Neurology Asia 2020; 25(4) : 519 – 526

Medical hypnotic management associated with drug dependence in patients with insomnia and neurological disorders

Jung-Won Shin *MD PhD*, Darda Chung *MD*, Seung-Hun Oh *MD PhD*, Hyun Sook Kim *MD PhD*, Won Chan Kim *MD PhD*, Ok-Joon Kim *MD PhD*

Department of Neurology, CHA University, CHA-Bundang Medical Center, Republic of Korea

Abstract

Objectives: We aimed to investigate the demographics and medical management factors associated with dependence on hypnotics among outpatients with neurological disorders and insomnia. *Methods:* We reviewed electronic medical records of patients who received an initial hypnotic prescription between January 2014 and January 2016 and had later visited a neurological outpatient clinic before January 2018. We assessed patient demographics, the effectiveness of hypnotics, prescription periods, and hypnotic intake methods during the follow-up period. *Results:* Of 242 patients diagnosed with insomnia, we enrolled 114 patients (more women than men, at 61.4 versus 38.6%) who visited outpatient clinics regularly during the follow-up period. The mean age at onset was 65.8 ± 14.4 years. The most frequent neurological disorder was cerebrovascular disease, followed by neurodegenerative disease. During the 2-year period, 35.9% of participants remained hypnotics-free. Patients on zolpidem showed significantly greater insomnia improvement with hypnotic discontinuation than those on benzodiazepines and combination therapy (p=0.004). However, the type of hypnotics and demographic factors were not found to be independent risk factors. Multivariable analysis showed that longer periods between regular visits and a lower ratio of receiving number of pills to the time interval (days) between regular visits were independent risk factors for dependence on hypnotics.
Conclusions: We found that low-dose and/or intermittent intake of hypnotics as well as frequent doctor visits could prevent dependence on hypnotics. It is important to establish the best practical guidelines for medical hypnotics management in outpatient primary care settings, including neurological clinics.

Keywords: Insomnia, neurological disorder, hypnotics, outpatient clinic, dependence

INTRODUCTION

Chronic insomnia disorder is among the most widely reported clinical conditions and has a significant impact on neurological patients.[1] Moreover, it has a significant public health impact with one study reporting it to be among the top ten neuropsychiatric causes of burden worldwide.[2] There are associations between various neurological disorders and insomnia; specifically, sleep disturbances affect 25-35% of patients with Alzheimer's disease (AD). Moreover, almost one third of patients with Parkinson's disease report moderate to severe overall nighttime problems.[3] Insomnia affects 20-56% of patients with stroke, and about 18% report new-onset insomnia after their stroke.[4] Insomnia can also significantly affect patients with epilepsy. Anxiety and depression have been shown to be prevalent in patients with epilepsy and are frequently associated with insomnia.[5] A study of patients with consecutive headache reported sleep-related headaches in 28 out of 50 patients, with 82% having difficulties initiating and 92% maintaining sleep.[6] Hence, in patients with neurological disorder, sleep disturbances negatively affect cognitive function and result in irritability, mood changes, trouble with motor skills, and decreased ability to function.[7] This could contribute to a suboptimal performance during rehabilitation. Frequent arousals have been shown to be both a trigger and a manifestation of the seizure itself in patients with epilepsy.[5] In addition, 50% of migraine attacks have been shown to be triggered by sleep problems.[6]

Address correspondence to: Jung-Won Shin, MD, PhD, Department of Neurology, CHA Bundang Medical Center, CHA University, 59 Yatap-dong, Bundang-gu, Seongnam-si, Gyeonggi-do 463-712, Republic of Korea. Tel: +82-31-780-5058, E-mail: limitsum@gmail.com

Date of Submission: 28 April 2020; Date of Acceptance: 22 June 2020

Regarding the treatment of chronic insomnia, pharmacotherapy and/or cognitive behavior therapy for insomnia (CBT-I) are the most common. However, the insomnia treatment options in outpatient clinics are generally limited to pharmacotherapy and/or general sleep hygiene education. Standard CBT-I, delivered over 4-6 weekly or bi-weekly hour-long sessions, may not be feasible for many. Additionally, as patients with neurological disorders have functional disabilities and cognitive impairments, the need to arrange and keep appointments can further complicate patients' compliance with CBT-I.[8] Hypnotics are therefore widely prescribed for controlling insomnia at outpatient clinics. Accordingly, the American Academy of Sleep medicine has suggested guidelines for the pharmacologic treatment of chronic insomnia through systemic reviews given the currently weak recommendations for hypnotics in general.[9]

The WHO defines dependence as a desire or a sense of compulsion to take a substance, difficulty in controlling its use, tolerance to the substance, and the occurrence of a withdrawal state after use cessation. With respect to hypnotics, the most common phenomenon are rebound effects during use, and after cessation, the insomnia can return in an exaggerated from, time to sleep onset is prolonged, and sleep is more disturbed than before. These symptoms can lead to panic in patients who then often resume the medication.[8] Hence, long-term use of hypnotic medications should be considered carefully in patients with neurological disorders, as they can cause falls, worsen balance, and impair cognition.

For preventing dependency on hypnotics, when such drugs are prescribed initially, the appropriate management at outpatient clinics is important. However, at present, there is no best initial treatment regimen, with general clinical practice guidelines only suggesting that hypnotic medications are used at the lowest effective dose for the shortest necessary duration.[10] Therefore, here, we aimed to assess the effectiveness of and dependence on hypnotics in outpatients with neurological disorders and insomnia. Moreover, we aimed to determine the medical management factors, including prescription methods, associated with dependence on hypnotics at neurological outpatient clinics.

METHODS

We used electronic medical records (EMRs) from a single university hospital to conduct a chart review on each patient. The study was approved by the Institutional Review Board of CHA University Hospital. The inclusions criteria were as follows: (1) Patients assigned the diagnostic code G47.0 (insomnia) according to the Korean Standard Classification of Disease, Sixth Revision, based on the International Classification of Disease, Tenth Revision; (2) Age ≥ 18 years; and (3) Hypnotics use during a follow-up period of at least 2 years at a neurological outpatient clinic. The exclusion criteria were as follows: (1) A history of psychiatric disorders, including depression and anxiety; and (2) Use of antidepressants or antipsychotics for psychiatric symptoms.

We reviewed demographic characteristics including age, sex, comorbidities, underlying neurological disorders with disease severity determined using the modified Rankin Scale (favorable functional status, 0–3; unfavorable functional status, 4–6), types of hypnotics (zolpidem, benzodiazepine, antidepressant, and melatonin), and side effects. We investigated prescription methods, including monotherapy or combination therapy, dosing of hypnotics, as well as whether patients took hypnotics daily or intermittently as needed. We reviewed the frequency of outpatient clinic visits for receiving hypnotics; specifically, the time interval (number of months) between regular visits. Moreover, we investigated the calculated prescription dose; specifically, the ratio of the number of pills to the time interval (days) between regular visits.

Study outcomes

The efficacy outcomes were measured by two investigators (D.D.J. and J.W.S.) through reviews of EMRs. Sleep quality was self-measured on a 0 or 1 scale (0, good to fairly good; 1, bad or not improved). Dependence or tolerance was defined as the patient maintaining the use of hypnotics at similar or higher doses or addition of other hypnotics during the 2-year follow-up period. We also determined the proportion of patients who managed to taper out their hypnotics and thereby improved their insomnia symptoms during the 2-year follow-up period. Safety measurements based on symptom reports by the patients and two investigators (D.D.J. and J.W.S.) were used to identify the relationships between symptoms and hypnotics-related side effects.

Data analysis

Results are presented as means ± standard deviations or numbers (%). We compared the

demographic and baseline characteristics of the hypnotics groups using analysis of variance (ANOVA) and Chi-squared tests combined with Fisher's exact test. The rates of patients who managed to taper out their hypnotics were calculated via Kaplan-Meier analysis, and a log-rank test was used to compare differences in retention rates. A binary logistic regression model was used to assess independent factors and compare between demographic and dependence factors. Statistical significance was set at $p < 0.05$. SPSS for Windows (version 23.0; SPSS Inc., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Of all 242 patients diagnosed with insomnia, we excluded 128 patients who made only one initial visit and were lost to follow-up. The mean age at onset was 65.8 ± 14.4 years, and the sample contained more women (61.4%) than men (38.6%). The most frequently observed neurological disorder was cerebrovascular disease (n = 52, 45.6%), followed by neurodegenerative disease (n = 27, 23.7%), headache (n = 11, 9.6%), epilepsy (n = 8, 7.0%), dizziness (n = 6, 5.3%), peripheral neuropathy (n = 5, 4.4%), neuroinfection (n = 2, 1.8%), restless legs syndrome (n = 2, 1.8%), and fibromyalgia (n = 1, 0.9%). Table 1 presents the clinical characteristics of patients in each group, namely, Group 1: zolpidem; Group 2: benzodiazepine; and Group 3: combination therapy. Due to low proportions, we excluded one patient who was treated with melatonin and two patients who used antidepressants (trazodone) from the group analysis. The zolpidem and combination therapy groups had similar neurological disorder distributions. However, the benzodiazepine group contained more patients with epilepsy than the zolpidem group. Three groups had similar comorbidity and disease severity. Regarding the intake method, the number of patients who intermittently took hypnotics as needed was much higher in the zolpidem group than in the other two groups. Moreover, the zolpidem group had a significantly lower ratio of number of pills to the time interval between visits compared to the other two groups (Table 1).

Clinical outcomes

During the 2-year follow-up period, 35.9% of participants remained hypnotics-free. The zolpidem group had the shortest mean duration of hypnotics intake (Table 1.) The 2-year retention rates estimated by the Kaplan-Meier method were 52.7% for zolpidem, 77.3% for benzodiazepine, and 99.3% for combination therapy; moreover, there was a significant among-group difference ($p = 0.004$; Figure 1). Univariable analysis revealed that the type of hypnotics, intake method, and demographic factors were not risk factors for dependence on hypnotics. Multivariable analysis showed that a longer time interval between regular clinic visits and a ratio of number of pills/interval time between regular visits closer to 1 were risk factors for dependence on hypnotics (Table 2). Two patients had side effects, namely, morning headaches and fall-down events upon waking up.

DISCUSSION

In our study, 60.5% of patients with insomnia and neurological disorders were treated with zolpidem and 63.3% of all patients continued their hypnotic treatment for a 2-year period. Regarding neurological disorders, about two thirds of the patients had cerebrovascular and neurodegenerative disorders. The zolpidem and combination therapy groups exhibited the highest and lowest discontinuation rate with remission, respectively. However, the type of hypnotics was not a risk factor for dependence on hypnotics. Notably, short-term clinic visits and a smaller ratio of number of pills compared to interval time between regular visits were important factors for tapering out hypnotics with remission.

Similarly, an earlier Korean study reported that zolpidem was the most widely prescribed medication among patients with insomnia and that zolpidem prescriptions increased significantly between 2011 and 2015. Moreover, another study based on the National Health and Nutrition Examination Survey (NHANES) conducted in the USA reported that zolpidem was the most common.[11,12] A survey on benzodiazepines for insomnia reported that visits for benzodiazepine prescriptions doubled from 3.5 to 7.5% between 2003 and 2015. Moreover, visits to primary care physicians accounted for approximately half of all visits for benzodiazepine prescriptions. However, this visit rate did not vary among psychiatrists and increased from 6.8 to 8.7% among patients with neurological conditions.[13] Given the exponential increase in the worldwide population of older adults, there has been a concomitant increase in the rates of neurodegenerative and cerebrovascular disorders and the importance of sleep disturbances. This has led to the need for detailed studies on

Table 1: Clinical characteristics of patients with insomnia and neurological disorders according to type of hypnotic

	Zolpidem	Benzodiazepine	Combination therapy	*p*-value
n (%)	75 (65.8)	22 (20.2)	15 (12.3)	N/A
Drug: n (median of dose, range)	Zolpidem: 67 (10 mg, 5–10 mg) Zolpidem CR: 8 (9.375 mg, 6.25–12.5 mg)	Alprazolam: 16 (0.25 mg, 0.125–1 mg) Clonazepam: 3 (0.5 mg) Ativan: 1 (0.5 mg) Flurazepam: 1 (15 mg) Triazolam: 1 (0.25 mg)	- Zolpidem, 5 mg + Benzodiazepine: 2 (alprazolam, 2 (0.125 mg)) - Zolpidem 10 mg + Benzodiazepine: 5 (alprazolam, 2 (0.25 mg), clonazepam, 1 (0.25 mg), ativan, 1 (0.5 mg), etizolam, 1 (0.25 mg)): - Zolpidem 10 mg + Trazodone 25 mg: 4 - Zolpidem 10 mg + Quetiapine 25 mg: 1 - Alprazolam 0.125 mg + Trazodone 150 mg: 1 - Alprazolam 0.25 mg + Triazolam 0.25 mg: 1 - Alprazolam 0.125 mg + Quetiapine 25 mg: 1	
Top 3 ranking of neurological disorders	CVA: 50.7% ND: 20.0% Headache: 9.3%	CVA: 30.4% ND: 21.7% Epilepsy: 21.7%	CVA: 50% ND: 35.7% Headache: 7.1% Dizziness: 7.1%	0.289
Comorbidity, n (%)	41 (54.6) Hypertension: 18 Hyperlipidemia: 11 Diabetes mellitus: 17 Heart disease: 3 Cancer: 1 Hypothyroidism: 1 Gastroesophageal reflex disease: 1	11 (50) Hypertension: 7 Hyperlipidemia: 4 Heart disease: 4 Diabetes mellitus: 2 Chronic kidney disease:1	4 (26.7) Hypertension: 2 Hyperlipidemia: 3 Heart disease: 2 Diabetes mellitus: 1	0.145
mRS, mean (SD)	1.87 (1.21)	1.86 (1.21)	2.33 (1.23)	0.363
Intake methods, n (%)				<0.001
- Daily	14 (18.7)	7 (31.8)	5 (33.3)	
- As needed	61 (81.3)	15 (68.2)	10 (66.7)	
Tapering out of hypnotics with remission	35 (46.7)	5 (22.7)	1 (6.1)	0.003
Duration of intake (m)	15.96±9.25	20.77±6.15	22.67±5.16	0.004
No effect (%)	12 (16)	5 (22.7)	5 (33.3)	0.321
- Dose up	0	1 (dose up and add on)	1	
- Change	6	3	2	
- Add on	6	2	2	
Interval time between regular visits (month)	2.5±1.2	2.7±0.7	2.4±0.7	0.759
Ratio: number of pills/interval time between regular visits (days)	0.5±0.3	0.8±0.3	0.9±0.3	<0.001
Side effects	1, fall	1, headache		N/A

CVD, cerebrovascular disease; ND, neurodegenerative disease; mRS, modified Rankin Scale

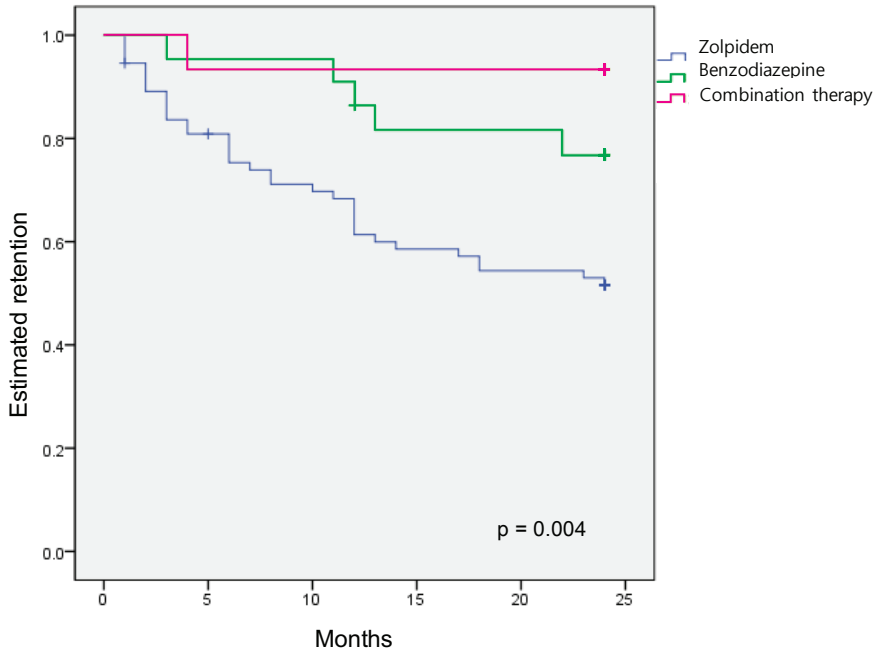

Figure 1. Retention rates of hypnotics. Retention rates were estimated via Kaplan-Meier analysis and p values were calculated using a log-rank test.

Table 2: Factors associated with dependence on or tolerance to hypnotics

	Univariable			Multivariable		
	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**
Age, (years)	0.668	0.991	0.952–1.032			
Gender, male	0.179	2.020	0.725–5.633			
Type of neurological disease						
Cerebrovascular disease	0.648					
Neurodegenerative disease	0.728	0.788	0.205–3.030			
Headache	0.203	5.183	0.411–65.377			
Epilepsy	0.160	0.198	0.021–1.897			
Dizziness	0.537	0.517	0.064–4.201			
Peripheral neuropathy	0.327	0.279	0.022–3.591			
Neuroinfection	0.700	0.554	0.027–11.205			
Restless legs syndrome	0.250	0.140	0.005–3.980			
Comorbidity, Y	0.932	0.953	0.316–2.879			
Severity of Neurological disease -mRS score ≥ 4	0.997	0.979	0.226–4.236			
Type of hypnotics						
Zolpidem	0.294					
Benzodiazepine	0.616	1.515	0.298–7.695			
Combination therapy	0.127	6.220	0.594–65.101			
Intake method (daily intake)	0.151	3.233	0.638–16.386			
Interval time between regular visits (months)	0.015	2.011	1.143–3.537	0.025	1.721	1.070–2.771
Ratio: number of pills to interval time between regular visits (number of pills/interval time between regular visit (days))	0.025	12.233	1.378–108.609	0.010	12.634	1.832–87.143

Y, yes; mRS, modified Rankin Score

the optimal strategy for insomnia management, and our findings could be applied to future studies on insomnia with neurological disorders.

Previous studies have reported complete discontinuation rates ranging from 24 to 61%; however, the reported frequencies of office visits and follow-up periods have varied.[14-18] The evidence regarding the safety or efficacy of long-term use of hypnotics is scarce, which could be associated with drug tolerance, psychological dependence, rebound insomnia, and daytime complaints caused by morning somnolence.[19] Moreover, some studies suggested that the long-term use of hypnotics itself increases the risk of ischemic stroke[20,21] and the incidence of dementia.[22] Another study showed that hypnotics increase the risk of bone fractures in hospitalized patients with dementia.[23] The use of hypnotics or antidepressants should therefore be carefully considered, as they can lead to undesirable side effects such as falls, hallucinations, sedation, and cognitive deficits in patients with neurological disorders. However, there is no evidence regarding the long-term use of hypnotics in patients with neurological disorders visiting outpatient clinics. As only few well-designed pharmacological insomnia studies on neurological disorders have been published, only experts' opinion may be proposed.[24] Several studies have investigated the clinical demographic factors associated with the long-term use of hypnotics in psychiatric patients and patients with general chronic insomnia.[25,26] Our study is, however, the first on dependence in the long-term use of hypnotics in patients with neurological disorders at outpatient clinics, and further studies on the use of hypnotics in neurological disorders are needed.

There have been only few studies on the association between medical management factors, including medication type, dose, and timing, and the long-term use of hypnotics, especially at outpatient clinics. Here, we investigated the frequency of clinic visits and the dosage of hypnotics received during one visit. A greater ratio of hypnotic pills to interval days between clinical visits was associated with an increased risk of dependence. Compared with intermittent intake, daily intake showed a tendency to increase the risk of dependency. The zolpidem group had more patients on an intermittent intake regime than the other two groups. This may be attributable to Korea's general insurance policy that states that patients with insomnia cannot take zolpidem for more than 28 days. The Korean Food and Drug Administration (KFDA) introduced this system based on a drug utilization review (DUR) for hypnotics and narcotics to prevent the misuse of zolpidem.[27] In the USA, the rate of emergency department visits for adverse events due to zolpidem declined after a zolpidem-attributed adverse reporting system was set in place by the FDA.[28] This shows that a national hypnotics management system could make an important contribution to the prevention of hypnotics dependence. Consequently, patients would have to make monthly clinic visits or would receive fewer pills relative to interval days until the next visit. Under the latter circumstances, the patients could either divide pills in half or adapt to an intermittent intake regime. Low doses and intermittent intake of hypnotics could be important factors for the discontinuation of hypnotics. There have been few studies on the medical management of hypnotics. Two randomized double-blind studies reported that fixed schedules of "as needed" drug administration had significant benefits for patients with insomnia. Also, these schedules showed no rebound effect on non-treatment nights and were highly effective at decreasing sleep latency and improving total sleep time.[29,30] Hajak *et al*. investigated the efficacy of "as needed" zolpidem pharmacotherapy with optional use of stimulus control in primary care settings and reported that it was feasible, safe, and effective.[31] Moreover, patients attempted to gradually reduce their medication intake and tended to switch from pharmacological to behavioral therapy.

Recently, Perlis *et al*. compared the potential of a partial reinforcement strategy involving nightly and intermittent dosing as maintenance therapy.[32] They treated chronic insomnia using 10 mg or 5 mg zolpidem, intermittent dosing with 10 mg, or partial reinforcement dosing with 10 mg zolpidem (nightly pill use with 50% and 50% placebo). The authors showed that lower doses and/or less frequent dosing with partial reinforcement could prevent or delay insomnia relapse. However, since the real-world use of placebo is limited, interventions such as stimulus control therapy or brief CBT-i could substitute placebo use.[33] In our study, long interval times between regular visits were independent risk factors for dependence on hypnotics. This indicates that frequent doctor visits and receiving psychoeducation for sleep could be helpful and act as reinforcement.

According to the clinical practice guidelines by the American Academy of Sleep Medicine, hypnotic medications, as well as management of comorbidities and non-pharmacological interventions such as CBT-i, are important

therapeutic options for chronic insomnia. However, CBT-i has several pros and cons.[19] The pros include allowing clinical improvement with long-term remission gains and being a favorable treatment option for patients with comorbid conditions. However, its treatment effect appears slowly and could be insufficient for individuals with insomnia and short sleep durations. Moreover, CBT-i practitioners may not be available at all outpatient clinics, which forces the prescription of hypnotics at clinics by neurologists and primary care physicians. Therefore, at outpatient clinics, including neurological clinics, it is important to determine the best practice guidelines for medical management of hypnotics regarding medication types, dose, timing, and the frequency of clinical visits, for the prevention of hypnotic dependence and tolerance.

This study has several limitations. First, we used a small-sized sample, which limits the significance of our findings. Second, as this retrospective study was based on chart reviews, patients with psychiatric problems including anxiety and depression were not excluded, and we could not use objective tools such as structured interviews or sleep questionnaires to identify patients with insomnia. Demographic factors were not associated with hypnotic dependence, while many other confounders such as co-morbid depression, pain, other sleep disorders, or seizure frequency may be related to hypnotic dependence. Larger prospective studies are thus needed to confirm our findings, especially studies that take into account the confounding factors for each neurological disorder.

DISCLOSURE

Finanical support: This work was supported by a grant from the National Research Foundation of Korea (NRF) funded by the Korean government (No. NRF- 2017R1D1A1B03029293).

Conflicts of interest: None

REFERENCES

1. Avidan AY, Neubauer DN. Chronic insomnia disorder. *Continuum (Minneap Minn)* 2017;23(4):1064-92.
2. Collins PY, Patel V, Joestl SS, *et al*. Grand challenges in global mental health. *Nature* 2011;475(7354):27-30.
3. Dauvilliers Y. Insomnia in patients with neurodegenerative conditions. *Sleep Med* 2007;8:S27-S34.
4. Hepburn M, Bollu PC, French B, Sahota P. Sleep medicine: stroke and sleep. *Mo Med* 2018;115(6):527.
5. Kataria L, Vaughn BV. Sleep and epilepsy. *Sleep Med Clin* 2016;11(1):25-38.
6. Paiva T, Esperança P, Martins I, Batista A, Martins P. Sleep disorders in headache patients. *Headache Quarterly* 1992;3(4):438-42
7. Malhotra RK. Neurodegenerative disorders and sleep. *Sleep Med Clin* 2018;13(1):63-70.
8. Koffel E, Bramoweth AD, Ulmer CS. Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *J Gen Intern Med* 2018;33(6):955-62.
9. 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(02):307-49.
10. Merrigan JM, Buysse DJ, Bird JC, Livingston EH. Insomnia. *JAMA* 2013;309(7):733-3.
11. Lee MH, Choi JW, Lee J, *et al*. Trends in prescriptions for sedative–hypnotics among Korean adults: a nationwide prescription database study for 2011–2015. *Soc Psychiatry Psychiatr Epidemiol* 2019;54(4):477-84.
12. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep* 2014;37(2):343-9.
13. Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States. *JAMA Netw Open* 2019;2(1):e187399-e187399.
14. Hopkins DR, Sethi KB, Mucklow JC. Benzodiazepine withdrawal in general practice. *JR Coll Gen Pract* 1982;32(245):758-62.
15. Murphy SM, Tyrer P. A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *Br J Psychiatry* 1991;158(4):511-6.
16. Voshaar RCO, Gorgels WJ, Mol AJ, *et al*. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry* 2003;182(6):498-504.
17. Gorgels WJ, Voshaar RCO, Mol AJ, *et al*. Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drug Alcohol Depend* 2005;78(1):49-56.
18. Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 2004;161(2):332-42.
19. Boland E, Goldschmied J, Kayser MS, Gehrman PR. Precision medicine for insomnia. *Sleep Med Clin* 2019;14(3):291-9.
20. Lee CC, Tsai KY, Hung YT, Chou FHC, Huang YS. Association of hypnotics with stroke risk: a population-based case-control study. *Prim Care Companion CNS Disord* 2014;16(2): PCC.13m01583.
21. Huang WS, Tsai CH, Lin CC, *et al*. Relationship between zolpidem use and stroke risk: a Taiwanese population-based case-control study. *J Clin Psychiatry* 2013;74(5):e433-438.
22. James W. Hypnotics and the risks of dementia. *J Clin Sleep Med* 2017;13(06):837.

23. Tamiya H, Yasunaga H, Matusi H, Fushimi K, Ogawa S, Akishita M. Hypnotics and the occurrence of bone fractures in hospitalized dementia patients: a matched case-control study using a national inpatient database. *PLoS One* 2015;10(6): e0129366.
24. Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases–occurrence and management. *Sleep Med Rev* 2011;15(6):369-78.
25. Enomoto M, Kitamura S, Tachimori H, Takeshima M, Mishima K. Long-term use of hypnotics: Analysis of trends and risk factors. *Gen Hosp Psychiatry* 2020;62:49-55.
26. Takaesu Y, Komada Y, Asaoka S, Kagimura T, Inoue Y. Factors associated with long-term use of hypnotics among patients with chronic insomnia. *PLoS One* 2014;9(11): e113753
27. Jeong SC. A Study on the Systematic Management of Zolpidem. *J Korean Contents Assoc* 2020;20(2):462-71.
28. Geller AI, Zhou EH, Budnitz DS, Lovegrove MC, Dal Pan GJ. Changes in emergency department visits for zolpidem- attributed adverse drug reactions after FDA Drug Safety Communications. *Pharmacoepidemiol Drug Saf* 2020;29(3):352-6
29. Walsh JK, Roth T, Randazzo A, *et al*. Eight weeks of non-nightly use of zolpidem for primary insomnia. *Sleep* 2000;23(8):1-10.
30. Allain H, Arbus L, Schück S. Efficacy and safety of zolpidem administered 'as needed'in primary insomnia. *Clin Drug Investig* 2001;21(6):391-400.
31. Hajak G, Bandelow B, Zulley J, Pittrow D. "As needed" pharmacotherapy combined with stimulus control treatment in chronic insomnia-assessment of a novel intervention strategy in a primary care setting. *Ann Cclin Psychiatry* 2002;14(1):1-7.
32. Perlis M, Grandner M, Zee J, *et al*. Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study. *Sleep Med* 2015;16(9):1160-8.
33. Ellis JG, Cushing T, Germain A. Treating acute insomnia: a randomized controlled trial of a "single-shot" of cognitive behavioral therapy for insomnia. *Sleep* 2015;38(6):971-8.