

## Do Chronic Hypnotics Users Truly Develop Tolerance?

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### Abstract

**Study Objectives:** Insomnia is a common sleep disorder with a prevalence of 10-15% in the population. The primary aim of our study is to assess the development of tolerance to chronic hypnotic administration in patients with insomnia. An additional aim is to describe the prevalence of hypnotic treatment among patients with insomnia.

**Methods:** This is a retrospective study including all members of Maccabi Health Services above the age of 18 years (N=1.6 million), of data collected between 2011 and 2014. A chronic user was defined as a person who purchased 180 and more sleeping pills per year.

**Results:** Only 20% of the insomnia patients treated with hypnotics (n=122,496) were chronic users. Between 2011 and 2014, we observed a constant increase of 2.5% per year in the number of chronic users. The number of hypnotics taken by chronic users was not different between the genders or between types of hypnotics. A positive correlation was found between age and number of hypnotics among chronic users. The majority of the long-term chronic patients either did not change or decreased the number of sleeping pills they consumed.

**Conclusion:** Our results suggest that chronic insomnia patients do not develop tolerance to treatment with hypnotics.

**Keywords:** Chronic Insomnia; Hypnotic Treatment; Tolerance; Occasional User; Chronic User

**List of abbreviations:** ICSID: 3 - International Classification of Sleep Disorders; BZD: Benzodiazepines; BzRA: Benzodiazepine receptor agonists; MHS: Maccabi Health Services; HMO: Health Maintenance Organization; ANOVA: Analysis of Variance

### Introduction

Insomnia is the most common sleep disorder in the general adult population, with about 25% of adults stating they are dissatisfied with their sleep and 10–15% reporting symptoms of insomnia associated with daytime consequences [1,2]. For some individuals, insomnia can persist for a long period of time, even after the initial cause has disappeared. Persistent or chronic insomnia refers to those patients who suffer from the clinical symptoms for more than 3 months [3]. The prevalence of chronic insomnia in industrialized nations is estimated to be 5-10% [4]. Results of longitudinal studies show that nearly 70% of individuals with insomnia at baseline continue to report insomnia a year later, and 50% still have insomnia up to 3 years later [5,6].

Insomnia is considered to be a contributing risk factor for cardiovascular diseases, chronic pain syndromes, depression, anxiety, diabetes, obesity, and asthma. In addition, insomnia is associated with increased health care utilization and elevated morbidity, and decreased quality of life and daily function [7-11]. Treating insomnia is therefore highly important due to a positive effect on the individual's health and quality of life, and is also cost effective. Treatment options for insomnia include: 1. Sleep hygiene treatment – educating and guiding the patients for healthy lifestyle 2. Relaxation techniques such as Guided Imagery, Yoga, breathing exercise, and meditation 3. Cognitive Behavioral Therapy for insomnia (CBTi) 4. Pharmacological treatment: The use of hypnotics benzodiazepines (BZD) and benzodiazepine receptor agonists (BzRA) to treat insomnia is common [12].

Several clinical trials in humans reported rapid tolerance to the sleep-promoting effects of BZD after repeated administrations [13,14]. Therefore, physicians are frequently apprehensive about chronic use of hypnotics [15-17], and it is generally advocated that this treatment should be limited to no more than four weeks, or avoided [18,19]. Long-term use has been suspected to result in tolerance, dependence, and rebound insomnia upon discontinuation [15-17], but it is important to note that the quality of the data in these studies is weak [18-23]. According to Rush [24], there is some evidence to suggest that the tolerance and dependence-producing effects of zolpidem, a BzRA hypnotic, may be less than those of benzodiazepines.

A major issue regarding the use of hypnotic agents for chronic insomnia is the safe duration of hypnotic treatment. Insomnia disorder often lasts months or years; however, there have been relatively few long-term, randomized controlled studies performed to assess long-term treatment with sleep-promoting medications [25-28].

There is insufficient data at this time to determine the efficacy and safety of long-term hypnotic treatment. The European guideline for the diagnosis and treatment of insomnia states (18): "Long-term treatment of insomnia with BZ or BZRA is not generally recommended because of a lack of evidence and possible side-effects". Meaning that after major and comprehensive review of available data there is still uncertainty about the efficacy and safety of long-term use of hypnotic medication for insomnia. We find this inconsistency in the literature regarding the existence of tolerance to chronic hypnotic use for insomnia to be a major problem in clinical practice. Therefore, the aim of our study is to assess the development of tolerance to chronic hypnotic administration in patients with insomnia. An additional aim is to describe the prevalence of hypnotic treatment among patients with insomnia in Israel.

## Methods

### Study Population and Database

This is a retrospective analysis of data from the computerized pharmacy records of Maccabi Health Services (MHS), the second largest health maintenance organization (HMO) in Israel, insuring roughly 1.6 million members over 18 years old. Maccabi Health Care Services has had a cumulative reliable and quality-controlled database since 1994. This database is highly reliable and contains all physician visits, all prescribed medications, and over 98% of all patient diagnoses [29]. The Maccabi Health Services national pharmacy database is a very well-managed database containing full annotation of every prescription dispensed by MHS, with details on class of medication, generic name, commercial name, and dosage. This data is combined with other MHS databases including the demographic database and the health and illnesses status of all MHS insures. Data were collected for all patients over the age of 18 years who were prescribed with hypnotics between January 2011 and December 2014. The use of the following medications was sought: benzodiazepines: Brotizolam, lorazepam, clonazepam, Nitrazepam, and flunitrazepam; BzRA drugs: zolpidem and zopiclone (eszopiclone and Zaleplon are not in use in Israel). Data collected included: (1) Demographic details: age, gender. (2) Data regarding hypnotic's consumption: duration of consumption in treatment days per year, consumption distribution according to medication group type (benzodiazepine and BzRA).

Three groups were defined: occasional, chronic, and long-term chronic users. 1. Occasional usage of hypnotics was defined as consuming or purchasing fewer than 180 sleeping pills per year. 2. Chronic usage of hypnotics was defined as purchase of 180 or more sleeping pills per year. 3. Long-term chronic usage was defined as purchase of 180 or more sleeping pills for four consecutive years (2011-2014). In addition, we defined an increase or decrease of hypnotic usage as change of 30 or more sleeping pills purchase between 2011 and 2014.

Since our observation was based on a pharmacy database, we chose to use this definition for chronic usage, assuming that purchase of 180 sleeping pills per year reflects a constant and routine use of hypnotics. The long-term chronic usage definition reflects chronic and prolonged usage for four consecutive years of hypnotic's consumption. The decision to use thirty sleeping pills to define a change in consumption of hypnotics was made to reflect one month's worth of additional or reduced treatment time per year.

### Statistical Analyses and Ethical Issues

No names or personal identity details were included in the data-base. The study was approved by the ethics committee of Maccabi Health Services. Data were analyzed using SPSS software version 25. The statistics consisted of predominantly descriptive statistics and comparative analyses (ANOVA) between the various periods or groups.  $p < 0.05$  was considered statistically significant.

## Results

### Characteristics of chronic and occasional users

Our data show (Table 1) a minor and insignificant increase in the mean number of consumed sleeping pills in the occasional and chronic user groups between 2011 and 2014. We observed a negligible increase of two pills in the occasional users between 2011 and 2014 and only eight pills for the whole time period in the chronic user's group. Moreover, the mode index was not changed between the years 2011-2014 and was 360 in the chronic users and 30 sleeping pills for the occasional group.

Our results revealed that the number of chronic users is increasing gradually each year, with nearly three thousand patients added to the chronic user's group. This is an increase of 2.5% each year from 16.6% to 24.3% between 2011 and 2014. It is important to note that although the number of chronic patients increased, the number of hypnotics taken by chronic patients did not increase.

Two thirds of the chronic users were female, showing that the majority of chronic users are women. Forty-two percent of the chronic users use benzodiazepine type of hypnotics, approximately 30% use BzRA and 28% use both type of hypnotics. The type of hypnotic medication taken by chronic users did not change over time according to our data. We observed an increase in the prevalence of chronic users in the two youngest age groups, with a decreased percentage in the oldest age group, and almost no change in the 65-75 years age group. In summary, the number of chronic users is increasing each year, the majority of them are women and they are younger, but we did not notice an increase in the number of sleeping pills taken per chronic user.

	2011	2012	2013	2014
<b>Occasional</b>				
Mean	58.1	58.9	59.6	60.0
Median	30.0	30.0	30.0	30.0
Mode	30.0	30.0	30.0	30.0
STD	48.6	48.9	48.9	49.2
<b>Chronic</b>				
Mean	327.7	333.2	335.8	335.7
Median	330.0	330.0	333.0	340.0
Mode	360.0	360.0	360.0	360.0
STD	98.5	105.6	107.9	103.4
<b>Number (%)</b>				
N chronic	20,365	23,199	26,297	29,827
chronic	16.6%	18.9%	21.5%	24.3%
Occasional	83.4%	81.1%	78.5%	75.7%
<b>Gender</b>				
Female	65.9%	65.2%	64.5%	64.0%
Male	34.1%	34.8%	35.5%	36.0%
<b>Type</b>				
Bz	42.1%	41.9%	41.7%	41.7%
BzRA	30.2%	30.5%	30.5%	30.8%
Both	27.8%	27.6%	27.8%	27.5%
<b>Age Group</b>				
18-45	3.1%	3.3%	3.5%	4.0%
45-65	23.6%	24.9%	25.9%	26.7%
65-75	27.0%	27.1%	27.5%	27.6%
75+	46.4%	44.6%	43.1%	41.7%

**Table 1:** The Central tendencies indexes and STD for occasional and chronic users, number and percentage of chronic and occasional users, type of treatment, and demographic data 2011-2014

(Table 2) presents the number of occasional and chronic patients in 2011 and 2014. According to our data, in 2011, 102,131 patients (83.4%) were occasional users and 20,365 (16.6%) were chronic users. In 2014, the number of occasional users decreased to 92,669 patients (75.7%), and the number of chronic users increased to 29,827 patients (24.3%). These results show that between 2011 and 2014 only 7.9% were added to the chronic user's group. In addition, we explored the transition between the groups during the study years. We found that 88,395 patients (72.2%) were occasional users in 2011 and remained occasional users in 2014, while 16,091 (13.1%) patients were chronic users in 2011 and remained chronic users in 2014. However, of the 14.7% who changed their usage status, 13,736 patients (11.2%) who were occasional users in 2011 became chronic users in 2014, while 4,274 patients (3.5%) who were chronic users in 2011 became occasional users or quit the pharmacology treatment in 2014.

		2014		
		Occasional	Chronic	Total
2011	Occasional	88,395	13,736	102,131
	Chronic	4,274	16,091	20,365
	Total	92,669	29,827	122,496

**Table 2:** Number of occasional and chronic users in 2011 and 2014

### Characteristics of long-term chronic users

According to our data, 14,460 (11.8%) met our definition of long-term chronic users – meaning they have purchased 180 or more sleeping pills per year each year between 2011 and 2014. (Table 3) presents the descriptive statistics of the number of purchases of sleeping pills among long-term chronic users between 2011 and 2014. We observed an increase of 13.6 in the mean number of sleeping pills purchased between 2011 and 2012, while between 2012 and 2014 there is only a negligible increase of five sleeping pills. In addition, when we compute the central tendencies of mode and median, we revealed no change in the quantity of consumed sleeping pills between 2011 and 2014, except for the minor change in the first year (2011-2012). Our results show that the mode index was 360 sleeping pills per year in all four years of the study (2011-2014). The median index was 350 sleeping pills in 2011 and increased to 360

sleeping pills per year in all three following years 2012-2014. Again, as was found in the chronic user's group – two-thirds (66%) of the long-term chronic users were women (9,603). Most of the long-term chronic patients, 6036 (41.8%), used benzodiazepine type of hypnotics, BzRA was consumed by 4,372 (30.2%), and the rest, 4052 patients (28%), used both type of hypnotics. This proportion of distribution is similar to those we report above regarding chronic users. Long-term chronic users are older than chronic users, with almost half of them in the older than 75 years age group and only 1.8% in the under 45 years old age group.

	2011	2012	2013	2014
<b>Mean</b>	329.8	343.4	346.9	348.2
<b>Median</b>	350.0	360.0	360.0	360.0
<b>Mode</b>	360.0	360.0	360.0	360.0
<b>STD</b>	71.0	66.0	63.7	64.0
<b>N</b>	14460			
<b>Gender</b>				
<b>Female</b>	9603 (66.3%)			
<b>Male</b>	4857 (33.7%)			
<b>Type</b>				
<b>Bz</b>	6036 (41.8%)			
<b>BzRA</b>	4372 (30.2%)			
<b>Both</b>	4052 (28.0%)			
<b>Age group</b>				
<b>18-45</b>	263 (1.8%)			
<b>45-65</b>	3099 (21.4%)			
<b>65-75</b>	3960 (27.4%)			
<b>75+</b>	7138 (49.4%)			

**Table 3:** The Central tendencies indexes and STD, number of long-term chronic users, type of treatment, and demographic data between 2011 and 2014

## Trends in consumption of hypnotics among long-term chronic users

The majority of the patients (53.5%) either did not change (23.8%) or decreased (29.7%) the number of sleeping pills they consumed, while only 46.5% of the long-term chronic user patients increased the number of sleeping pills used.

## Discussion

### Main findings

Our study provides a database analysis of four years of use of hypnotic medications in the second largest health service provider in Israel with more than two million members. First, the majority of hypnotic medication users are occasional. Second, we noticed that among the chronic users, each year quite a few became occasional users or quit using hypnotics. Our results revealed that although more insomnia patients are treated chronically with pharmaco-therapy they apparently do not develop tolerance, as the pattern of usage of these patients is usually one pill per night. We report that age is correlated with escalation of hypnotic usage, and that the majority of users are women – about two-fold compared to men.

In our study 7.6% of the general population used hypnotic medication at least once during the study years. This is slightly higher than reported in a UK study and nearly the same as reported in a recent study in Germany [30,31]. Only 1.9% of the population was defined as chronic users, according to our definition. Our results support the notion that the majority of hypnotic medication users are occasional users; only one in five was defined as a chronic user and only one in nine can be defined as a long-term chronic user. This result is in line with a recently published epidemiological study using a comparable definition of chronic usage [32].

The majority of chronic users (two out of three) were women. This result is in line with previous study reporting similar results [33]. Chronic patients have a tendency to use benzodiazepine type of hypnotics, while BzRA type was used by 30% and the rest (28%) used both types of hypnotics. We didn't observe gender or type of hypnotic medication effect on the consumption of sleeping pills. A positive correlation was found between advanced age and an increase in hypnotics purchased, similar relation was reported by Zhang & Wing [33] between advancing age and increased consumption of hypnotics.

Our results revealed that chronic patients do not increase their consumption of hypnotic medication over time. This finding challenges the common concept in the general population and among physicians that chronic usage of hypnotics leads to development of tolerance. We noticed that an increase in consumption of hypnotic medication is occurring only in the first year, with no further increase in the following years. This pattern, of increase in the first year only, was reported previously in a

comparable study that explored the pattern of purchased hypnotics in Israel [34]. We believe that this pattern of increase in the purchase of hypnotics during the first year is the result of dose titration – increased dose until reaching therapeutic effect, or the need to change the type of medication used due to side-effects or ineffectiveness. Additional support to our idea comes from the central indexes (median and mode in our study), presenting a constant value of 360 sleeping pills per year reflecting usage of one pill per night among chronic users over a prolonged period of time.

We report an increase of 8% in the number of chronic users between 2011 and 2014, an average increase of 2% per a year. When we check the cross-over of patients between groups, occasional vs. chronic, we found that for every 3 occasional users who became chronic users we can find one chronic user who became an occasional user. To the best of our knowledge, this study is the first to report this, as studies usually focus on the rate and number of patients that become chronic users with no reporting of the rate of chronic users that become occasional. This finding challenges the fundamental fear and belief that a newly diagnosed insomnia patient who starts using hypnotics will eventually become a chronic user and dependent on the treatment. Our retrospective data with large numbers of chronic patients over the long-term follow-up found that there are many chronic users that become non-chronic and even quit treatment with hypnotics. In addition, an important finding is the change in the proportion of patients in the healthcare system that is chronic users; this might suggest changes in prescribing patterns of hypnotics.

The majority of the long-term chronic users of hypnotic medications did not increase the number of sleeping pills purchased during the study period, which suggests that they did not increase their use of sleeping pills during the study period. It is important to note that although nearly one in two long-term chronic patients did increase the number of hypnotic pills used between 2011 and 2014, this group of patients' numbers only about 6000, nearly 5.5% of the general population of patients that uses hypnotic medications. In other words, if one is a newly diagnosed patient suffering from insomnia and begins to consume hypnotics, their odds to become a chronic user that develops tolerance is only 5%. This is a key point in our study, as many insomnia patients as well as their treating physicians are hesitant to begin treatment for insomnia with hypnotic medication due to fear of tolerance. Riemann [18] state that: "It is undisputed that BZ and BZRA have a potential for tolerance and dependency. However, there are little data available on the number of patients who will become dependent when taking BZ or BZRA for certain period of time". Our results show that the probability to develop tolerance is rare and usually happened under long-term consumption of hypnotics. A further support to our claim comes from pharma-physiological studies, in which tolerance to hypnotics is explained by downregulation of the receptor as the aftermath of neuroplasticity. However, it is demonstrated that even after chronic administration of benzodiazepines, the number of benzodiazepine sites does not decrease, nor does the sensitivity of the benzodiazepine site [35,36].

Our study has several limitations. First, it was a retrospective pharmacy database study and not a prospective controlled clinical trial. However, there is evidence that hypnotics that are bought are usually used [37,38]. This suggests that hypnotic purchases recorded in the pharmacy data base of MHS is a good proxy for actual medication use. Moreover, this retrospective study method allows us to collect data from more than 100,000 patients over a long time period. Second, several definitions for chronic hypnotic medication usage were previously applied and there is a lack of standardization in the literature, which makes comparing between studies difficult [39]. We addressed this issue by using two different definitions of chronicity: chronic and long-term chronic use. Our definitions of chronic and long-term chronic use are very rigorous definitions of chronic usage of hypnotics, allowing us to explore the effects of consumption hypnotics over a long time period and their effects on insomnia patients.

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## Compliance with ethical standards

The study was approved by the institutional ethical review board at Maccabi Health Service Care in Israel.

## Conflict of interest

Dr. Green Amit, Dr. Lilach Kemer, Dr. Merav Bensky, Dr. Orit Stein and Prof. Dagan Yaron, declare that they have no conflict of interest.

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