBT-I (waiting list), an appointment by a clinical nurse, or pharmaceutical treatment. Our study population consisted of all consecutive adult patients who opted for treatment with low dose amitriptyline and who started this treatment. Diagnosis of insomnia disorder was based on the DSM-IV-TR[21] and DSM-5 criteria.[1] Sleep maintenance problems were defined as difficulties with maintaining sleep and/or an early-morning awakening problem based on clinical interviewing. Patients were excluded from our analysis in case of age below 18 years, missing age, and when they reported that they had not started amitriptyline after prescription.

2.3 | Study procedures

Treatment consisted of amitriptyline (10–20 mg) for 16 weeks; starting with one tablet of 10 mg per day before going to bed and after 3 weeks the possibility to double the dose to 20 mg/day and return to 10 mg/day based on perceived effect and side effects ('self-titration'). A follow-up consultation at the Sleep Clinic was usually planned after about 6 weeks of treatment, but patients could come earlier if they wished so. A few days before this follow-up consultation, patients filled out an online treatment evaluation questionnaire. In case of an incomplete questionnaire, patients were reminded to complete it at the Sleep Clinic. This non-validated treatment evaluation questionnaire was developed at the Sleep Clinic to help to guide the follow-up of pharmacological treatment of insomnia disorder patients and included multiple-choice questions and room for free-text elaboration. For the purpose of this analysis relevant multiple-choice questions pertaining to amitriptyline treatment evaluation were selected (Appendix), covering patient and treatment characteristics (age, time of questionnaire, dose, adherence), and patient reported outcomes (sleep maintenance, sleep onset, daytime fatigue treatment satisfaction and side effects).

Patients were offered an opt-out *in* the treatment evaluation questionnaire by answering the question "I give permission to use the anonymized answers to this questionnaire for scientific research purposes; Yes/No". None of the patients chose to opt-out. If a patient had submitted more than one online questionnaire, only the questionnaire completed nearest to 6 weeks since planned start treatment, was included.

2.4 | Patient reported outcome measures

All variables were derived from the questionnaire. The English translation of original wording (Dutch) and categorization of outcome variables can be found in Table A1.

2.4.1 | Patient and treatment characteristics

Based on self-reported dose at the time of the questionnaire, patients were categorized into three groups; those taking a dose up to the starting dose of 10 mg/day, those who had increased the dose (all dosages above 10 mg/day), and patients who had discontinued treatment (i.e., reporting discontinuation in the free text field). Age at completion of questionnaire was calculated. The use of co-medication was derived from the free text field answers to the question 'Which medication are you currently taking other than amitriptyline?' and categorized by the first author (MHB) into Sleep medication (BZRAs and/or melatonin), Psychotropics (i.e., anxiolytics, antidepressants, antipsychotics, anticonvulsants and stimulants) and Other co-medication (e.g., cardiovascular medication, contraceptive medication and including <3% of the cases in which the patient referred to 'co-medication already known to the physician'). Daily intake (yes versus no) was based on the question 'Are you taking amitriptyline every day?'. Patients were categorized into four groups based on the timing of the completion of the questionnaire relative to the treatment start date: those who completed the questionnaire between >4–8 weeks after starting the medication, those who completed it earlier (>0–4 weeks), later (>8–16 weeks), or with unknown timing since start treatment because of missing 'start treatment date' (unknown).

2.4.2 | Patient reported outcomes

The outcome variables sleep maintenance, sleep onset and daytime fatigue were assessed by multiple-choice questions. Patients were asked to choose the best fitting answering option out of five to eight answering options. Answering options were categorized into Improvement, No change, Worsened and Other (Table A1). Any missings were

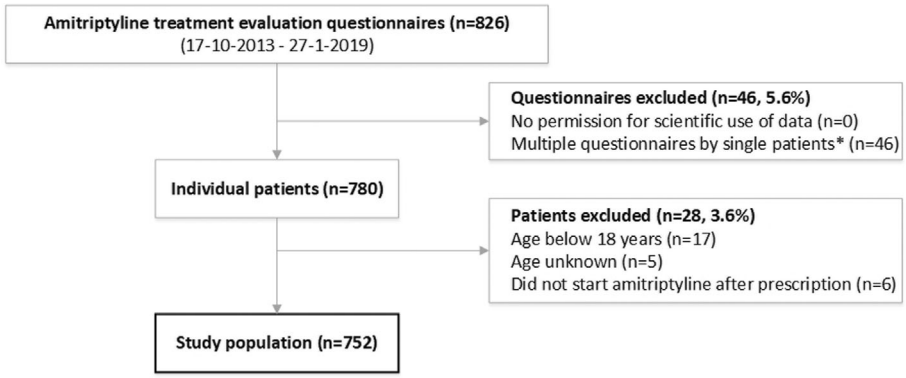

FIGURE 1 Flow of the patient and questionnaire selection process. Asterisk indicate: per patient only one questionnaire was included, that is, the one nearest to the scheduled follow-up consultation at approximately 6 weeks since start treatment

reported as Unknown. Sleep maintenance (outcome of main interest) was based on the question 'Did sleep maintenance change since you started taking amitriptyline?'. Improvement compromised both 'Yes, I wake up less frequently during the night' and 'I fall asleep more quickly upon nightly awakening'. Treatment satisfaction was defined based on the question: 'Are you satisfied with the results of the amitriptyline treatment?' using a 5 point Likert scale (i.e., very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied).

Side effects were measured by means of the question 'Which health complaints occurred that according to you could be the consequence of amitriptyline?' followed by a checklist from which multiple answers could be selected, if applicable: No side effects, Headache, Restless sleep, Vivid dreams and Dry mouth, and 'Other side effects that is, (free text)'. The occurrence of side effects was defined as the report of at least one side effect, either on the checklist or in the free text field. Free text elaborations were classified by the first author (MHB) according to the preferred Medical Dictionary for Regulatory Activities (MedDRA) term as used in the summary of product characteristics (SPC) of Amitriptyline.[17] Any doubts were discussed with the other authors until consensus was reached. The nature of a self-reported side effect not mentioned in the SPC was only reported when mentioned by more than one patient of the 752 (>0.13%).

2.5 | Statistical analysis

Descriptive statistics in the total study population were analyzed. Exploratory subgroup analyses were performed for all variables according to (self-titrated) dose group and for the outcome of primary interest (sleep maintenance) according to the timing of the questionnaire since start treatment using SPSS 26.0.

3 | RESULTS

Figure 1 presents a flowchart of the patient and questionnaire selection process. Seven hundred fifty-two patients with insomnia disorder treated with low dose amitriptyline were included in our study population. All consecutive patients completed their questionnaires.

3.1 | Patient and treatment characteristics and co-medication

Table 1 presents patient and treatment characteristics and patient-reported outcomes. Missings (categorized as Unknown) were <5%. At the time of questionnaire that is, a few days before the scheduled treatment follow-up consultation, 53.7% of the patients reported to use amitriptyline up to 10 mg/day (range 5–10 mg/day), 42.9% used an self-increased dose of mostly 20 mg/day (range 15–50 mg/day), while 3.5% reported to have stopped taking amitriptyline. 92.2% of the total study population reported daily intake. Of the study population, 15.5% reported to use other sleep medication (BZRA and/or melatonin), 1.6% anxiolytics and 4.8% other antidepressants. 67.8% had completed the questionnaire between 4 and 8 weeks after start treatment, 11.0% earlier than 4 weeks, 17.2% later than 8 weeks and for 4.0% the timing of questionnaire was unknown.

3.2 | Patient-reported outcomes

As shown in Table 1 556 (73.9%) patients reported improved sleep maintenance, while worsening was reported by less than 1% of the patients. 361 (48.0%) patients reported that this improvement mainly consisted of 'waking up less frequently during the night' and 195 (25.9%) reported that this improvement mainly consisted of 'falling asleep more quickly upon nightly awakening'. Improved sleep onset was reported by 31.3% and worsening by 7.7%. Daytime fatigue improved in 35.2% of the patients and worsened in 6.4%. Almost half (45.8%) of the patients reported to be (very) satisfied with the treatment result at that time, whereas 23.3% were (very) dissatisfied.

3.3 | Nature and frequency of patient-reported side effects

About two third of the patients reported at least one side effect (66.1%). An overview of the nature and frequency of the reported side effects is listed in Table 2. The pre-defined check list items Dry mouth during the day, Vivid dreams, Headache and Restless sleep were reported by 29.0%, 18.1%, 7.8%, and 6.3% of the total study

TABLE 1 Self-reported patient and treatment characteristics and patient reported outcomes in the total study population and by dosage group

	Total study population *N* = 752	Amitriptyline 10 mg/day *N* = 404 (53.7%)	Amitriptyline 20 mg/day *N* = 322 (42.8%)	Discontinued treatment *N* = 26 (3.5%)
Patient characteristics				
Age				
Mean (SD)	49.7 (SD 13.3)	49.6 (SD 13.1)	49.8 (SD 13.6)	49.5 (SD 11.8)
18–25 years	44 (5.9%)	23 (5.7%)	21 (6.5%)	0 (0.0%)
26–40 years	126 (16.8%)	68 (16.8%)	53 (16.5%)	5 (19.2%)
41–65 years	499 (66.4%)	269 (66.6%)	211 (65.5%)	19 (73.1%)
>65 years	83 (11.0%)	44 (10.9%)	37 (11.5%)	2 (7.7%)
Co-medication				
Other sleep medication	117 (15.5%)	55 (13.6%)	58 (18.0%)	4 (15.4%)
BZRA(s)	58 (7.7%)	23 (5.7%)	34 (10.6%)	1 (3.8%)
Melatonin	56 (7.4%)	31 (7.7%)	22 (6.8%)	3 (11.5%)
BZRA(s) and melatonin	3 (0.4%)	1 (0.2%)	2 (0.6%)	0 (0.0%)
Psychotropics (excl. sleep medication)	82 (10.9%)	41 (10.1%)	37 (11.5%)	4 (15.4%)
Other co-medication	288 (38.3%)	149 (36.9%)	131 (40.7%)	8 (30.8%)
Treatment characteristics				
Dosage				
5 mg/day	19 (2.5%)	19 (4.7%)	n.a.	n.a.
10 mg/day	385 (51.2%)	385 (95.3%)	n.a.	n.a.
15 mg/day	3 (0.4%)	n.a.	3 (0.9%)	n.a.
20 mg/day	311 (41.4%)	n.a.	311 (96.6%)	n.a.
25–50 mg/day	8 (1.1%)	n.a.	8 (2.5%)	n.a.
Not on treatment anymore	26 (3.5%)	n.a.	n.a.	26 (100%)
Daily intake (i.e., according to prescription)				
Yes	693 (92.2%)	370 (91.6%)	312 (96.9%)	n.a.
Timing of questionnaire (i.e., time since start treatment)				
>0 to 4 weeks	83 (11.0%)	52 (12.9%)	23 (7.1%)	8 (30.8%)
>4 up to 8 weeks	510 (67.8%)	279 (69.1%)	216 (67.1%)	15 (57.7%)
>8 weeks up to 16 weeks	129 (17.2%)	56 (13.9%)	72 (22.4%)	1 (3.8%)
Unknown	30 (4.0%)	17 (4.2%)	11 (3.4%)	2 (7.7%)
Patient reported outcomes				
Sleep maintenance				
Improved	556 (73.9%)	312 (77.2%)	238 (73.9%)	6 (23.1%)
No change	148 (19.7%)	65 (16.1%)	68 (21.1%)	15 (57.7%)
Worsened	7 (0.9%)	5 (1.2%)	2 (0.6%)	0 (0.0%)
Other	41 (5.5%)	22 (5.4%)	14 (4.3%)	5 (19.2%)
Sleep onset				
Improved	235 (31.3%)	134 (33.2%)	99 (30.7%)	2 (7.7%)
No change	459 (61.0%)	239 (59.2%)	200 (62.1%)	20 (76.9%)
Worsened	58 (7.7%)	31 (7.7%)	23 (7.1%)	4 (15.4%)
Daytime fatigue				
Improved	265 (35.2%)	152 (37.6%)	111 (34.5%)	2 (7.7%)
No change	371 (49.3%)	185 (45.8%)	173 (53.7%)	13 (50.0%)
Worsened	48 (6.4%)	28 (6.9%)	15 (4.7%)	5 (19.2%)
Other	67 (8.9%)	39 (9.7%)	23 (7.1%)	5 (19.2%)
Unknown	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (3.8%)

(Continues)

TABLE 1 (Continued)

	Total study population $N = 752$	Amitriptyline 10 mg/day $N = 404$ (53.7%)	Amitriptyline 20 mg/day $N = 322$ (42.8%)	Discontinued treatment $N = 26$ (3.5%)
Treatment satisfaction				
Very satisfied	65 (8.6%)	44 (10.9%)	21 (6.5%)	0 (0.0%)
Satisfied	280 (37.2%)	168 (41.6%)	112 (34.8%)	0 (0.0%)
Neither satisfied, nor dissatisfied	232 (30.9%)	116 (28.7%)	115 (35.7%)	1 (3.8%)
Dissatisfied	140 (18.6%)	56 (13.9%)	69 (21.4%)	15 (57.7%)
Very dissatisfied	35 (4.7%)	20 (5.0%)	5 (1.6%)	10 (38.5%)
Side effects				
Any side effect reported	497 (66.1%)	286 (70.8%)	189 (58.7%)	22 (84.6%)

Note: Dosage groups are based on self-titration; self-reported dosages of 10 mg/day and lower were categorized as 10 mg/day, increased dosages above 10 mg/day were categorized as 20 mg/day.

population, respectively. Further, 28.7% reported one or more 'Other side effects' in free text. The most frequently reported 'Other side effects' (i.e., reported by at least 2% of the total study population) were Drowsiness (5.2%), Somnolence (3.9%), Dizziness (2.7%) and Fatigue (2.0%), which are all mentioned in the SPC of amitriptyline.[17] Depressed mood, Muscle pain and Increased appetite, were reported by more than one patient, yet these are not described as known side effects of amitriptyline in the SPC.[17]

3.4 | Exploratory subgroup analyses by dose and timing of completing the questionnaire

Table 1 shows the descriptive results by dosage group. 77.2% of patients in the 10 mg/day group and 73.9% in the 20 mg/day group reported improved sleep maintenance, respectively 33.2% and 30.7% reported improved sleep onset, and 37.6% and 34.5% reported improved daytime fatigue respectively. At least one side effect was reported by 70.8% of the patients who used 10 mg/day and 58.7% of the patients who used 20 mg/day. Of the patients using 10 mg/day and 20 mg/day 52.5% and 41.3% were satisfied with the treatment result during treatment, respectively.

As expected given the treatment (follow-up) plan, 67.8% of the patients completed the questionnaire between 4 and 8 weeks since start treatment. Of these ($N = 510$), 75.9% reported sleep maintenance improvement. Patients with an earlier ($N = 83$), later ($N = 129$) or unknown ($N = 30$) timing of completing the questionnaire, had sleep maintenance improvement rates of 66.3%, 72.1%, and 70.0% respectively.

Among those with an earlier timing ($N = 83$), 9.6% had discontinued treatment at the time of the questionnaire.

4 | DISCUSSION

The present routine care study shows that almost three quarters (73.9%) of patients with insomnia disorder and sleep maintenance problems reported improved sleep maintenance after about 6 weeks of low dose amitriptyline treatment (10–20 mg based on self-titration). About a third reported that sleep onset improved (30%), about a third that daytime fatigue improved (33%) and about half (45%) of the patients were (very) satisfied with treatment results at the time of the questionnaire. Only 3.5% had discontinued treatment at that time. A third of the patients (33%) reported that they experienced no side effects. The patient-reported side effects were generally of the type known to the use of amitriptyline. With respect to patient dose preferences, roughly half of the patients reported to use up to the starting dose of 10 mg/day, whereas approximately the other half reported to use a self-increased dose of mostly 20 mg/day.

To our knowledge, this study is the first to report patient-reported outcomes among a considerable number of patients with insomnia disorder treated off-label with low dose amitriptyline. However, as result of the convenience sampling in routine care some important limitations need to be considered in the interpretation of the results. First of all, our open study lacks a control group and therefore it cannot be ruled out that the reported improvements might be (partially) based on placebo effects and natural disease course. Our study population consists of 752 consecutive patients who started treatment and there were virtually no missing values. Therefore, the results are deemed to be representative of the target population of interest. However, secondly, it is unknown how many insomnia disorder patients in total were offered this treatment but opted for another treatment and for which reasons. Thirdly, the timing of the follow-up questionnaire and consultation varied between patients. This timing may have affected the reported outcomes, because sleep, daytime symptoms and side-effects may vary over time and might be a reason to advance or postpone the follow-up consultation. However, the majority of patients did complete the questionnaire in the period that was advised at the start of treatment, i.e. between 4–6 weeks. In addition, our exploratory subgroup analysis showed similar sleep maintenance improvement rates according to both an earlier and a later timing of the questionnaire during treatment. A possible explanation for this could be that most effects of amitriptyline are known to stabilize after two to 4 weeks.[17] Fourthly, the physician asked

TABLE 2 Self-reported side effects in the total study population

Which health complaints occurred that according to you could be the consequence of amitriptyline?	
Preferred MedDRA term	**Total study population *N* = 752**
Checklist items (original wording between brackets)	
Dry mouth (dry mouth during the day)	218 (29.0%)
Nightmares (vivid dreaming)	136 (18.1%)
Headache (headache)	59 (7.8%)
Insomnia (restless sleep)	47 (6.3%)
Other, namely (based on free text information)	
Drowsiness	39 (5.2%)
Somnolence	29 (3.9%)
Dizziness	20 (2.7%)
Fatigue	15 (2.0%)
Depressed mood[a]	13 (1.7%)
Constipation	9 (1.2%)
Disturbance in attention	8 (1.1%)
Palpitations	8 (1.1%)
Accommodation disorder	7 (0.9%)
Weight increased	7 (0.9%)
Epigastric distress	6 (0.8%)
Nausea	6 (0.8%)
Hyperhidrosis	5 (0.7%)
Muscle pain[a]	5 (0.7%)
Agitation	4 (0.5%)
Dysgeusia	4 (0.5%)
Increased appetite[a]	4 (0.5%)
Paraesthesia	4 (0.5%)
Tremors	4 (0.4%)
Dry eye	3 (0.4%)
Hallucinations	3 (0.4%)
Rash	3 (0.4%)
Anxiety	2 (0.3%)
Ataxia	2 (0.3%)
Confusional state	2 (0.3%)
Diarrhoea	2 (0.3%)
Libido decreased	2 (0.3%)
Pyrexia	2 (0.3%)
Tinnitus	2 (0.3%)
Tachycardia	2 (0.3%)
Aggression	1 (0.1%)
Arrhythmias	1 (0.1%)
Extrapyramidal disorder	1 (0.1%)
Feeling thirst	1 (0.1%)
Micturition disorders	1 (0.1%)
Pruritis	1 (0.1%)
Speech disorders (dysarthria)	1 (0.1%)
Stomatitis	1 (0.1%)

(Continues)

TABLE 2 (Continued)

[a]Not listed in the summary of product characteristics of amitriptyline and reported by >1 patient.

patients to fill out the questionnaire before and for the purpose of their treatment follow-up consultation. This motivated patients complete the questionnaire, yet it may also have affected their answering. They might have been inclined to please or influence their physician or treatment. Lastly, the questionnaire was not validated and data on the magnitude of the perceived changes and potentially relevant covariates such as the patients' sex, comorbidities, previous treatments for insomnia and sleep medication usage at the start of treatment were not available.

The vast majority of the target population of this treatment reported improvement on sleep maintenance (i.e., the intended treatment effect). However, improvement in sleep onset, daytime fatigue and treatment satisfaction were less often reported and a subgroup reported worsening of sleep onset (7.7%) and daytime fatigue (6.4%). For sleep onset, no data were available on whether or not patients had additional difficulty initiation sleep prior to the treatment. Therefore is yet to be established whether or not low dose amitriptyline positively affects sleep onset. For daytime fatigue, the lower improvement rate suggests that the self-reported improved sleep maintenance did not (yet) always improve the daytime aspects of insomnia disorder. Lastly, the limited satisfaction with treatment results at the time of questionnaire in about half of the patients might suggest that amitriptyline potentially is not sufficient effective in all patients. However, this variable should be interpreted with caution, because it is most likely based on more components than treatment effect and side effects (e.g. patient expectations, physician factors), and because of the timing of the questionnaire at approximately 6 weeks relative to the planned treatment duration of 16 weeks.

Although the study was not designed to investigate dose-effect relationships, we observed that about half of the patients did make use of the possibility to self-titrate amitriptyline dose. In both 10 and 20 mg/day groups, patient and treatment characteristics were similar and comparable sleep and daytime improvement rates were reported. Patients in the 20 mg/day group, however, reported somewhat lower rates of side effects and satisfaction with treatment results. Apparently, some patients did benefit from a higher dosage without an increase in side-effects, whereas there were also patients that were not satisfied with neither dosage. Differences in pharmacokinetics may underlie these differences.[17] Patients who discontinued treatment (3.5%) reported less favorable outcomes.

Results from randomized (placebo) controlled trials on low dose amitriptyline for insomnia disorder to put our findings in perspective

are not available. Data on other sedating antidepressants in patients with insomnia disorder are scarce.[20,22–26] Pharmacologically most comparable to amitriptyline is the tricyclic antidepressant doxepin, which is the only antidepressant licensed for the treatment of sleep maintenance problems in the USA.[25–27] In two placebo controlled industry funded trials on doxepin for elderly insomnia patient with sleep maintenance problems a Patient Global Impression scale (PGI)[28] assessing 'Increased sleep duration' was reported. In the treatment groups the proportion of patients reporting 'Yes' on this item was comparable to the proportion of patients reporting Sleep maintenance improvement in our study and was significantly higher than in the placebo groups; approximately 45% among patients using 6 mg doxepin for 4 weeks,[25] and 59 and 69% among patients using 1 and 3 mg doxepin for 12 weeks,[24] versus approximately 35% in the placebo groups ($p < 0.05$). This suggest that it is worthwhile to further investigate the effect of amitriptyline on sleep maintenance in a randomized placebo controlled study.

5 | CONCLUSION

All in all, our descriptive results support the clinical observations of potential improvement in sleep maintenance and treatment tolerability of low dose amitriptyline on the short term. In addition, it illustrates patient's dose preferences and the feasibility of self-titration in clinical practice during an intended treatment period of 16 weeks. However, rigorously conducted randomized placebo-controlled trials are needed to assess the effectiveness of low dose amitriptyline on sleep maintenance in patients with insomnia disorder both on the short and long term. Since the ultimate goal of treating patients with insomnia disorder is to lessen night-time suffering and to improve daytime functioning, future studies should investigate not only sleep maintenance and sleep onset, but also daytime functioning during and after treatment.

AUTHOR CONTRIBUTIONS

Marcel G. Smits conceived of the study and supervised data collection. Mette H. Bakker analysed the data and drafted the manuscript. All authors contributed to the manuscript from a multidisciplinary perspective and approved the final version.

CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AKNOWLEDGEMENTS

We would like to thank the patients and staff members from the outpatient Sleep Clinic for Sleep disorders and Chronobiology of the Hospital Gelderse Vallei in Ede who contributed or collected data.

ETHICS STATEMENT

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The local Research Committee had confirmed that this observational study, based on anonymized routine treatment monitoring data does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). Patients were offered an opt-out in the treatment evaluation questionnaire by answering the question "I give permission to use the anonymised answers to this questionnaire for scientific research purposes; Yes/No". The anonymised questionnaire data were analysed by the researchers at Amsterdam UMC who were not involved in patient treatment and had no access to the medical records of the patients.

ORCID

Mette H. Bakker https://orcid.org/0000-0003-0663-1981

REFERENCES

1. American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6(2):97-111. doi:10.1053/smrv.2002.0186
3. Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Med*. 2009;10(4):427-438. doi:10.1016/j.sleep.2008.04.005
4. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*. 2011;21(10):718-779. doi:10.1016/j.euroneuro.2011.08.008
5. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
6. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/m15-2175
7. Ree M, Junge M, Cunnington D. Australasian Sleep Association position statement regarding the use of psychological/behavioral treatments in the management of insomnia in adults. *Sleep Med*. 2017;36(Suppl 1):S43-S47. doi:10.1016/j.sleep.2017.03.017
8. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675-700. doi:10.1111/jsr.12594
9. Galbiati A, Sforza M, Fasiello E, Castronovo V, Ferini-Strambi L. Impact of phenotypic heterogeneity of insomnia on the Patients' response to cognitive-behavioral therapy for insomnia: current perspectives. *Nat Sci Sleep*. 2019;11:367-376. doi:10.2147/nss.S198812
10. Cortoos A, Verstraeten E, Cluydts R. Neurophysiological aspects of primary insomnia: implications for its treatment. *Sleep Med Rev*. 2006;10(4):255-266. doi:10.1016/j.smrv.2006.01.002
11. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ (Clin Res Ed)*. 2005;331(7526):1169. doi:10.1136/bmj.38623.768588.47
12. Everitt H, McDermott L, Leydon G, Yules H, Baldwin D, Little P. GPs' management strategies for patients with insomnia: a survey and qualitative interview study. *Br J General Pract*. 2014;64(619):e112-e119. doi:10.3399/bjgp14X677176
13. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic

prescribing system. *BMJ (Clin Res Ed)*. 2017;356:j603. doi:10.1136/bmj.j603
14. Lai LL, Tan MH, Lai YC. Prevalence and factors associated with off-label antidepressant prescriptions for insomnia. *Drug Healthc Patient Safety*. 2011;3:27-36. doi:10.2147/dhps.S21079
15. Wilson S, Nutt D. Management of insomnia: treatments and mechanismsi. *Br J Psychiatry*. 2007;191:195-197. doi:10.1192/bjp.bp.107.036301
16. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *J Neurol Neurosurg Psychiatry*. 2010;81(12):1372-1373. doi:10.1136/jnnp.2008.144964
17. ElectronicMedicinesCompendium. Amitriptyline 10 mg Tablet BP—Summary of Product Characteristics (SPC)—(eMC). Updated 26-03-2021. Accessed June 03, 2021, https://www.medicines.org.uk/emc/product/5698/smpc#DOCREVISION
18. Krystal AD, Richelson E, Roth T. Review of the histamine system and the clinical effects of H1 antagonists: basis for a new model for understanding the effects of insomnia medications. *Sleep Med Rev*. 2013;17(4):263-272. doi:10.1016/j.smrv.2012.08.001
19. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Hum Psychopharmacol*. 2005;20(8):533-559. doi:10.1002/hup.726
20. Everitt H, Baldwin DS, Stuart B, et al. Antidepressants for insomnia in adults. *Cochrane Database Syst Rev*. 2018;5(5):Cd010753. doi:10.1002/14651858.CD010753.pub2
21. Association AP, ed. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. 4th ed. Association AP; 2000 (text revision ed.).
22. Ivgy-May N, Roth T, Ruwe F, Walsh J. Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a 2-week randomized outpatient trial. *Sleep Med*. 2015;16(7):831-837. doi:10.1016/j.sleep.2015.03.005
23. Savarese M, Carnicelli M, Cardinali V, Mogavero MP, Federico F. Subjective hypnotic efficacy of trazodone and mirtazapine in patients with chronic insomnia: a retrospective, comparative study. *Arch Ital Biol*. 2015;153(2–3):231-238. doi:10.12871/0003982920152348
24. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *Sleep*. 2010;33(11):1553-1561. doi:10.1093/sleep/33.11.1553
25. Lankford A, Rogowski R, Essink B, Ludington E, Heith Durrence H, Roth T. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. *Sleep Med*. 2012;13(2):133-138. doi:10.1016/j.sleep.2011.09.006
26. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep*. 2011;34(10):1433-1442. doi:10.5665/sleep.1294
27. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry*. 2008;69(10):1557-1564. doi:10.4088/jcp.v69n1005
28. Food and Drug Administration. Methods to identify what is important to patients & select, develop or modify fit-for-purpose clinical outcomes assessments. Meeting material Attachment to Discussion Document for Patient-Focused Drug 2 Development Public Workshop on Guidance 3 Workshop Date 15/16-10-2018. 2019. Accessed June 03, 2021, https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select.

How to cite this article: Bakker MH, Hugtenburg JG, Smits MG, van der Horst HE, Slottje P. Off-label low dose amitriptyline for insomnia disorder: Patient-reported outcomes. *Pharmacoepidemiol Drug Saf*. 2022;1-11. doi:10.1002/pds.5561

APPENDIX A

TABLE A1 Online amitriptyline treatment evaluation questionnaire, English translation of original wording (Dutch) and categorisation of outcome variables [between brackets]

Date of questionnaire administration (electronically logged)
Date of birth (DDMMYYYY)
Which dose amitriptyline do you use? Choose one of the following answers
10 mg
20 mg
30 mg
Other, namely:
When did you start taking amitriptyline? (Date picker)
Are you taking amitriptyline every day?
Yes
No
Are you satisfied with the results of the amitriptyline treatment? Choose one of the following answers
Yes, very satisfied
Yes satisfied
Neither satisfied, nor dissatisfied
Dissatisfied
Very dissatisfied
Did you, since you started taking amitriptyline, experience an improved sleep onset? Choose one of the following answers
Yes, 5–10 min earlier [Improved]
Yes, 30–60 min earlier [Improved]
Yes, 1–1½ h earlier [Improved]
Yes, 1½–2 h earlier [Improved]
Yes, more than 2 h earlier [Improved]
No, the moment of sleep onset has not changed [No change]
No, generally I fell asleep 1–30 min later [Worsened]
No, generally I fell asleep more than 30 min later [Worsened]
Did sleep maintenance change since you started taking amitriptyline? Choose one of the following answers
No, sleep maintenance has not changed [No change]
Yes, I wake up less frequently during the night [Improved]
I fall asleep more quickly upon nightly awakening [Improved]
I wake up more frequently [Worsened]
Other, namely [Other]
Did daytime fatigue change since you started taking amitriptyline? Choose one of the following answers
I am less tired during the day [Improved]
I am more tired during the day [Worsened]
I was not tired during the day and this hasn't changed [No change]
I remain somewhat tired during the day [No change]
I remain very tired during the day [No change]
Other, namely [Other]
Which health complaints occurred that according to you could be the consequence of amitriptyline? Select if applicable
No side effects
Headache
Restless sleep
Vivid dreams
Dry mouth during the day
Other, namely

TABLE A1 (Continued)

Which medication are you currently taking other than amitriptyline? (free text)?
I give permission to use the anonymized answers to this questionnaire for scientific research purposes
Yes
No