

Comparison of the Use of Hypnotic in Psychiatric Patients with Insomnia at the Mental Health Centre Prolet in Skopje

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Abstract

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BACKGROUND: Insomnia is a symptom complex that comprises difficulties falling asleep, staying asleep or non-refreshing sleep in combination with daytime dysfunction or distress. Most people experience insomnia at some time during their lives. Because of its high incidence, and also because its symptoms are usually mild and transient, the importance of insomnia is frequently underestimated. Various conditions are associated with insomnia and can contribute to its development. They can be related to neurological or psychiatric disorders, which in turn may be aggravated by a deficiency of restorative sleep and daytime fatigue.

AIM: In this study, the authors compare the hypnotically effect of Flurazepam and Zolpidem applied on psychiatric cases treated in the Mental Health Centre "Prolet" in Skopje, Republic of Macedonia.

METHODS: The investigation covers 45 patients who have insomnia, in addition to their primary mental illness. The examination took six weeks, and it was divided into 3 equal phases. In the first phase of three weeks, Zolpidem was used, and in the third phases, Flurazepam was administrated. We used a self-estimating scale of 13 items and methods of global clinical estimation in the evaluation of received effects.

RESULTS: The results show that referring to the induction of the sleeping period, its duration and quality and the number of awakenings, there are no significant differences between the two medicaments used, but there was a significant difference between hypnotic medicaments and placebo.

CONCLUSION: The termination with the therapy, didn't lead to the appearance of abstinent symptoms.

Introduction

Sleep medicine has been emerging with more public concerns over the past quarter-century, which involves multidisciplinary fields of specialists, including pulmonology, neurology, cardiology, otolaryngology, psychology, psychiatry, endocrinology, geriatrics, paediatrics, dentistry, physiology, pharmacology, and even alternative medicine. Among a wide variety of sleep disorders, insomnia is a particular example that heavily involves multidisciplinary efforts. Insomnia is highly prevalent in clinical practice, independently or comorbidity with another medical or psychiatric disorder [1], [2], and its management usually involves clinicians or specialists from various academic backgrounds.

Insomnia is a symptom complex that comprises difficulties falling asleep, staying asleep or

non-refreshing sleep in combination with daytime dysfunction or distress. The symptom complex can be an independent disorder (primary insomnia) or the result of another condition (secondary insomnia) [3]. Insomnia is commonly divided into 3 types based on duration. Transient insomnia lasts up to 1 week and is often referred to as adjustment sleep disorder because it is caused most often by acute situational stress, such as a test or deadline. It is often recurrent with the same or similar stresses. The second type, short-term insomnia, by definition, lasts 1 to 6 months and is usually associated with more persistent stressful situational (death or illness) or environmental (noise) factors. Finally, chronic insomnia is insomnia lasting more than 6 months.

Most people experience insomnia at some time during their lives. Because of its high incidence, and also because its symptoms are usually mild and transient, the importance of insomnia is frequently

underestimated. However, as a chronic disorder, which affects about 10% of the population, its treatment is often challenging and, moreover, it is associated with a substantial number of comorbid symptoms [4], [5], [6]. Various conditions are associated with insomnia and can contribute to its development. They can be related to neurological or psychiatric disorders, which in turn may be aggravated by a deficiency of restorative sleep and daytime fatigue. Insomnia can also result from a primary dysfunction or an age-related decline in the circadian system.

Insomnia is characterized by one or more of the following: difficulty falling asleep [e.g. sleep onset latency (SOL) of more than 30 minutes], insufficient sleep [e.g. total sleep time (TST) of less than 5.5 – 6 hours], numerous nocturnal awakenings, early morning awakenings with inability to resume sleep, or non-restorative sleep. Common daytime complaints include somnolence, fatigue, irritability, and difficulty concentrating and performing everyday tasks. Because insomnia is associated with reductions in attention span, affected individuals can often be impulsive and experience impaired judgment, and thus are at an increased risk for having injuries at home or work, or involvement in accidents while driving. Psychiatric and other medical illnesses, including cardiovascular diseases, weight gain and glucose intolerance, are other conditions which include insomnia in their overall symptom complex [7].

The International Classification of Sleep Disorders (ICSD-2) [8] considers severity criteria as a guide to be applied in conjunction with consideration of the patient's clinical status. Mild insomnia refers to complaints of an insufficient amount of sleep almost every night or of not feeling rested the following day. There is little or no impairment in social and / or occupational functioning. Moderate and severe insomnia refers to complaints of experiencing an insufficient amount of sleep every night or of not being rested after the impaired sleep episode, accompanied by moderate and severe impairment of social and/or occupational functioning, respectively. The challenge for clinical treatment is to select the therapy, which is most appropriate for these differing degrees of severity.

The last several decades have seen an evolution in thinking about the classes of medications which are to be preferred for treating insomnia. The benzodiazepines (BZDs) were introduced in the 1970s and rapidly increased in popularity because of their efficacy and better safety compared to the barbiturates, carbamates, chloral derivatives and methaqualone [9]. In recent years, however, prescriptions for BZDs have progressively declined, especially because of their associated side effect profile, including their tendency to promote dependence, the occurrence of rebound insomnia following the withdrawal of short- and intermediate-acting derivatives, and the loss of efficacy after

several weeks of treatment. The clinical need for medications which did not have these side effects was an important factor leading to the development of structurally dissimilar non-BZD hypnotics. These included the sedating antihistamines, the melatonin receptor agonists ramelteon and tasimelteon, certain antidepressants, and the so-called z-drugs, i.e. the cyclopyrrolones zopiclone and eszopiclone, the pyrazolopyrimidine zaleplon, and the imidazopyridine derivative, zolpidem, imidazole.

Flurazepam (flurazepam hydrochloride), a benzodiazepine derivative, is a hypnotic agent which does not appear to decrease dream time as measured by rapid eye movements (REM). Flurazepam decreases sleep latency and several awakenings for a consequent increase in total sleep time.

The duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., about the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night; and 2) the appearance of increased daytime anxiety. Flurazepam is a benzodiazepine with a long half-life [10].

Zolpidem has proved to be a suitable hypnotic, especially about efficacy in sleep initiation. As will be discussed below, it is relatively well tolerable and almost devoid of the side effects typically associated with BDZs. The low incidence of side effects is, in part, a consequence of a relatively short half-life in the circulation. At usual doses of immediate-release (IR) Zolpidem, the peak plasma concentrations are attained between about 45 min and 2 h after intake [11], a kinetics profile that corresponds well with the time course of psychomotor tests, in which the maximum efficacy was found around 1.5 h followed by a rapid decline [12]. The pharmacokinetics of such a short-acting drug, when given as an IR formulation, maybe not ideal in terms of promoting sleep maintenance. To respond to the clinical need for an agent which could reduce the number of nocturnal awakenings, Zolpidem extended-release was developed.

In this study, we want to compare the effects of two drugs Flurazepam-15 mg and Zolpidem -10 mg at psychiatric patients with sleeping disturbance.

Material and Methods

A blind, placebo-controlled, comparative study was made. The study lasted for six weeks.

The study involved 45 patients, divided into three equal phases (two weeks each), in the first phase receiving zolpidem, in the second phase placebo only, and in the third phase was administered flurazepam only as an evening therapy. 35 (77.8%) of them had a diagnosis of schizophrenia, and 10 (22.2%) had psychosis. Thirty (66.7%) were men, and 15 (33.3%) were women. The average age is 42.5 y., ranging from 36 to 56 (minimum 36 y and a maximum of 56 y). The drugs are taken at night before bedtime.

The patients were informed about the study, and they had to follow the investigator's instructions. Patients were instructed not to nap or drink alcohol during the weeks of the study, or to consume food or caffeinated beverages after 7:00 p.m.

We used a self-administrative questionnaire to evaluate the effects of 13 items. Every day the quality of sleeping was estimated by the authors and patients helped by standardised questionnaires. The questionnaire referred to sleeping induction; its duration and quality, several awakenings through the night, subjective feeling of "good rest", hangover, tiredness through the day. One week after the third phase patients were observed whether they should appear any abstinence symptoms.

Answers were summarised and statistically evaluated. Statistical analysis of quantitative data was performed by an analysis of variance (ANOVA) for repeated measures. In those cases, in which the ANOVA showed a significant drug effect, comparisons between individual treatments were performed by a post hoc least significant difference test. Categorical data were assessed by the use of chi-square tests and Fisher's exact 2-tailed test.

There were no reports of amnesia, disorientation, hallucinations or other major side effects.

Results

Results showed that the active drugs were efficient in controlling insomnia.

Both drugs improved a measure of "how good a night's sleep", and zolpidem improved the score on a question of "how rested do you feel". There was a trend for both compounds to reduce "difficulty getting to sleep" (Table 1).

TABLE 1: Drug-induced changes in subjective measures of sleep over the entire night as seen on the Morning Sleep Questionnaire

	Placebo	Flurazepam	Zolpidem	P
How good a night's sleep? ^a	2.3 ± 0.4	3.2 ± 0.3*	3.2 ± 0.3*	< 0.05
How rested do you feel? ^b	1.2 ± 0.2	1.5 ± 0.2	1.8 ± 0.2*	< 0.05
Difficulty getting to sleep? ^c	3.0 ± 0.2	2.2 ± 0.3	2.1 ± 0.4	> 0.05

^a"p" values in the right-hand column refer to the results of an analysis of variance; ^a = very poor; 2 = poor; 3 = usual quality; 4 = excellent; ^b = much less rested; 2 = rested as usual; 3 = much more rested; ^c = less difficult; 2 = usual amount; 3 = more difficult; 4 = didn't sleep; * Differs from placebo by $p < 0.05$ by post hoc least significant difference test.

The results of this trial/study show that there is no statistically significant difference between Zolpidem and Flurazepam referred to the induction of sleep. Significant differences appear between the hypnotics and placebo (Table 2).

Table 2: Comparison between periods of investigation

		Placebo	Flurazepam	Zolpidem	F/P p	Z/P p	F/Z p
1. How much time you need to fall asleep	≤ 30min	10	37	36	< 0.05	< 0.05	> 0.05
	> 30min	35	8	9			
2. How you fall asleep	fast	10	37	36	< 0.05	< 0.05	> 0.05
	slow	35	8	9			
3. Habitual total sleep time (hours)	> 5h	11	39	35	< 0.05	< 0.05	> 0.05
	< 5h	34	6	10			
4. Do you feel sleepy enough	yes	11	39	35	< 0.05	< 0.05	> 0.05
	no	34	6	10			
5. How many times did you wake during the night	0 - 1	12	39	36	< 0.05	< 0.05	> 0.05
	> 2	33	6	9			
6. How you slept	well	10	40	37	< 0.05	< 0.05	> 0.05
	bad	35	5	8			
7. You wake up	easy	36	41	40	> 0.05	> 0.05	> 0.05
	difficult	9	4	5			
8. How do you feel after waking up	good	29	39	31	< 0.05	> 0.05	< 0.05
	bad	16	6	14			
9. Do you dream	yes	32	37	35	> 0.05	> 0.05	> 0.05
	no	13	8	10			
10. Do you feel tired through the day	yes	18	9	15	< 0.05	> 0.05	> 0.05
	no						

Significant differences appear between the Flurazepam and placebo at Q1-6 and Q8, not significant at Q7 and Q9-10 (SS Q1 and Q2: chi square = 32.4641, $p = 0.000000$; Q3 and Q4: chi square = 35.2800, $p = 0.000000$; Q5: chi square = 32.4641, $p = 0.000000$; Q6: chi square = 40.500, $p = 0.000000$; Q8: chi square = 6.0160, $p = 0.014176$; Q10: chi square = 4.2857, $p = 0.0384339$; NS Q7: chi square = 2.2478, $p = 0.133808$; Q9: chi square = 1.5528, $p = 0.212723$).

Significant differences appear between the Zolpidem and placebo at Q1-6, not significant at Q7-10 (SS Q1 and Q2: chi square = 30.0593, $p = 0.000000$; Q3 and Q4: chi square = 26.9720, $p = 0.000000$; Q5: chi square = 21.7143, $p = 0.000000$; Q6: chi square = 32.4641, $p = 0.000000$; NS Q7: chi square = 1.3534, $p = 0.244680$; Q8: chi square = 0.2000, $p = 0.654720$; Q9: chi square = 0.5256, $p = 0.468448$; Q10: chi square = 4.2857, $p = 0.511683$).

Significant differences appear between the Zolpidem and Flurazepam at Q8 (SS Q8: chi square = 4.1143, $p = 0.042522$), Not significant at Q1-7 and

Q9-10 (NS Q1 and Q2: chi square = 0,0725, p = 0.787699; Q3 and Q4: chi square =1,2162, p = 0.270104; Q5: chi square = 0.7200, p = 0.396143; Q6: chi square = 0.8092, p = 0.368595; Q7: Fisher exact 2 tailed p = 0.5; Q9: chi square = 0.2778, p = 0.598161; Q10: chi square = 2.0455, p = 0.152661).

Total sleeping time for both tested hypnotic drugs is approximately equal but significantly longer than the time when placebo administrated. The subjective judgment of the quality of sleep did not show a significant difference between the two hypnotics as well. Experience of "sleeping well" (pleasant dream) was present in both cases. Dreaming was also present.

Several "wakenings" was significantly lower when the hypnotic was administrated compared to placebo, which corresponds with the subjective judgment of the quality of the sleep.

Difficulties with morning wake up described as dizziness, hangover, drowsiness frequently present when Zolpidem was used, which was statistically as a not significant difference.

Daily tiredness and drowsiness particularly in the afternoon as a side effect appeared with Zolpidem, which was statistically as a not significant difference.

During the administration of both drugs, worsening of the principal disorder did not occur, as well as any somatic complication. Interruption of Flurazepam treatment did not cause abstinential difficulties.

Discussion

Individuals have different opinions they sleep well or not. Sleeping well usually means short time "to fall asleep" few times wakening up through the night, filling for "good rest" in the morning, opposite to "sense of tiredness" in lack of sleeping [13], [14]. The "ideal hypnotic drug" has to ensure quick falling asleep, permanent sleeping for 6-8h, without side effects in the next day [2], [15]. In the psychiatric population, we often meet insomnia as initial one, in introductory and developed form of psychosis, such, also as terminal in depression.

At the beginning of treatment, hypnotics are commonly administrated besides other antipsychotic or antidepressant therapy.

Insomnia is a frequent symptom in everyday psychiatric practise and prescribing hypnotic medicines as well. Because of this, there are specific risks for developing psychophysical addiction and possibility for suicide abuse, before prescribing priority, it is necessary to estimate ethiology and

possibility for correction of the causes.

Global statistical analysis regarding all parameters shows the equivalence of both of the hypnotics. Basic qualities of the used drugs, efficiency, tolerance and compatibility are present in both of them, but there is a difference in favour of Flurazepam in terms of better tolerance.

About recommendations in the treatment of insomnia, one should have to distinguish between the different causes and clinical phenomenology of the various forms of this disorder. If sleep disturbances are primarily associated with psychiatric disorders, in particular, depression, the usefulness of hypnotics needs to be carefully monitored, and interference with antidepressants has to be taken into consideration. Zolpidem may be used and has already been successfully tested in MDD [16], [17], [18] and GAD [19], but due caution is still recommended for long-term treatment [20], [21]. In these cases, a drug like agomelatine may be an alternative medication of choice, in as much as it combines sleep-inducing, melatonergic properties with actions of an antidepressant [22], [23], [24].

Most of the patients chronically use hypnotics together with other psychotropic drugs, so this examination does not fill full all requirements from a pharmacological point of view which we should consider and also commonly used a combination of medicaments should be considered as well.

The perceived and measured effectiveness of Zolpidem and Flurazepam in decreasing sleep latency, increasing and maintaining sleep duration, and improving sleep quality without causing significant side effects or affecting next day performance suggests that Zolpidem and Flurazepam are important in the treatment of insomnia.

To conclude Flurazepam beside its clinically equal efficiency as Zolpidem, most common hypnotic drug, has an advantage with good tolerance and the possibility of safe combination with antipsychotic or antidepressant medicines. But still, psychiatric observation and control are often necessary also reduction or discontinuing the usage as prevention to a possible threat of addiction particularly in risk cases. Adverse effects are moderate, frequently in the incidence range of placebos, and certainly less frequent and severe.

We had a very similar conclusion with Montie et al. [16]. The evaluation and management of insomnia are often challenging. Insomnia is a multidimensional disorder, and consequently, any approach to its management should consider a combination of both pharmacological and non-pharmacological measures. In practice, pharmacological approaches tend to be used with greater frequency than psychotherapy and other treatment methods. In patients with chronic insomnia and a coexisting psychiatric, neurologic or medical

condition, the underlying disorder needs to be treated appropriately [16].

Insomnia involves multidisciplinary fields of research. In recent years, advances have been made in the understanding of insomnia and its treatment options [2], [25]. However, the breakdown of disciplinary boundaries makes it more difficult for scientists or clinicians to reconcile all of the publications relevant to their research [2], [26]. We recommend that both pharmacological and nonpharmacological treatment for insomnia can have great potential for advancement in future years. Although sedative and hypnotic drugs dominated insomnia treatment for a long time, nonpharmacological therapies such as cognitive behavioural therapy have attracted considerable attention in recent years, for the benefits of reducing dosage and side effects of medication and providing alternative options. Also, the treatment efficacy and clinical outcome were not equally established for insomnia treatment modalities.

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