mhc MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Trazodone versus doxepin as a pharmacologic sleep aid in psychiatric inpatients: A retrospective cohort study

Kevin Chen, PharmD[1,2]
Megan Maroney, PharmD, BCPP[1,2]

How to cite: Chen K, Maroney M. Trazodone versus doxepin as a pharmacologic sleep aid in psychiatric inpatients: a retrospective cohort study. Ment Health Clin [Internet]. 2025;15(2):51-5. DOI: 10.9740/mhc.2025.04.051.

Submitted for Publication: August 13, 2024; **Accepted for Publication:** January 3, 2025

Abstract

Introduction: Trazodone and doxepin are non–habit-forming options often used to treat insomnia in the psychiatric inpatient population. At our institution, trazodone 50 mg is the suggested initial treatment for insomnia included in the admission order set. The objective of this study was to determine if doxepin 25 mg is an effective alternative to trazodone 100 mg after the patient has failed treatment with trazodone 50 mg.

Methods: This retrospective cohort study included voluntary adult inpatients admitted to an academic medical center between July 2020 and June 2022 who received trazodone 100 mg or doxepin 25 mg after treatment failure with trazodone 50 mg for insomnia. The primary endpoint was treatment failure due to poor efficacy or tolerability. Secondary endpoints included changes in subjective sleep quality, subjective total sleep time, and estimates of objective total sleep time, time to sleep onset, wakefulness after sleep onset, and nighttime awakenings.

Results: A total of 122 patients were included in the analysis. Treatment failure was noted in 35.2% of trazodone patients and 41.2% of doxepin patients ($P = 0.58$). There were no statistically significant differences in the secondary endpoints.

Discussion: After treatment failure with trazodone 50 mg, there was no statistically significant difference in efficacy or tolerability between trazodone 100 mg and doxepin 25 mg for insomnia. A prospective trial would be necessary to directly compare the 2 treatment options.

Keywords: trazodone, doxepin, insomnia, psychiatric inpatient

[1] (Corresponding author) Psychiatric Pharmacy Resident, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey, kc970@scarletmail.rutgers.edu, ORCID: https://orcid.org/0000-0002-5262-0602; [2] Clinical Associate Professor, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey; Clinical Psychiatric Pharmacist, RWJ Barnabas Health Monmouth Medical Center, Long Branch, New Jersey, ORCID: https://orcid.org/0000-0002-2718-6787

Disclosures: MM reports advisory boards: Boehringer Ingelheim, Bristol Myers Squibb; consulting fees: Novus Medical Education; honoraria/lecture fees: American Association of Psychiatric Pharmacists, American Journal of Managed Care, Elsevier, Medical Logix, New Jersey Society of Health Systems Pharmacists, Pharmacy Times Continuing Education. KC has no conflicts of interest to disclose.

Introduction

Insomnia is one of the most common complaints among patients with psychiatric disorders, and patients admitted to inpatient psychiatric units frequently complain of insomnia.[1-4] Comorbid insomnia in patients with psychiatric illness has been shown to negatively impact treatment response and exacerbate symptoms related to comorbid conditions.[1,4,5] Despite its prevalence and impact, there is limited research on the treatment of insomnia in the mixed psychiatric inpatient population.[6] Per clinical practice guidelines, the first-line approach includes nonpharmacologic strategies such as cognitive behavioral therapy for

insomnia.[7-10] However, these approaches require resources, which are often inaccessible and may not be suitable for acutely ill patients in the hospital setting. As such, pharmacological sleep aids are often used instead, though such medication options are limited and not recommended for long-term use.[7-10] Current pharmacotherapy options for insomnia that are approved by the FDA include benzodiazepines, barbiturates, non-benzodiazepine hypnotics ("Z-hypnotics"), dual-orexin receptor antagonists, ramelteon, sedating antihistamines (diphenhydramine, doxylamine), and very low-dose doxepin (3-6 mg). The majority of these options are either habit-forming, costly, or have significant side-effect profiles, so many facilities use off-label sleep aids such as trazodone or low-dose doxepin (10-25 mg).[11]

Trazodone is a sedating antidepressant with a proposed mechanism to improve sleep through antagonism of the 5-HT2 serotonin receptors.[12,13] It is one of the most frequently used sleep aids in the inpatient psychiatric setting because of its lack of risk for dependence, low cost, and relative safety.[14] Despite how common its use is, the literature regarding the efficacy of trazodone for insomnia is conflicting. A Cochrane review on the use of trazodone for insomnia found an improvement in subjective sleep outcomes and sleep efficiency, though the evidence was only of very low to moderate quality.[11] Most of the current insomnia treatment guidelines focus on the management of chronic insomnia and do not recommend trazodone for long-term use.[7,8] The guidelines that comment on the short-term treatment of insomnia state that sedating antidepressants such as trazodone may be effective, especially in the case of comorbid mood disorders.[9,10]

Doxepin is another sedating antidepressant with antihistaminic properties that is often used as an alternative to trazodone because of a similar low risk of misuse and safe side-effect profile.[14] It is a tricyclic antidepressant that is primarily studied for insomnia at doses of 3 or 6 mg per day, where it has been shown to improve subjective sleep quality, total sleep time (TST), sleep efficiency, and wakefulness after sleep onset, with safety profiles comparable to placebo.[15-17] Current insomnia treatment guidelines generally recommend these doses of doxepin for treatment of either acute or chronic insomnia over no treatment.[7-9] However, owing to cost concerns, many institutions do not carry these doses of doxepin on formulary; rather, higher doses of 10 or 25 mg are often used. While higher doses are not as well studied for insomnia, they appear to be comparably safe to the FDA-approved doses, with 1 study demonstrating a similar incidence of treatment-emergent adverse events with 6 and 50 mg.[18]

This study aimed to evaluate the efficacy and tolerability of trazodone 100 mg versus doxepin 25 mg for psychiatric inpatients who, after initial failure with the commonly ordered trazodone 50 mg, require a change in medication.

Materials and Methods

Study Design

This institutional review board–approved retrospective cohort study was conducted on the voluntary psychiatric inpatient unit of an academic medical center. Patients were eligible for inclusion if they were at least 18 years of age and admitted to the study site's adult voluntary psychiatric unit between July 2020 and June 2022. Subjects received at least 1 dose of trazodone 50 mg as needed for sleep (as documented in the medication administration record), followed by the use of either trazodone 100 mg or doxepin 25 mg as needed for sleep on a subsequent night of the admission. Patients treated with trazodone 100 mg were designated as the trazodone group, and patients treated with doxepin 25 mg were designated as the doxepin group.

Exclusion criteria included an active prescription for either trazodone or doxepin before admission, as evidenced by admission medication reconciliation documentation, which was a combination of outside sources and patient reports. Patients were also excluded if they returned to their treatment group after switching to an alternative treatment (eg, if a patient in the doxepin group switched to a different sleep aid but then switched back to doxepin 25 mg, they would be excluded). If patients had multiple admissions that fit the criteria, only the most recent admission was included in the analysis.

Additional data collected included other sleep aids used before admission (eg, melatonin, benzodiazepines) and concomitantly administered inpatient medications with the potential to cause sedation. These data were obtained from the admission medication reconciliation documentation and the medication administration record respectively.

Endpoints

The primary endpoint was treatment failure of trazodone 100 mg or doxepin 25 mg, which was defined as (1) a dose increase, indicating poor efficacy, (2) a dose decrease, indicating poor tolerability, (3) a change to an alternative medication, indicating either poor efficacy or tolerability, or (4) discontinuation, similarly indicating either poor efficacy or tolerability. Discontinuation of the sleep aid at discharge would only be considered a treatment failure if the patient reported subjectively poor sleep the night before discharge, which was documented daily by nursing staff. The reason for treatment failure was determined using clinician progress notes, which specified whether the dose adjustment or change in sleep aid was due to poor efficacy or poor medication tolerance.

TABLE 1: Secondary endpoint definitions

Endpoint	Definition	Documentation
Subjective sleep quality	The proportion of nights in which the patient reported a good sleep pattern	Documented daily by nursing staff in nursing flowsheet using structured phrases such as "restful" or "quiet with easy respirations"
Subjective total sleep time	The number of hours slept as reported by the patient	Documented daily by nursing staff in nursing flowsheet
Estimated objective total sleep time	The number of hours the patient's current activity was recorded as "eyes closed, lying down" after taking the sleep aid	Patient current activity was documented through visual observation of patients every 15 minutes by mental health associates as part of their safety check documentation
Estimated time to sleep onset	The number of minutes between the patient taking the sleep aid as per the medication administration record and the time the patient fell asleep[a]	Medication administration was documented in medication administration record Patient current activity documented using same method as "estimated objective total sleep time"
Wakefulness after sleep onset	The number of minutes in which the patient's current activity of "eyes closed, lying down" was interrupted by another activity after initially falling asleep[a]	Patient current activity documented using same method as "estimated objective total sleep time"
Nighttime awakenings	The number of times the patient's current activity of "eyes closed, lying down" was interrupted after initially falling asleep[a]	Patient current activity documented using same method as "estimated objective total sleep time"

[a]Falling asleep is defined as documentation of "eyes closed, lying down" for at least 30 minutes.

Secondary endpoints included subjective sleep quality, subjective TST, estimated objective TST, estimated time to sleep onset, wakefulness after sleep onset, and nighttime awakenings (Table 1). Each secondary endpoint was recorded as an average between all nights the study medication was taken. All patients were weighted equally for these endpoints regardless of the number of study nights incorporated into the average. If documentation were missing from a study night, the entire night would be excluded such that the average for each patient would only include nights with complete data; however, this was very uncommon because of standardized documentation procedures.

Statistical Analysis

The primary endpoint was analyzed using Fisher's exact test to compare the treatment failure rate. The rate of side effects leading to discontinuation was also compared using Fischer's exact test to determine the number of treatment failures caused specifically by poor tolerability. The secondary endpoints were statistically analyzed using unpaired *t*-tests to quantify the difference in means. A 2-sided α of 0.05 was used to represent statistical significance.

Results

All patients admitted to the adult voluntary inpatient psychiatric unit who received at least 1 dose of trazodone 50 mg between July 2020 and June 2022 were screened for eligibility. Of those, 122 patients fit the eligibility criteria, 54 subsequently received trazodone 100 mg, and 68 received doxepin 25 mg. One patient was excluded because of an excluded treatment sequence of trazodone 50 mg, doxepin 25 mg, trazodone 100 mg, followed by doxepin 25 mg once again. No patients were excluded for actively using trazodone or doxepin for sleep before admission. The baseline characteristics and concomitantly used sedating medications were similar between the 2 groups (Table 2).

The primary outcome of treatment failure was noted in 35.2% of patients in the trazodone group and 41.2% in the doxepin group ($P = 0.58$) (Table 3). Most treatment failures were related to poor efficacy of the treatment medication, with only a few patients requiring treatment adjustments due to adverse events. Adverse events leading to discontinuation were next-day somnolence, which occurred in 1 patient in the trazodone group and 2 patients in the doxepin group, and constipation, which occurred in 1 patient in the doxepin group (Table 3).

The secondary endpoints were also similar between the 2 groups (Table 3). Patients in the trazodone group had a nonstatistically significant higher fraction of subjectively good sleep days. Patients in the doxepin group had nonstatistically significantly more sleep time according to average subjective TST and average estimated objective TST, faster average time to fall asleep, less average wakefulness after sleep onset, and lower frequency of nighttime awakenings.

Discussion

To our knowledge, this was the first study to compare trazodone and doxepin as sleep aids. After treatment failure with trazodone 50 mg, there was no statistically significant difference between trazodone 100 mg and doxepin 25 mg as a pharmacologic sleep aid in the psychiatric inpatient

TABLE 2: Patient baseline characteristics

Characteristic	Trazodone (N = 54)	Doxepin (N = 68)	*P* Value
Age, yr	40.6 ± 13.7	38.8 ± 14.1	0.48
Male, n (%)	34 (63.0)	35 (51.4)	0.27
Primary diagnosis, n (%)			
Major depressive disorder	27 (50.0)	43 (63.2)	0.20
Substance-induced mood disorder	7 (13.0)	7 (10.3)	0.78
Schizophrenia or schizoaffective disorder	8 (14.8)	4 (5.9)	0.25
Bipolar disorder, depressed episode	9 (16.7)	10 (14.7)	0.81
Bipolar disorder, manic episode	1 (1.9)	1 (1.5)	>0.999
Bipolar disorder, mixed episode	2 (3.7)	3 (4.4)	>0.999
Home sleep-aid use, n (%)			
Melatonin	0	2 (2.9)	0.50
Second generation antipsychotic	4 (7.4)	4 (5.9)	0.73
Benzodiazepine	1 (1.9)	0	0.44
Z-hypnotic	0	1 (1.5)	>0.999
Mirtazapine	0	1 (1.5)	>0.999
Marijuana	1 (1.9)	0	0.44
Concomitantly administered medications with potential for sedation,[a] n (%)	40 (74.1)	51 (75.0)	>0.999

[a]Concomitant medications were counted if taken after 6:00 PM on more than half of the nights the sleep aid was used. Medications included aripiprazole, buprenorphine, buspirone, cariprazine, chlordiazepoxide, clonidine, clonazepam, cyclobenzaprine, diphenhydramine, divalproex sodium, gabapentin, haloperidol, hydroxyzine, lamotrigine, lithium, lorazepam, lurasidone, mirtazapine, olanzapine, oxcarbazepine, oxycodone, perphenazine, prazosin, quetiapine, risperidone, topiramate, tramadol, and ziprasidone.

population. As neither option was superior to the other, it is reasonable to consider either option as an acceptable step-up therapy to trazodone 50 mg.

Of note, the doses used in this study were not concordant with insomnia clinical practice guideline recommendations for the off-label use of trazodone or doxepin. For trazodone, the initial dose of 50 mg is the most commonly used.[11] Trazodone 100 mg is often used as a step-up dose after poor efficacy with trazodone 50 mg, as it may be more effective for insomnia.[19] For doxepin, most of the guidelines base their recommendations on doxepin doses of 3 or 6 mg, as these doses have the most data.[7-10] One small study of 47 patients used doxepin doses of 25 to 50 mg and found an acute improvement in sleep efficiency and better sleep quality with doxepin, which was the basis for the use of 25 mg at the study facility.[20] Doxepin doses of 10 mg are used as the starting dose for sleep at some other facilities, which may more closely approximate the better-studied 6 mg dose; however, this dose has not been formally studied at the time of writing.

This study had multiple limitations. Group assignments to either trazodone 100 mg or doxepin 25 mg could not be randomized, given the retrospective nature of the study. Potential confounding variables cannot be ruled out, though baseline

TABLE 3: Efficacy and safety endpoints

Efficacy/Safety Outcome	Trazodone (N = 54)	Doxepin (N = 68)	*P* Value
Treatment failure, n (%)	19 (35.2)	28 (41.2)	0.58
Change in therapy due to poor efficacy, n (%)	18 (33.3)	25 (36.8)	0.71
Change in therapy due to adverse events, n (%)	1 (1.9)	3 (4.4)	0.63
Somnolence	1 (1.9)	2 (2.9)	–
Constipation	0	1 (1.5)	–
Secondary endpoints			
Fraction of subjectively good sleep days	0.66	0.63	0.62
Subjective total sleep time, hr	6.08	6.36	0.19
Objective total sleep time, hr	7.48	7.67	0.51
Time to sleep onset, min	74.9	64.9	0.22
Wakefulness after sleep onset, min	29.5	24.1	0.45
Nighttime awakenings, n	0.69	0.64	0.72

characteristics were similar between the groups, and the primary prescribing physician on the voluntary psychiatric inpatient unit did not cite a particular reason for picking one option over the other. Additionally, the sleep-parameter endpoints were estimated based on staff member documentation rather than confirmatory sleep studies. It cannot be certain whether patients were truly asleep when they were noted as "eyes closed, lying down" (eg, a patient who is facing away from the door and appears to be asleep might be documented as "eyes closed, lying down" even if they are not asleep). This contributes to a probable overestimation of objective TST and a possible underestimation of time to sleep onset. The subjective TST is also unlikely to be an accurate estimate of actual TST, as patients with insomnia tend to overestimate their sleep problem.[21] Last, power could not be calculated for this study due to a lack of existing estimates for treatment differences between trazodone and doxepin.

Further data are needed to determine if there is a significant difference between trazodone and doxepin for the treatment of insomnia in an inpatient setting. A comparison between trazodone and doxepin as the initial sleep aid of choice upon admission could support change in the common practice of using trazodone 50 mg in admission order sets. Ultimately, there is insufficient evidence to preferentially recommend either trazodone or doxepin as a pharmacological sleep aid for psychiatric inpatients, and a randomized controlled trial directly comparing these 2 agents could be beneficial to guide treatment in this setting.

References

1. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep. 2005;28(11):1457-64. DOI: 10.1093/sleep/28.11.1457
2. Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. Am J Manag Care. 2020;26(4 Suppl):S76-84. DOI: 10.37765/ajmc.2020.42769
3. Collier E, Skitt G, Cutts H. A study on the experience of insomnia in a psychiatric inpatient population. J Psychiatr Ment Health Nurs. 2003;10(6):697-704. DOI: 10.1046/j.1365-2850.2003.00654.x
4. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci. 2008;10(4):473-81. DOI: 10.31887/DCNS.2008.10.4/plfranzen
5. Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: a critical review of the empirical literature. J Anxiety Disord. 2010;24:1-15. DOI: 10.1016/j.janxdis.2009.08.002
6. Haynes PL, Parthasarathy S, Kersh B, Bootzin RR. Examination of insomnia and insomnia treatment in psychiatric inpatients. Int J Ment Health Nurs. 2011;20(2):130-6. DOI: 10.1111/j.1447-0349.2010.00711.x
7. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13:307-49. DOI: 10.5664/jcsm.6470
8. Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. Ann Intern Med. 2016;165(2):103-12. DOI: 10.7326/M15-1781
9. Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol. 2010;24(11):1577-601. DOI: 10.1177/0269881110379307
10. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Groselj LD, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675-700. DOI: 10.1111/jsr.1259413
11. Everitt H, Baldwin DS, Stuart B, Lipinska G, Mayers A, Malizia AL, et al. Antidepressants for insomnia in adults. Cochrane Database Syst Rev. 2018;5(5):CD010753. DOI: 10.1002/14651858.CD010753.pub2
12. Yi XY, Ni SF, Ghadami MR, Meng HQ, Chen MY, Kuang L, et al. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med. 2018;45:25-32. DOI: 10.1016/j.sleep.2018.01.010
13. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, et al. Trazodone for insomnia: a systematic review. Innov Clin Neurosci. 2017;14(7-8):24-34. PMID: 29552421
14. De Crescenzo F, D'Alò GL, Ostinelli EG, Cianattini M, Di Franco V, Watanabe N, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022;400(10347):170-84. DOI: 10.1016/S0140-6736(22)00878-9
15. Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, 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):1557-64. DOI: 10.4088/jcp.v69n1005
16. Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, 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):1553-61. DOI: 10.1093/sleep/33.11.1553
17. Roth T, Rogowski R, Hull S, Schwartz H, Koshorek G, Corser B, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep. 2007;30(11):1555-61. DOI: 10.1093/sleep/30.11.1555
18. Mansbach RS, Ludington E, Rogowski R, Kittrelle JP, Jochelson P. A placebo- and active-controlled assessment of 6- and 50-mg oral doxepin on cardiac repolarization in healthy volunteers: a thorough QT evaluation. Clin Ther. 2011;33(7):851-62. DOI: 10.1016/j.clinthera.2011.05.092
19. Mashiko H, Niwa S, Kumashiro H, Kaneko Y, Suzuki S, Numata Y, et al. Effect of trazodone in a single dose before bedtime for sleep disorders accompanied by a depressive state: dose-finding study with no concomitant use of hypnotic agent. Psychiatry Clin Neurosci. 1999;53(2):193-4. DOI: 10.1046/j.1440-1819.1999.00532.x
20. Hajak G, Rodenbeck A, Voderholzer U, Riemann D, Cohrs S, Hohagen F, et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry. 2001;62(6):453-63. DOI: 10.4088/jcp.v62n0609
21. Frankel BL, Coursey RD, Buchbinder R, Snyder F. Recorded and reported sleep in chronic primary insomnia. Arch Gen Psychiatry. 1976;33(5):615-23. DOI: 10.1001/archpsyc.1976.01770050067011