Do non-benzodiazepine-hypnotics prove a valuable alternative to benzodiazepines for the treatment of insomnia?

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Introduction
In this article insights with regard to sleep physiology and insomnia are discussed, as well as the pharmacological approach of insomnia. The main pharmacological mechanisms of action of benzodiazepines (BZDs) and the newest generation of non-benzodiazepine hypnotics, cyclopyrrolone- and imidazopyridine-derivatives, are evaluated.

Sleep: physiological insights

Macrostructure of sleep
During sleep, 5 to 6 sleepcycles occur during the night, lasting approximately 1.5 hours. Every sleep cycle consists of one REM stage, characterised by rapid eye movements, paradoxical cortical activation and muscular atonia, and four non-REM stages (‘macrostructure’ of sleep). The first three to five hours of the night are considered to be most important and responsible for the restorative function of sleep, since during these hours the largest amount of slow wave sleep (non-REM 3&4) occurs. The sleep in the second part of the night is dominated by superficial REM sleep and sleep stage 2.1

Microstructure of sleep
Additional microstructural characteristics such as the cyclic alternating patterns (CAPs) can also be obtained in insomnia patients for more detailed evaluation of sleep. CAP is a physiological microcomponent of sleep that undergoes measurable changes in several sleep disorders and is rated in %ratio to NREM sleep.2 The CAP rate is decreased during night sleep recovery, whereas it is increased by any perturbing factor, especially noise. The CAP rate is significantly correlated with the subjective appreciation of sleep quality and sleep stability.
Pharmacological management of sleep disorders
Insomnia is best characterized as a complaint of difficulty in initiating or maintaining sleep or having a non-restorative sleep. Over the last century a variety of hypnotic agents have been introduced for the treatment of insomnia of which the BZDs have been used on a large scale for a long time now. Their main therapeutic aims are: a shortening of sleep onset latency, a reduction of awakenings and a decrease of arousability.

The side effects can be an important reason to restrict prescription. The most significant are: a negative impact on daytime alertness, memory, cognitive functions performance, and mood (residual effects), tolerance (reduction of hypnotic efficacy after several weeks), difficulties in discontinuing treatment due to withdrawal symptoms and/or rebound insomnia (causing a non-negligible risk of dependence and abuse). The anxiolytic effects of BZD’s may last for months. Therefore patients might still consider the hypnotics to be effective; this may also be responsible for chronic use or abuse by patients. Furthermore, the BZD’s can affect sleep architecture: 1) an increase of non-REM 2 sleep, 2) a reduction of the amount of non-REM 3/4 sleep (SWS or deep sleep) and 3) suppression of REM-sleep.

The most recently developed hypnotic compounds are the non-benzodiazepines (non-BZD): The cyclopyrrolone zopiclone and the imidazopyridine zolpidem. Their profiles are described below.

Pharmacological profile
BZDs, zolpidem and zopiclone bind to GABA_A-receptors in the brain and are effective by potentiating the activity of the inhibitory neurotransmitter GABA. However, they show a different binding affinity for the GABA-A receptors. The GABA_A-receptor sites are each made up of three distinct sets of high-affinity binding sites recently designated as ω_1-, ω_2-, and ω_3-subtypes, which are modulatory sites of the GABA_A-receptor complex. BZDs and the cyclopyrrolone zopiclone present no selectivity for the ω-receptor subtypes. BZDs bind to all three receptor-subtypes (ω_1, ω_2, ω_3), zopiclone to ω_1 and ω_2 subtypes. The BZD’s have sedative, anticonvulsant, anxiolytic and myorelaxant properties. Zopiclone has a similar profile, although it causes less myorelaxation. In contrast, zolpidem shows high selectivity for the ω_1-receptor subtype which mainly can be found in the cerebellum, cortex and subcortex. This receptor selectivity probably explains why the hypnotic action of zolpidem occurs at doses much lower than those needed for its anticonvulsant or myorelaxant activities and its lack of anxiolytic properties.
Zopiclone

Hypnotic effects
Zopiclone is indicated for the short-term treatment of insomnia. It has a short half-life (3.5-7 hours), which is being prolonged in elderly and patients with liver cirrhosis. The drug is metabolized by the liver to inactive metabolites that are eliminated for 75%-80% by renal excretion. Zopiclone, like most BZDs, demonstrates no selectivity for the \(\omega\)-receptor subtypes of the GABA\(\_A\)-receptor complex. Zopiclone acts favourably on sleep parameters such as sleep onset latency and total sleep time, but doesn’t affect the total duration of REM-sleep. Zopiclone’s pharmacological profile resembles to a greater extent that of BZDs than zolpidem.\(^5\)

Comparative clinical trials with zopiclone
Results from placebo-controlled trials show that zopiclone significantly improved quality of sleep in patients with insomnia as well as in healthy subjects who were working in night-shifts. The effectiveness of zopiclone was superior to placebo in both treatment groups measured in a subjective and objective manner. In several smaller studies zopiclone also demonstrated an improvement of sleep quality which was similar to the effect demonstrated by temazepam, nitrazepam, flunitrazepam, flurazepam and triazolam. Comparative trials including other short-acting BZDs have not been performed. In five comparative studies zopiclone demonstrated no adverse effects on daily functioning during the following day and did not promote rebound-insomnia, whereas nitrazepam and flurazepam did.

Tolerance & dependency
Use of zopiclone doesn’t promote tolerance during the first 4 weeks of treatment. However, some data indicate that chronic use in higher dosages can induce dependency.\(^6\)

Withdrawal of treatment and rebound insomnia
Discontinuation of clinical administration of zopiclone to healthy volunteers during a two-week treatment period hardly led to any withdrawal symptoms. However, rebound-insomnia occurred after discontinuation of the drug after a 3-week treatment period. In three other, short studies with zopiclone withdrawal of treatment did not induce marked rebound-insomnia, possibly due to the short period of observation (7, 10 and 14 days). In another clinical trial, a gradual withdrawal of medication was investigated in persons who had used zopiclone for at least 3 consecutive months. Trial results mainly showed the occurrence of sleep disorders following withdrawal of zopiclone, with minor other withdrawal symptoms.
Zolpidem

**Hypnotic effects**
Zolpidem is indicated for the short-term treatment of insomnia. It shows a high selectivity for the \( \omega_1 \)-receptor and is considered to be a pure hypnotic without other significant effects. It has a short half-life of 2.4 hours, and has no active metabolites. No accumulation occurs during repeated administration. It is oxidized and hydroxylated by the liver to inactive metabolites that are eliminated primarily by renal excretion. After oral intake of zolpidem, the onset of sleep is within 12-25 minutes and the hypnotic effect has a duration of approximately 6 hours. Zolpidem in the recommended dose of 10 mg has no negative influence on overall sleep architecture, both in adults and elderly. A prolonged restorative non-REM3/4 sleep (slow wave sleep) has been observed, which can be considered as a beneficial effect. The duration and latency of REM sleep stays unmodified. Furthermore, the drug has a favourable influence on nocturnal awakenings and increases the number of sleep cycles.

**Comparative clinical trials**
It was confirmed that 10 mg zolpidem is superior to placebo with, in contrast to most BZD hypnotics, no or minimal impact on sleep architecture. In studies involving insomniac patients, zolpidem induced a significantly higher quality of sleep compared to placebo, subjectively (questionnaires) as well as objectively (polysomnography). The same effect was observed in elderly patients with psychiatric disorders. Furthermore, the comparative efficacy of zolpidem has been established for diazepam, flunitrazepam, lorazepam, midazolam and many other BZDs in controlled studies, showing that zolpidem had at least similar or superior activity in terms of sleep onset in insomniac patients.

**Tolerance & dependency**
It has been hypothesized that the rate at which the GABA-receptor complex is occupied pharmacologically plays a role in the development of physical dependency. The low receptor occupancy (around 14%) necessary for zolpidem to induce hypnotic activity could imply that the risk of physical dependency will be lesser. Furthermore, zolpidem lacks anxiolytic activity. Persistent anxiolytic effects, as seen with BZD’s are perceived as effectiveness by patients and could cause chronic use. This suggests that the risk of chronic use/abuse with zolpidem is lower. Indeed, studies have shown that the efficacy of zolpidem doesn’t diminish even after longer use (up to 360 days) However, hypnotic drugs are not meant to be taken for such long periods.
Residual effects
Due to its pharmacological profile, zolpidem has a limited effect on psychomotor performance. Twelve double-blind comparative trials (with placebo and/or benzodiazepine) have been performed, including a total of 1521 subjects/patients and of whom approximately 900 subjects received zolpidem treatment in order to assess daytime impact on alertness, attention, psychomotor skills and memory. Several standard techniques and procedures were used to obtain objective data. Daytime alertness after drug intake has been studied and no significant impairment was found after zolpidem in the recommended dose. Assessments of attention and psychomotor skills (for instance driving tests) objectively showed the lack of residual effects of zolpidem on vigilance, concentration and coordination performances on the morning after intake of zolpidem 5 or 10 mg. Also, no significant memory impairment has been observed six hours after intake of zolpidem 5 or 10 mg. In addition, zolpidem intake did not cause significant subjective residual effects the following morning.

Withdrawal symptoms and rebound insomnia
Five placebo-controlled studies focussing on the objective assessment of rebound symptoms in 229 insomniac patients, of whom 115 received zolpidem treatment for a period of 14-35 days, demonstrated that up to 5 weeks treatment in the recommended dose of 10 mg, no objective evidence of rebound insomnia after abrupt cessation of the drug. In one study, withdrawal of triazolam was compared with withdrawal of zolpidem in 22 insomniac patients. Only patients in the triazolam treatment group suffered a marked rebound-insomnia. The above mentioned studies show that abrupt discontinuation with zolpidem is easy to manage in the vast majority of patients: rebound insomnia is unlikely to occur if zolpidem is used within the current recommendations.

Summary and conclusions
Zopiclone and zolpidem exert their hypnotic effects through a interaction with the \( \omega \)-receptor in the central nervous system. It is suggested that the selectivity of zolpidem for the \( \omega_1 \)-receptor determines its different pharmacological profile compared to BZDs and zopiclone. Zolpidem has a greater potency in producing hypnotic effects relative to anticonvulsant effects and myorelaxant effects and is devoid of anxiolytic effects. Zopiclone has demonstrated no clinically significant advantages in controlled clinical trials comparing the drug with BZDs such as nitrazepam, flunitrazepam, temazepam, triazolam and flurazepam. The adverse events are comparable to those of BZDs. Whether zopiclone leads to less rebound insomnia, cannot be concluded from available data of clinical trials. Should be decided for prescription, a maximum treat-
ment period of 2-4 weeks is advised. Comparison of zolpidem with reference BZDs in controlled studies showed that zolpidem had at least similar efficacy in terms of sleep onset in insomniac patients, whilst having a very limited impact on sleep architecture (especially on REM sleep stages) and on cognitive functioning. Furthermore, zolpidem preserved or may prolong deep, restorative sleep NREM 3/4. In contrast to most BZDs hypnotics, zolpidem lacks important mechanisms concerning dependency potential and the risk of chronic use: the abrupt discontinuation of treatment does not induce rebound insomnia, tolerance seems to be very unlikely to appear and it lacks anxiolytic effects. Therefore, the dependency potential and the risk of chronic use/abuse are considered to be low.

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References


A psychophysiological study of sleep onset by means of dynamic spectral analysis and ERP

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Introduction
Sleep onset (SO), as defined by Rechtschaffen and Kales (1968), is identified by the first sleep spindle or K-complex. Polysomnographic scoring of all night EEG recordings makes it possible for researchers to identify this moment of SO in subjects. Using a sleep spindle or K-complex as the start of the second sleep stage (S2), and hence the start of sleep, only serves as a rule of thumb. When subjects are in the preceding first stage of sleep (S1), they are not considered to be sleeping. However, several physiological changes do occur before the start of S2 and should be the focus of sleep onset research. The use of a sleep spindle or K-complex as a marker for the start of sleep does not take into consideration the interaction of physiological systems responsible for the lowering of the level of consciousness in the process of falling asleep.

The interaction of the ascending reticular activating system (ARAS), with an activating input, and neurocortical neurons, with a synchronizing input, seems to be important for falling asleep. In order to examine the level of (de)synchronization, and its change across time during the wake/sleep transition Fast Fourier Transformation (FFT) can be used. FFT was used by Ogilvie et al. (1997). Both the alpha and beta frequency bands decreased in power in S2 compared to S1. The slower theta and delta frequency bands both increased in power in S2 compared to S1. Using behavioral responses in sleep research provides additional insight into the level of arousal. The experiment of Harsh et al. (1994) showed an increase in latency and a simultaneous lowering of amplitude for the P3 component during S2 compared to S1. Both FFT and ERP will be used to examine physiological changes across time during the wake/sleep process. By calculating the FFTs for each trial (standard tones only) a dynamic change of power can be observed.

Methods
Thirteen first year students (3 males, 10 females) of the University of Amsterdam participated in the experiment. Average age was 21.27 (SD 2.43). Five tasks were administered consecutively in one session in the evening. A ten-minute rest period was taken between each task. Tones were presented