RUNNING TITLE:
Discontinuation of hypnotics in therapy of insomnia

KEY WORDS:
chronic insomnia - polysomnography - cognitive-behavioural therapy – hypnotics

INTRODUCTION

Many patients suffering from chronic insomnia are prescribed, particularly if treated by non-psychiatrists, various types of hypnotics. Among these drugs, 3rd generation hypnotics became increasingly popular. In contrast to benzodiazepines, it is believed that zolpidem may restore physiological sleep. According to Voderholzer et al., zolpidem has only slight and non-significant rebound effect and therefore it does not trigger chronic use or a risk of tolerance and dependence. However, there is a group of patients chronically using the drug every day in the long term. Many of them increase the daily dose, but their insomnia continues. The aim of the present study was to investigate the changes in sleep parameters after abrupt discontinuation of zolpidem during an adequate therapy of insomnia.

METHODS

Patients. The study was based on continuous 28 outpatients (19 females and 9 males) aged 25 to 74 years (mean 43.6 y, s.d. 13.8) with non-organic insomnia F 51.0 (ICD-10). The mean duration of the disorder was 7.5 years (s.d. 3.6). Patients with psychotic disorder, bipolar disorder, personality disorders, chronic alcoholism, dementia or other organic brain disorders were not included in the study. All the patients were in good physical health. According to the polysomnographic examination, done as a part of the study, no signs of sleep-disordered breathing could be found in any of the patients. Among the patients, 15 of them used zolpidem for more than one year in doses 15-20 mg daily in 12 patients, 30-40 mg daily in 2 patients and 70 mg daily in one patient. The characteristics of this subgroup, compared with the patient group without hypnotics abuse, can be found in Table 1. The patients gave their informed consent to be enrolled in the study with was approved by the ethics committee before starting the investigation.

Clinical examination. The clinical examination consisted of a psychiatric interview and somatic examination supplemented with a study of sleep quality. All patients kept sleep logs, starting one week before the first polysomnography. The sleep interviews and the medical examination were conducted by a physician board-certified in psychiatry and sleep medicine. To characterize the insomnia more precisely and to assess the therapy outcome, Insomnia Severity Index, Epworth Sleepiness Scale were completed prior to and following CBT.
Further, the following scales and inventories were applied, both before and after the therapy: the Beck Depression Inventory, the Beck Anxiety Inventory, the Hamilton Rating Scale for Anxiety and Clinical Global Impression (CGI). The scores, separately for both subgroups, can be found in Table 1.

TABLE 1 HERE

**Design of the study.** After the clinical examination, the study was started by one-week observation period when the patients were asked to fill in their sleep logs. Afterwards, a polysomnographic examination ("adaptive") was done. On the following day, the subjective scores were registered and another polysomnographic examination ("baseline") was performed. Cognitive-behavioural treatment was then applied in the course of next 8 weeks. In 15 patients previously receiving hypnotics, their administration was successively withdrawn in the course of week 2-6. The day after the completed treatment period, subjective scores were registered and a third polysomnographic examination ("post-treatment") was done.

**Polysomnographic recording.** The polysomnography concerned EEG derived from 9 channels (F3-T3, T3-T5, T5-O1, F8-T4, T4-T6, T6-O2, Fz-Cz, T3-Cz, Cz-T4), ECG, naso-oral airflow, chest movements, oxygen saturation, electrooculogram (EOG) and EMGs from the submandibular, thoracic and anterior tibialis muscles. The time to switch the light off was chosen by the patient. The recording was then started and continued until spontaneous awakening in the morning. The polysomnographic records were scored "blind" by an expert according to Rechtschaffen and Kales´ criteria.5

**Psychotherapy** consisted of 8 sessions (lasting 1 hour) of c/e-behavioural group treatment for chronic insomnia.6 The purpose of this treatment is to help the patients to identify and modify their dysfunctional insomnia-related thoughts, beliefs and behavior and break the recurring cycle of anticipatory anxiety. The major components of CBT are: (a) education and information on sleep hygiene, (b) behavior therapy, sleep restriction (c) cognitive therapy, and (d) progressive relaxation. Sessions were supplemented with educational and directive reading materials.

**Statistical analysis.** To compare the pre- and post-treatment variables, the pair t-test was applied. For data with non-normal statistical distribution, non-parametric general linear model (statistical software SPSS v.12.0) was used instead. The intention was to examine the changes of sleep variables achieved by therapy. The influence of hypnotics discontinuation, as a possible factor in the therapy effect, was investigated by ANOVA completed by post-hoc t-test. In this part of statistical treatment, investigating the changes during therapy, differences between the pre- and post-treatment values were used as input data.

**RESULTS**
Effect of CBT on polysomnographic variables

The baseline data obtained by polysomnography are displayed in the left column of Table 2. As shown in the right column of the Table 2, all the sleep variables, with exception of the amount of sleep 2 stage, were significantly improved after the therapy.

TABLE 2 HERE

Effect of hypnotic discontinuation on polysomnographic variables

While all the patients were treated by CBT, another factor could also influence the effect of therapy. 15 patients had chronically used hypnotics and in these patients their administration was successively withdrawn during the observation period. Thus, the withdrawal of hypnotic could also influence the effect of therapy. When this additional factor was studied by analysis of variance, completed by post-hoc t-test, it was found that SE as well as WASO were additionally improved after the discontinuation of 3rd generation hypnotics (Table 3)

TABLE 3 HERE

Effect of therapy as reflected in clinical variables

The above described results were obtained by means of polysomnography. It was of interest to see whether the changes of polysomnographical variables were paralleled by changes of clinical variables. Therefore, a possible relationship among the improvement of sleep variables and improvement in clinical scores was studied. Among various combinations, such a relationship was found for diminished anxiety (Beck Anxiety Inventory) and decrease of WASO. A detailed analysis of this result, as displayed in Table 4, showed that the WASO decrease was actually influenced by a combination of two factors, i.e. decrease of anxiety in combination with the discontinuation of hypnotics.

TABLE 4 HERE

DISCUSSION

In patients with chronic insomnia, using hypnotics of 3rd generation for a long time, the effect of discontinuation of these drugs was studied[^7^][^8^]. The whole-night polygraphy showed that sleep efficacy was improved, and not impaired, when the patient did not take hypnotics any longer. Unexpectedly, the anxiety level was also lower, and not higher, after discontinuation of hypnotics.
As shown in the Table 1, both subgroups were mutually comparable, with one exception. The score of subjective feeling of depression according to Beck Depression Inventory was lower in the patients with abusing hypnotics. It can be speculated that zolpidem influences the subjective feeling of depression, having some stimulative effect in higher doses. If this is true, it can explain the tendency to abuse the drug.

A possible objection would be that several factors, influencing the sleep in parallel, could not be studied separately since it was necessary to respect the patients’ interests to get an efficient therapy by means of CBT\(^9\). The therapy was obviously successful, as shown by the improvement of anxiety level as well that of sleep variables. However, it remained unclear why both anxiety and sleep were further improved by discontinuation of hypnotics. A possible explanation could be that anxiety belongs to the side-effects of zolpidem\(^{10}\).

These drawbacks are certainly compensated by using an objective method to follow the quality of the sleep and its change. Many studies are based on the subjective reports of the patients, even if, as shown in our previous study, the subjective data are less reliable than expected\(^{12}\). Another limitation, i.e. the presence of several factors influencing the sleep, could be compensated, to a certain degree, by use of analysis of variance, where the individual factors are separated. Summarizing all the positive and negative points, it seems to be undisputable that the discontinuation of chronically taken hypnotics improves the results of the therapy in chronic insomnia. The results of the study can be interpreted so that chronic abuse of hypnotics of 3rd generation can be discontinued without any hesitating in the patients starting adequate treatment by cognitive-behavioural therapy.

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**REFERENCES**


Additional files provided with this submission:

Additional file 1: hypnotika tab.doc, 60K
http://www.biomedcentral.com/imedia/1963541369158269/supp1.doc