



Prescribing Practices of Hypnotics for Elderly Patients With Insomnia at Six University Hospitals

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Objective: This study aimed to investigate prescription patterns in patients with insomnia who still met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria despite having already been taking hypnotics, and to determine which drug(s) and what combination therapies were preferred. **Methods:** Sixty-three patients were enrolled in this study. Patients were selected from participants registered at six university hospitals for a prospective study to evaluate the efficacy of melatonin (Circadin). **Results:** The prescribed hypnotics were clonazepam (n=33), trazodone (n=23), zolpidem (n=22), quetiapine (n=14), mirtazapine (n=12), lorazepam (n=10), alprazolam (n=7), triazolam (n=5), doxepin (n=5), diazepam (n=3), etizolam (n=2), and flunitrazepam (n=1). There were five types of monotherapies (benzodiazepine, zolpidem, trazodone, mirtazapine, and doxepin) and 18 types of combination therapies. The total number of hypnotics used ranged from one to six. The frequency of benzodiazepine use was quite high, at 51/63. **Conclusion:** This study showed that insomnia can be treated in a wide variety of ways. In particular, 63% of the insomnia treatments in this study used combination therapy. This means that the gap between evidence-based pharmacotherapy and pharmacotherapy used in clinical practice is substantial. This also means that insomnia is still not fully understood and is a heterogeneous condition. In the future, more studies are needed to deepen our understanding of the pathophysiology of insomnia.

Keywords: Insomnia; Prescription; Benzodiazepine; Zolpidem; Hypnotics

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INTRODUCTION

Insomnia is a common and painful condition. One study found that 29.9% of the general population had symptoms of insomnia [1]. Some hypnotics have been approved by the US Food and Drug Administration (FDA) for the treatment of insomnia [2]. However, insomnia treatments have many limitations and most insomnia treatments are only recommended for short-term acute

treatment periods. Therefore, prescription patterns for insomnia treatment vary widely depending on the clinician. The clinical aspects of insomnia are quite heterogeneous. In this study, we analyzed the prescription patterns of patients who still met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for insomnia despite having already been on hypnotics, to determine which drugs and which combination therapies were preferred.

METHODS

This study analyzed the prescription patterns of 63 patients who were already receiving pharmacotherapy for insomnia but showed insufficient responses to existing hypnotic(s), among subjects registered at six university hospitals, for a prospective and multi-institutional study to evaluate the efficacy of melatonin (Circadin), a common insomnia treatment. The six university hospitals were the Pusan National University Hospital, Inje University Ilsan Paik Hospital, Gachon University Gil Hospital, Eulji University Hospital, Korea University Ansan Hospital, and Gyeong-sang National University Hospital. The selection criteria were patients over the age of 55 years who satisfied the DSM-5 diagnostic classification criteria for insomnia disorder. Patients with sleep and mental disorders other than insomnia were excluded from the study; however, patients with mild depression (<15 points) with Hamilton Depression Rating Scale (HAMD) were included. For the purposes of this study, hypnotics were defined as including zolpidem, benzodiazepine (BDZ), doxepin, trazodone, mirtazapine, and quetiapine, which are all commonly used in patients with clinical insomnia. The study protocol was approved by the Ethics Committees of each University Hospital, and informed consent was obtained from the participants.

Participants were divided into two groups according to their number of prescribed hypnotics: monotherapy and combination therapy. Statistical tests such as t-tests and chi-square tests were

conducted for data analysis. All tests were two-tailed, and the cut-off p-value for statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS software (version 25, IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of the 63 participants in this study are described in Table 1. The mean age was 67.18 years, and the mean Pittsburgh Sleep Quality Index (PSQI) score was 14.40, which meant that the participants were very poor sleepers. The prescribed hypnotics were clonazepam ($n=33$), trazodone ($n=23$), zolpidem ($n=22$), quetiapine ($n=14$), mirtazapine ($n=12$), lorazepam ($n=10$), alprazolam ($n=7$), triazolam ($n=5$), doxepin ($n=5$), diazepam ($n=3$), etizolam ($n=2$), and flunitrazepam ($n=1$). Participants were divided into two groups according to the number of prescribed hypnotics: monotherapy and combination therapy (Table 2). Monotherapy was performed in 23 patients, and combination therapy in 40 patients. However, none of the variables differed significantly between the two groups.

There were five types of monotherapies (BZD, zolpidem, trazodone, mirtazapine, and doxepin) and 18 types of combination therapies used by our patients (Table 3). The total number of hypnotics used ranged from one to six. The frequency of BZD use was 51/63, which was quite high. Forty patients were receiving one BZD, eight patients were receiving two, and two patients were receiving three. Among the BZDs, clonazepam was prescribed to 33 patients. Clonazepam monotherapy was being used in five cases and combination therapy in 28 cases. The mean clonazepam dose was 0.68 mg. Trazodone was prescribed in 23 patients. Trazodone monotherapy was performed in only one case, and combination therapy was administered in 22 cases. The mean dose for trazodone was 49.5 mg. Zolpidem was prescribed in 22 patients. Zolpidem monotherapy was being used in six cases, and 16 patients were using it in combination therapies. The mean zolpidem dose was 8.75 mg. In addition, 14 patients used BZD and zolpidem concurrently. Quetiapine was prescribed to 14 patients, the average dose was 242.0 mg, and there were no patients using it as a monotherapy. Mirtazapine was prescribed to 12 patients and had an average dose of 10.9 mg, with two patients using it as a

Table 1. Demographic and clinical variables in patients with insomnia

Variables	Patients with insomnia (n=63)
Age (yr)	67.18±8.14
Sex (male/female)	21/42
HAMD	8.65±3.82
Sleep latency (min)	83.16±70.61
Total sleep time (hr)	4.33±2.14
Sleep efficiency (%)	56.98±25.72
PSQI	14.40±3.40
WHO-5	7.73±5.74

Data are shown as mean±standard deviation or numbers only. HAMD, Hamilton Depression Rating Scale; PSQI, Pittsburgh Sleep Quality Index; WHO-5, WHO-5 well-being index

Table 2. Comparison between monotherapy and combination therapy groups

Variables	Monotherapy group (n=23)	Combination therapy group (n=40)	t	p-value
Age (yr)	66.30±7.99	67.68±8.29	-0.64	0.52
Sex (male/female)	7/16	14/26	0.14	0.71*
HAMD	8.00±3.72	9.03±3.87	-1.03	0.31
Sleep latency (min)	83.48±74.63	82.97±69.14	0.03	0.98
Total sleep time (hr)	4.00±1.71	4.53±2.36	-0.93	0.36
Sleep efficiency (%)	58.35±23.33	56.2±27.25	0.32	0.75
PSQI	14.48±3.23	14.35±3.53	0.14	0.89
WHO-5	8.57±4.95	7.25±6.15	0.87	0.39

Data are shown as mean±standard deviation or numbers only. *chi-square test. HAMD, Hamilton Depression Rating Scale; PSQI, Pittsburgh Sleep Quality Index; WHO-5, WHO-5 well-being index

Table 3. Frequencies of monotherapy and combination therapy

Types of therapy	Frequency of prescription
Monotherapy	n=23
BZD	13
ZOL	6
MIR	2
TRZ	1
DOX	1
Combination therapy	n=40
BZD+BZD	2
BZD+DOX	2
BZD+MIR	3
BZD+QTP	3
BZD+TRZ	6
BZD+ZOL	2
ZOL+TRZ	2
BZD+ZOL+DOX	1
BZD+ZOL+QTP	1
BZD+ZOL+TRZ	4
BZD+TRZ+DOX	1
BZD+TRZ+MIR	3
BZD+TRZ+QTP	1
BZD+QTP+DOX	1
BZD+QTP+MIR	2
BZD+ZOL+QTP+MIR	1
BZD+ZOL+TRZ+QTP	4
BZD+ZOL+TRZ+QTP+MIR	1

BZD, benzodiazepine; DOX, doxepin; MIR, mirtazapine; QTP, quetiapine; TRZ, trazodone; ZOL, zolpidem

monotherapy and 10 patients using it in combination therapies. Lorazepam was prescribed to 10 patients: as monotherapy in two cases and combination therapy in eight cases. Alprazolam was prescribed to seven patients: as monotherapy in two cases and combination therapy in five cases. Triazolam and doxepin were prescribed to five patients each: as monotherapy in one case and combination therapy in four cases. Diazepam was prescribed to three patients: as monotherapy in two cases and as party of a combination therapy in one case.

DISCUSSION

This study revealed that various types of pharmacotherapies are used to treat patients with insomnia. In our patients, insomnia was more commonly treated with combination therapy than with monotherapy. Among the hypnotics we reviewed, BZDs were prescribed most frequently as both monotherapies and in combination therapies. Eighteen types of combination therapies were prescribed.

In this study, BZD use was very high; 51/63 people in our patient pool had used BZD. In a previous 5-year sleep medication prescription analysis study conducted in China, the most common treatment for insomnia was BZD, although the prescription

of BZD declined year over year [3]. In this study, BZDs such as clonazepam, alprazolam, and lorazepam were prescribed more frequently than triazolam, which is FDA approved. This showed that clinicians use a variety of BZDs in the treatment of insomnia, regardless of their approval status for clinical practice. In addition, current American guidelines do not recommend some FDA-approved BZDs such as quazepam, estazolam, and flurazepam because of their long half-lives [2].

The non-BZD receptor agonist Z-drugs included in this study were zopiclone, eszopiclone, zolpidem, and zaleplon. Among them, only zopiclone and zolpidem are available in South Korea. None of the participants in this study was prescribed zopiclone or eszopiclone. Zolpidem was the third most commonly prescribed hypnotic, after clonazepam and trazodone. A total of 22 patients were being treated with these drugs, six as monotherapy and 16 as part of combination therapies. Zolpidem has been proven to be effective for sleep onset and maintenance [2]. Current American guidelines recommend zolpidem as a treatment for sleep onset and maintenance in adults with insomnia [2].

In this study, trazodone was administered to 23 patients and was prescribed at the highest frequency after clonazepam. One study found that among 357,380 patients with insomnia in the United States, 17.7% were prescribed trazodone, 60.7% were prescribed antidepressants, and 37% were prescribed BZD [4]. The most common comorbidities for these patients were anxiety, depression, and hypertension [4]. Trazodone has been approved as a major depressive disorder treatment, but it is more widely used as an off-label treatment for insomnia [5]. This is because, in addition to its hypnotic effect, it also has an anxiolytic effect and low addiction risk [6]. In addition, the efficacy of trazodone in patients with insomnia has been repeatedly demonstrated for both primary and secondary insomnia [5,7].

Quetiapine is an atypical antipsychotic drug that is often used as an off-label hypnotic drug because of its strong calming effect. In this study, 14 patients were prescribed quetiapine, making it the fourth most used drug in our patient group. Unlike the other drugs that we investigated, quetiapine was never used as a monotherapy. In one previous study, quetiapine ranked fourth among the most frequently prescribed medications, followed by Z-drugs, trazodone, and BZDs [8]. Lower doses of quetiapine mainly exert a hypnotic effect via histaminergic and adrenergic receptors [9]. Thus, quetiapine is emerging as an alternative treatment for insomnia [10]. However, evidence to support the extensive use of quetiapine to treat insomnia is scant, because it has disadvantages in terms of weight gain and other metabolic effects.

Mirtazapine is an antidepressant, but is also used as an off-label hypnotic because of its strong sedative effect. In this study, it was the fifth most commonly used drug in 12 patients, two patients used it as a monotherapy, and 10 patients used it in combination therapies. In a recent study, mirtazapine improved total sleep time and decreased wakefulness after sleep onset in depressed patients, although this study did not include a control group [11]. In another study, mirtazapine was found to improve

sleep efficiency index scores and slow-wave sleep [12]. However, according to current American guidelines, the use of mirtazapine is not recommended [13].

Doxepin is also an antidepressant, but unlike trazodone and mirtazapine, it has been FDA-approved at low doses such as 3 and 6 mg. In this study, it was used in five patients: as a monotherapy in one case, with the rest using it in some form of combination therapy. Current American guidelines do recommend the use of doxepin for sleep maintenance [13].

This study had several limitations. First, it is part of another larger study; therefore, it is difficult to generalize these results. However, unlike evidence-based pharmacotherapy, these results reflect pharmacotherapy for insomnia in a real clinical setting. Second, the sample size was fairly small. Thus, future studies involving larger samples are required.

In conclusion, this study revealed that insomnia can be treated in a wide variety of ways. In particular, 63% of the insomnia treatments in this study used combination therapies. This means that the gap between evidence-based pharmacotherapy and pharmacotherapy used in actual clinical practice is quite substantial. This also means that insomnia is still not fully understood and is a heterogeneous condition. In the future, more studies are needed to fully understand the pathophysiology of insomnia.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Young-Min Park. Data curation: all authors. Formal analysis: all authors. Funding acquisition: all authors. Investigation: all authors. Methodology: Young-Min Park. Project administration: Young-Min Park. Resources: Young-Min Park. Software: Young-Min Park. Supervision: Young-Min Park. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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