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A double-blind, randomized and placebo-controlled study on the polysomnographic withdrawal effects of zopiclone, zolpidem and triazolam in healthy subjects

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Abstract Rebound effects after withdrawal from hypnotics are believed to trigger their chronic use and to enhance the risk of tolerance and dependence. It was the purpose of this study to investigate the acute polysomnographic withdrawal effects after a 4 week treatment with standard doses of the non-benzodiazepine hypnotics zopiclone and zolpidem compared with triazolam and placebo. Healthy male subjects between 22 and 35 years of age participated in a parallel study design. They received either zopiclone 7.5 mg (n=11), zolpidem 10 mg (n=11), triazolam 0.25 mg (n=10) or placebo (n=7) over 4 weeks in randomized and double-blind order. Sleep EEG was registered during 2 nights before treatment under placebo, on days 1, 27 and 28 of treatment and on days 29, 30, 41 and 42 under placebo. Total sleep time and sleep efficiency were lower in the 1st night after discontinuation of triazolam ($p < 0.05$, t-test). After withdrawal from zopiclone or zolpidem slight but not significant rebound effects concerning sleep continuity were observed. Self-rating scales showed minimal rebound insomnia after discontinuation of all three hypnotics. In the placebo group no changes of sleep parameters were observed. Assuming that rebound insomnia is part of a withdrawal reaction, this study indicates that the risks of tolerance and dependency are low when administering zopiclone or zolpidem at the recommended doses.

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Introduction

Withdrawal and rebound symptoms such as insomnia are well-documented problems when discontinuing benzodiazepines, especially in physically dependent patients taking higher than recommended doses (Hollister et al. 1961, Roy-Byrne and Hommer 1988). Numerous studies, however, described withdrawal reactions such as rebound insomnia after discontinuation of benzodiazepine hypnotics even when administered at the therapeutically recommended doses (for reviews see Kales et al. 1983 a,b; Lader and Lawson 1987, Gillin et al. 1989), and, moreover, even after brief and intermittent use (Kales et al. 1990).

Rebound insomnia is defined as a deterioration of sleep continuity below the pretreatment level after the cessation of hypnotics (Kales et al. 1978). Patients suffering from insomnia might interpret this phenomenon as a persistence of their disturbed sleep and as evidence of being incapable to sleep without hypnotics. Rebound insomnia following withdrawal from benzodiazepine hypnotics hence may trigger chronic use of these drugs. Since long-term administration of hypnotics is not recommended for the majority of insomniac patients (Costa E Silva et al. 1996), it is important to evaluate any new hypnotic for its potential to induce rebound effects, which may increase the risk of chronic use.

In fact, epidemiological data on the prevalence and treatment of insomnia (Hohagen et al. 1993) support the view that in insomniacs drug dependence and the inability to tolerate rebound effects may be one of the main reasons for chronic intake of hypnotics. In this study, those patients using prescribed hypnotics (almost exclusively benzodiazepines) were asked about the duration of intake and the subjective effect of the hypnotics on their sleep. Whereas the duration of intake was longer than 6 months in 75 % of all patients – an interval far

longer than recommended – the overall effect was surprisingly small. Only 20 % reported a distinct, and 30 % a slight amelioration of their sleep. The other patients taking a prescribed hypnotic either denied a significant improvement of their sleep, or even noticed a deterioration despite the intake of a hypnotic. These findings clearly indicated that in many insomniac patients long-term use of hypnotics is maintained not because of the desired effect on sleep but in order to avoid rebound effects. In fact, all of these chronic users of hypnotics in Hohagen's study had reported one or more unsuccessful attempts to discontinue drug intake. It has to be mentioned, however, that in clinical practice not only pharmacological but also psychological factors may cause rebound effects. Hajak et al. (1998) reported rebound insomnia in insomniac outpatients after discontinuation of placebo sleeping pills.

The newer hypnotics zopiclone (see Goa and Heel 1986, Noble et al. 1998 for reviews) and zolpidem (Langtry and Benfield 1990, Wadworth and McTavish 1993, Freeman et al. 1996 for reviews), both non-benzodiazepines, are believed to be associated with a lower risk of tolerance and dependence compared with the classical benzodiazepines. The same has also been reported for zaleplon (see Hurst and Noble 1999, Walsh et al. 2000). However, many studies reporting on the rebound potential of zolpidem and zopiclone (see Lader 1992, Vogel & Poirrier 1996, Lader 1998) differ in regard to methodology, and did not incorporate night-by-night evaluation of sleep by means of polysomnography. In our view, no definite conclusion about their rebound potential can therefore be drawn at the moment.

Whereas zopiclone in comparison to benzodiazepines has different binding sites at the gaba-chloride receptor complex, zolpidem binds selectively at omega$_1$- (benzodiazepine$_1$) but not at omega$_2$-receptors. Zopiclone and zolpidem are currently widely used in European countries, the latter also in the United States. From a pharmacokinetic point of view both compounds are to some extent similar to triazolam in terms of their short action, having a comparatively short half life of 5 hours for zopiclone (Goa and Heel 1986), and about 2–3 hours for zolpidem (Langtry and Benfield 1990). Since triazolam's potential to induce rebound insomnia was partly explained by its rapid elimination (Kales et al. 1983 a, 1986, 1990, Bixler et al. 1985), it is of great interest to investigate possible rebound effects after abrupt withdrawal of zopiclone and zolpidem, since these drugs are also rapidly eliminated. Most studies showing rebound insomnia following discontinuation of triazolam used a dosage of 0.5 mg; however, the standard dose which is currently recommended is 0.25 mg. Since there is evidence that rebound insomnia is a dose-dependent phenomenon (Roehrs et al. 1986, 1990), the clinical significance of triazolam's rebound potential, as concluded from most earlier studies, might have been somewhat overestimated. In our view, when comparing withdrawal effects of hypnotics, it is important to use standard doses as currently used in clinical practice with a similar hypnotic effect.

This study was designed to investigate the withdrawal effects of zopiclone and zolpidem in comparison with triazolam and placebo as monitored by sleep EEG and subjective rating scales. Our hypothesis was that the non-benzodiazepines zopiclone and zolpidem do not induce significant polysomnographical rebound effects after discontinuation of a 4-week treatment.

Subjects and methods

Subjects

Forty-three healthy male subjects aged between 22 and 35 years (mean: 25.6 ± 2.3 years) were recruited. Subjects were screened by routine laboratory parameters including a urine test, hematology and blood chemistry, urine drug test for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, and cocaine, electroencephalogram, electrocardiography, psychiatric interview, physical and neurological examination, all of which had to be non-pathological. None of the subjects had a history or family history of psychiatric illness including alcohol and drug abuse, and none had a history of insomnia. Further exclusion criteria were intake of any medication, more than 10 % deviation from the ideal body weight according to the recommendations of the Metropolitan Life Insurance Company, body weight below 50 or above 95 kg, abnormalities of the gastrointestinal tract, which might interfere with the resorption of the study drugs, or any other significant medical illness. Written consent was obtained before participation in the study. The experiments were performed in accordance with the Helsinki Declaration of 1975. The protocol was approved by the Ethical Committee of the University of Freiburg.

Design

For this monocentric study, a double-blind, randomized parallel design with four treatment groups was used (Fig. 1). The whole study lasted 6 weeks, and subjects spent a total of 9 nights in the sleep laboratory. During the week before the start of the trial subjects were asked to maintain a regular sleep schedule with bedtimes from 23.00 to 7.00 hours. Polysomnographic recordings were obtained on nights –2 and –1 (placebo run in period), on nights 1, 27 and 28 (treatment period), and on nights 29, 30, 41 and 42 (placebo withdrawal period). This report primarily focuses on polysomnographic changes after withdrawal compared with baseline. Analysis of spectral power effects of the hypnotics during treatment and after withdrawal have been reported previously (Feige et al. 1999).

Nights –2, 27 and 41 served for adaptation to the sleep laboratory conditions, and polysomnographic parameters of these nights were not statistically analyzed. During the whole study period, subjects received one capsule immediately before going to bed. These indistin-

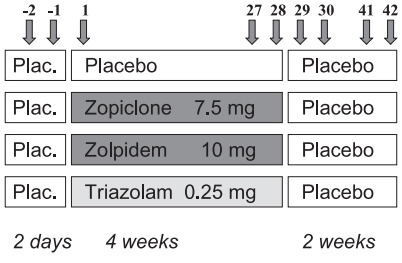

Fig. 1 Study design. Subjects were randomized to 4 treatment groups. Nights in the sleep laboratory are indicated as ⇓. All subjects received identical looking capsules throughout the whole study (days –2 until 42). Nights –2 and –1 served for adaptation to the sleep laboratory conditions. Nights 1, 27 and 28 were registered during treatment with the three different hypnotics or placebo, nights 29, 30, 41 and 42 under placebo.

guishable capsules contained placebo on nights –2 and –1 and on nights 29 to 42 in all four treatment groups. One group received placebo capsules throughout the whole study period; the other three treatment groups were administered either triazolam 0.25 mg, zopiclone 7.5 mg or zolpidem 10 mg on nights 1 to 28. Among the 43 subjects were four drop-outs (three in the placebo group, one in the triazolam group). All drop-outs were unrelated to the study medication. Two subjects in the placebo group dropped out during the run-in phase. One of them complained of side-effects during the run-in phase and desired to terminate the study; the other had a very low sleep efficiency of 50 and 75 %, resp., during the first two nights. A third subject in the placebo group had fever due to a viral infection on day 42 resulting in severely disturbed sleep on night 42. He completed the study, but his polysomnographic findings were excluded from the statistical analysis. One subject in the triazolam group dropped out on day 14 because of exclusion criteria which had not been recognized prior to inclusion. There were 7 subjects remaining in the placebo group (mean age: 26 ± 1.5 years), 10 in the triazolam group (mean age: 26 ± 1.2 years), 11 in the zopiclone group (mean age: 26 ± 3.4 years), and 11 in the zolpidem group (mean age: 26 ± 2.5 years).

Subjects had to swallow the study medication with 100 ml of water between 22.55 and 23.00 hours immediately before the start of polysomnographic recordings at 23.00 hours. Compliance controls were performed weekly by urine tests detecting the marker riboflavine (vitamin B2), which was contained in all capsules. Subjects were informed that payment for participation would not be provided if the marker was not detected in one of the urine samples.

Polysomnographic assessments

Sleep recordings were made on Nihon Kohden EEG polysomnographs from "lights out" (23.00 hours) to "lights on" (7.00 hours) at a paper speed of 10 mm/s. All sleep recordings registered EEG (C3-A2; C4-A1), ECG, horizontal EOG and submental EMG. During the first adaptation night (–2) all subjects were screened for sleep-related respiratory disturbances and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oxymetry and bilateral tibialis anterior EMG. More than 5 apneas or hypopneas per hour or more than 5 periodic leg movements per hour were exclusion criteria. The following filter settings were used: EEG: sensitivity 7 μV/mm, TC (time constant) 0.3 s, HI (high frequency filter) 70 Hz; EOG: sensitivity 30 μV/mm, TC 20 s, HI 35 Hz; EMG: sensitivity 5 μV/mm, TC 0.03 s, HI 500 Hz. Polysomnographic recordings were visually scored by experienced raters according to Rechtschaffen and Kales criteria (1968). The raters were blind to the experimental conditions.

For evaluation of rebound insomnia the following parameters of sleep continuity were analyzed: (1) total sleep time (TST); (2) sleep onset latency (SOL): time from lights out until sleep onset (defined as first epoch of stage 2).

Psychometric measurements

Self-rating scales were used to evaluate subjective sleep quality, daytime performance and possible withdrawal symptoms. On all mornings of study days subjects completed a visual analogue scale (Vis-M) with the items "subjective vigour" and "subjective global quality of sleep" and estimated the sleep onset latency, total sleep time, number of awakenings and the number of nightmares during the preceding night.

The Pittsburgh Sleep Quality index (PSQI) (Buysse et al. 1989), which measures subjective sleep quality over a period of two weeks (modified version), was completed on days –1, 28 and 42 to compare pretreatment levels with treatment and withdrawal effects. To evaluate potential withdrawal effects two further scales were completed on the morning of days –1, 28, 29, 30 and 42: EWL ("Eigenschaftswörterliste", Janke & Debus 1978), which is a list of adjectives describing the actual emotional and physical status; the WSS (withdrawal symptom scale; Merz & Ballmer 1983), which covers the typical symptoms observed during withdrawal from benzodiazepines. Side effects were monitored weekly by the study physician.

Statistical evaluation

For descriptive purposes, means and standard deviations (SD) were calculated. Statistical analysis of rebound effects was obtained by analysis of variance (ANOVA) for repeated measurements for the factors night and group. P-values obtained by ANOVA were statistically adjusted if Greenhouse-Geisser correction revealed epsilon-values < 0.75. Additionally, for the comparison of the withdrawal period with baseline, Student's t-tests (two-sided) were calculated. In order to avoid multiple testing, t-tests were only calculated in the case of a statistically significant night effect (p-value < 0.05) or statistical trend (< 0.10) by ANOVA.

Results

Polysomnographic findings (Table 1)

A significant reduction of total sleep time and of sleep efficiency was observed in the triazolam group only (ANOVA: p = 0.035, 0.030, resp.). Confirmatory t-tests revealed that this effect was limited to the first night after withdrawal (N 29, p = 0.048, 0.053, resp) only.

Fig. 2 demonstrates the baseline differences for the first and second night and 2 weeks after discontinuation from active treatment for the parameters total sleep time and sleep onset latency. In the zopiclone and zolpidem but not in the placebo group, non-significant trends towards a slight deterioration of sleep efficiency and sleep duration were observed in the first night after discontinuation from zolpidem and in the second night after discontinuation from zopiclone. Because of statistical trends in the zopiclone group (total sleep time p = 0.062, sleep efficiency p = 0.071), t-tests versus baseline were also calculated for this group. However, neither in the first (N 29) nor in the second withdrawal night (N 30) did a significant difference occur compared with baseline except a trend in the second withdrawal night for sleep efficiency (p = 0.098).

Mean sleep onset latency (Fig. 2) increased slightly above baseline values in the first and second night after withdrawal from triazolam, zopiclone or zolpidem but not in the placebo group. Statistical evaluation by ANOVA did not show significant night effects. There were, however, trends in the triazolam (p = 0.110) and in the zopiclone group (p = 0.092). Confirmatory comparisons by t-tests revealed a slight rebound effect in the first night after withdrawal from triazolam (p = 0.057) and in the second night after withdrawal from zopiclone (p = 0.076). In all 4 groups, the number of waking periods did not change significantly during the withdrawal period. Fourteen days after discontinuation of active treatment (night 42) none of the sleep continuity parameters differed significantly from baseline in any of the groups.

As expected with regard to the sample sizes and the low statistical power of the effects, group comparisons did not show statistically significant differences between all four different treatment groups.

Table 1 Polysomnographic parameters before (–1), during (1, 28) and after discontinuation (29, 30, 42) of triazolam, zopiclone or zolpidem in comparison to a placebo group; mean values ± standard deviations and results of t-test versus baseline (–1)

		Placebo (n = 7)					**ANOVA**	
	Baseline	Treatment period		Withdrawal period			Night, df = 5	
Night	–1	1	28	29	30	42	F	p
TST (min)	439 ± 22	436 ± 20	432 ± 27	446 ± 9	433 ± 46	445 ± 19	0.39	*0.853*
SE %	92 ± 4.8	91 ± 3.4	90 ± 5.6	93 ± 2.1	90 ± 9.4	92 ± 3.7	0.49	*0.782*
SOL (min)	21 ± 12	20 ± 10	18 ± 16	18 ± 14	16 ± 12	14 ± 10	0.38	*0.858*
		Triazolam (n = 10)						
	Baseline	Treatment period		Withdrawal period			Night, df = 5	
Night	–1	1	28	29	30	42	F	p
TST (min)	439 ± 19	446 ± 21	440 ± 22	405 ± 56	442 ± 16	434 ± 27	3.97	**0.035**
		0.387	*0.942*	**0.048**	*0.621*	*0.554*		
SE %	92 ± 3.6	94 ± 3.8	92 ± 4.6	85 ± 12	92 ± 3.5	91 ± 5.8	4.33	**0.030**
		0.253	*0.822*	*0.053*	*0.696*	*0.494*		
SOL (min)	21 ± 16	22 ± 15	26 ± 19	37 ± 22	23 ± 16	21 ± 17	2.17	*0.110*
		0.961	*0.295*	*0.057*	*0.695*	*0.991*		
		Zopiclone (n = 11)						
	Baseline	Treatment period		Withdrawal period			Night, df = 5	
Night	–1	1	28	29	30	42	F	p
TST (min)	442 ± 18	452 ± 18	450 ± 17	443 ± 17	426 ± 43	444 ± 19	3.16	*0.062*
		0.193	*0.052*	*0.844*	*0.142*	*0.444*		
SE %	93 ± 4.3	94 ± 4.0	94 ± 3.3	93 ± 3.5	90 ± 6.8	93 ± 2.6	2.68	*0.071*
		0.382	*0.320*	*0.847*	*0.098*	*0.445*		
SOL (min)	13 ± 11	14 ± 11	17 ± 12	19 ± 8.8	20 ± 18	11 ± 8.8	2.32	*0.092*
		0.881	*0.357*	*0.158*	*0.076*	*0.282*		
		Zolpidem (n = 11)						
	Baseline	Treatment period		Withdrawal period			Night, df = 5	
Night	–1	1	28	29	30	42	F	p
TST (min)	440 ± 34	437 ± 26	434 ± 32	421 ± 37	430 ± 44	442 ± 25	1.05	*0.385*
SE %	92 ± 7.1	91 ± 5.0	90 ± 6.7	88 ± 7.5	90 ± 9.2	92 ± 5.0	1.05	*0.384*
SOL (min)	15 ± 10	19 ± 15	13 ± 8.5	26 + 19	23 ± 22	18 ± 16	1.23	*0.315*

TST total sleep time, *SE* sleep efficiency, *SOL* sleep onset latency

Subjective rating scales

Generally, all scales showed only minor changes of self-rated sleep quality and subjective well-being during the active treatment and the discontinuation period. Statistical comparisons did not show significant differences between the groups during the withdrawal phase. The results are, therefore, not reported in detail. There were minor, statistically non-significant trends towards an increase of subjectively experienced sleep onset latency (Vis-M) in the first night after withdrawal from triazolam and from zolpidem, but not in the zopiclone group. Regarding subjectively estimated sleep time (Vis-M), there were trends in terms of a slight reduction after withdrawal from all hypnotics. Statistical evaluation by ANOVA demonstrated a significant night effect in the zopiclone group. Confirmation by t-test revealed a statistically obvious rebound effect on total sleep time in the second night after discontinuation from zopiclone ($p = 0.066$).

On day 42, i. e., two weeks after discontinuation of the active treatment, no differences compared with baseline were observed in any of the groups. Mean values of the Pittsburgh sleep quality index, which measures sleep quality over a two weeks period, did not show significant changes during the discontinuation period compared with baseline and did not significantly differ between the 4 groups. Rating scales focussing on withdrawal symptoms other than insomnia (EWL-K, WSS) did not demonstrate significant alterations during the discontinuation phase (data not shown). In all treatment groups subjects reported only minor side effects, which are therefore not reported in detail.

Discussion

This study was carried out in order to investigate polysomnographic rebound phenomena in healthy subjects after 4 weeks of treatment with hypnotics in comparison to placebo. The main findings can be summarized as follows: 1) Withdrawal from a 4-week treatment

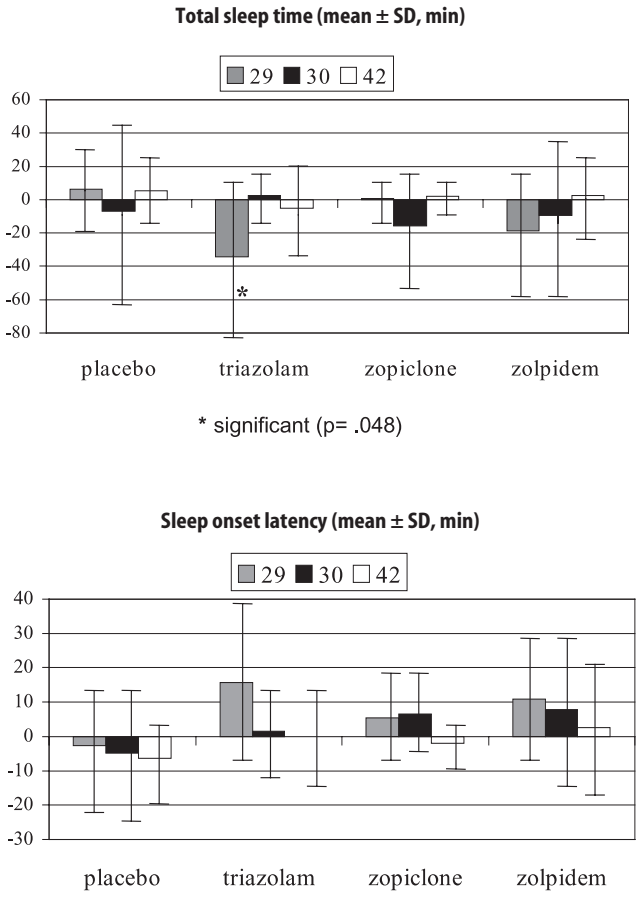

Fig. 2 Changes (from baseline night –1) of total sleep time (min, x ± SD) (upper panel) and of sleep onset sleep latency (min, x ± SD) (lower panel) after withdrawal of 3 different hypnotics compared with placebo in healthy male subjects. 29 = first withdrawal night, 30 = second withdrawal night, 42 = two weeks after withdrawal.

with the non-benzodiazepine hypnotics zopiclone 7.5 mg or zolpidem 10 mg did not induce a significant deterioration of sleep below pretreatment levels, as measured by polysomnography. There was, however, a non-significant trend towards a decrease of sleep continuity in the first withdrawal night of the zolpidem group, and in the second discontinuation night of the zopiclone group. 2) Withdrawal from triazolam 0.25 mg after 4 weeks of daily use caused a significant reduction of sleep duration and sleep efficiency below baseline levels during the first night of withdrawal, but not in the second night. Statistical comparisons between the zopiclone, zolpidem, triazolam and placebo groups, however, failed to detect significant differences of sleep continuity measures between the groups. This is explained by the statistical power of rebound effects requiring larger sample sizes to detect significant group differences. 3) Subjective ratings of sleep demonstrated minimal rebound effects on the first two days following withdrawal of all three hypnotics. These minor effects were slightly stronger on the first day after withdrawal from triazolam and zolpidem and on the second day after withdrawal from zopiclone.

The finding of a significant rebound insomnia following withdrawal of the benzodiazepine triazolam confirms a variety of earlier studies (see Gillin et al. 1989 for review). However, in our study rebound insomnia after triazolam was present only in the first night and was less pronounced than in most of the earlier studies. This can be explained by the low dose of 0.25 mg triazolam compared with 0.5 mg used in many of the previous studies. Roehrs et al. (1986) reported rebound insomnia during discontinuation of 0.5 mg of triazolam in normal sleepers but not during discontinuation of 0.25 mg, whereas Kales et al. (1986) found rebound insomnia with 0.25 mg in terms of a significant increase of total wake time for the first three nights after drug discontinuation.

Contrary to withdrawal of triazolam, we did not find significant rebound insomnia following discontinuation of zolpidem and zopiclone. There was, however, a trend towards a slight deterioration of sleep continuity measures below the baseline level during the first night after discontinuation of zolpidem and during the second night after discontinuation of zopiclone. A similar time course of slight rebound effects was also confirmed by self-rating scales. This might be explained by the very short elimination half-life of 2.2 h for zolpidem (Langtry and Benfield 1990) as compared with zopiclone which has a half-life of about 5 h (Goa and Heel 1986). It can be assumed that zopiclone is not entirely eliminated within the first day after discontinuation, thus, explaining the occurrence of slight rebound phenomena in the second night after withdrawal.

With regard to zopiclone, our results are comparable to earlier sleep laboratory studies (Mamelak et al. 1982, Pecknold et al. 1990, Mann et al. 1996), which also failed to prove a significant rebound insomnia following withdrawal of zopiclone. Mann et al. (1996), who investigated healthy subjects after withdrawal from zopiclone, reported a non-significant decrease of total sleep time in the second night after dicontinuation compared with baseline. Similar results have also been obtained for zolpidem, which did not induce a significant rebound insomnia in sleep laboratory studies by Monti (1989), Monti et al. (1994), and by a more recent study of Ware et al. (1997).

In summary, this study demonstrated a significant rebound insomnia by means of sleep EEG following discontinuation of triazolam 0.25 mg, but not after discontinuation of zopiclone 7.5 mg or zolpidem 10 mg. Since rebound insomnia has been associated with abrupt withdrawal of rapidly eliminated benzodiazepine hypnotics (Kales et al. 1983 a, Roehrs et al. 1992), it is remarkable that zopiclone and zolpidem, which are both rapidly eliminated, did not induce a significant rebound insomnia after abrupt withdrawal. This might point towards a lower rebound potential of these drugs despite their action on the gabaergic system and despite similar spectral changes of sleep EEG compared with triazolam (Feige et al. 1999). Based on the assumption that there is a relationship between withdrawal reactions and abuse

potential, our result of minimal rebound with zopiclone and zolpidem is in line with a recent report on data from a German "substance abuse warning system" which indicate a clearly lower abuse potential for zopiclone and zolpidem compared with benzodiazepine hypnotics (Keup 1998). In a recent review by Hajak (1999), who reviewed risks and benefits of zopiclone, it is concluded that the risk of withdrawal reactions with therapeutic dosages of zopiclone is very low, which is also in agreement with our findings.

On the other hand, rebound effects after withdrawal from zopiclone and zolpidem were not completely absent as demonstrated with trends in polysomnography and subjective rating scales. Whether the difference between the benzodiazepine triazolam and the non-benzodiazepines zopiclone and zolpidem, which was altogether not striking, is explained by the differences of receptor pharmacology, cannot be definitely answered by this study, since rebound phenomena are dose-related. The potential of triazolam to induce rebound insomnia might have been somewhat overestimated in the view of many studies using 0.5 mg instead of 0.25 mg, which is recommended as the standard today. Only a study with different dosages of each hypnotic could answer this question.

In conclusion, this study demonstrated that a four week treatment with the non-benzodiazepine hypnotics zopiclone or zolpidem is not able to induce a significant rebound reaction – at least not in young healthy adults. Further studies in elderly subjects and insomniac patients should be performed to confirm the clinical relevance of these results. Assuming that rebound insomnia is part of a withdrawal reaction, which – from the clinical point of view – is a predictor for long-term use and dependence, this study indicates that such a risk may be low with the non-benzodiazepines zopiclone and zolpidem in the recommended doses.

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References

Bixler EO, Kales JD, Kales A, Jacoby JA, Soldatos CR (1985) Rebound insomnia and elimination half-life: assessment of individual subject response. J Clin Pharmacol 25:115–124

Buysse DJ, Reynolds CFR III, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213

Costa E, Silva JA, Chase M, Sartorius N, Roth T (1996) Special report from a symposium held by the World Health Organization and the World Federation of Sleep Research Societies: an overview of insomnias and related disorders – recognition, epidemiology, and rational management. Sleep 19:412–416

Feige B, Voderholzer U, Riemann D, Hohagen F, Berger M (1999) Independent sleep EEG slow-wave and spindle band dynamics associated with 4 weeks of continuous application of short-halflife hypnotics in healthy subjects. Clin Neurophysiol 110:1965–1974

Freeman H, Puech AJ, Roth T (1996) Zolpidem: an Update of Its Pharmacological Properties and Therapeutic Place in the Management of Insomnia. Elsevier, Amsterdam, Oxford, Paris, New York, Tokyo

Gillin JC, Spinweber CL, Johnson LC (1989) Rebound insomnia: a critical review. J Clin Psychopharmacol 9:161–171

Goa KL, Heel RC (1986) Zopiclone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. Drugs 32:48–65

Hajak G, Clarenbach P, Fischer W, Rodenbeck A, Bandelow B, Broocks A, Rüther E (1998) Rebound insomnia after hypnotic withdrawal in insomniac outpatients. Eur Arch Psychiatry Clin Neurosci 248:148–156

Hajak G (1999) A comparative assessment of the risks and benefits of zopiclone. A review of 15 years' clinical experience. Drug Safety 6:457–469

Hohagen F, Rink K, Käppler C, Schramm E, Riemann D, Weyerer S, Berger M (1993) Prevalence and treatment of insomnia in general practice. A longitudinal study. Eur Arch Psychiatry Clin Neurosci 242:329–336

Hollister LE, Motzenbecker FP, Degan RO (1961) Withdrawal reactions from chlordiazepoxide (Librium). Psychopharmacology 2:63–68

Hurst M, Noble S (1999) Zaleplon. CNS Drugs 11:387–392

Janke W, Debus G (1978) Die Eigenschaftswörterliste. Hogrefe, Göttingen

Kales A, Scharf M, Kales J (1978) Rebound insomnia: a new clinical syndrome. Science 201:1039–1041

Kales A, Soldatos CR, Bixler EO, Kales JD (1983 a) Early morning insomnia with rapidly eliminated benzodiazepines. Science 220:95–97

Kales A, Soldatos CR, Bixler EO, Kales JD (1983 b) Rebound insomnia and rebound anxiety: a review. Pharmacology 26:121–137

Kales A, Bixler EO, Vela-Bueno A, Soldatos CR, Niklaus DE, Manfredi RL (1986) Comparison of short and long half-life benzodiazepine hypnotics: triazolam and quazepam. Clin Pharmacol Ther 40:378–86

Kales A, Manfredi RL, Vgontzas AN, Bixler EO, Vela-Bueno A, Fee EC (1990) Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. Clin Pharmacol Ther 49:468–476

Keup W (1998) Zolpidem und Zopiclon. Geringeres Mißbrauchspotential verglichen mit Benzodiazepin-Hypnotika. Psychopharmakotherapie 5:134–142

Lader M, Lawson C (1987) Sleep studies and rebound insomnia; methodological problems, laboratory findings, and clinical implications. Clin Neuropharmacol 10:291–312

Lader M (1992) Rebound insomnia and newer hypnotics. Psychopharmacology 108:248–255

Lader M (1998) The consequences of zopiclone use: rebound insomnia, development of tolerance, and abuse potential. Rev Contemp Pharmacother 9:131–140

Langtry HD, Benfield P (1990) Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 40:291–313

Mamelak M, Csima A, Price V (1982) Effects of zopiclone on the sleep of chronic insomniacs. Int Pharmacopsychiatry 17 (suppl 2):156–164

Mann K, Bauer H, Hiemke C, Röschke J, Wetzel H, Benkert O (1996) Acute, subchronic and discontinuation effects of zopiclone on sleep EEG and nocturnal melatonin secretion. European Neuropsychopharmacology 6:163–168

Merz WA, Ballmer U (1983) Symptoms of the barbiturate/benzodiazepine withdrawal syndrome in healthy volunteers: standardized assessment by a newly developed self-rating scale. J of Psychoactive Drugs 15:71–84

Monti JM (1989) Effect of zolpidem on sleep in insomniac patients Eur J Clin Pharmacol 36:461–466

Monti JM, Attali P, Monti D, Zipfel A, de la Giclais B, Morselli PL (1994) Zolpidem and rebound insomnia – a double-blind, controlled polysomnographic study in chronic insomniac patients. Pharmacopsychiatry 27:166–175

Noble S, Langtry HD, Lamb HM (1998) Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. Drugs 55:279–302

Pecknold J, Wilson R, le Morvan P (1990) Long term efficacy and withdrawal of zopiclone: a sleep laboratory study. Int Clinical Psychopharmacology 5 (suppl 2):57–67

Rechtschaffen A, Kales A (1968) A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Department of Health, Education, and Welfare, Washington, DC

Roehrs TA, Zorick FJ, Wittig RM, Roth T (1986) Dose determinants of rebound insomnia. Br J Clin Pharmacol 22:143–147

Roehrs T, Vogel G, Roth T (1990) Rebound insomnia: its determinants and significance. Am J Med 88, 3A:39S–42S

Roehrs T, Merlotti L, Zorick F, Roth T (1992) Rebound insomnia in normals and patients with insomnia after abrupt and tapered discontinuation. Psychopharmacology 108:67–71

Roy-Byrne PP, Hommer D (1988) Benzodiazepine withdrawal: an overview and implications for the treatment of anxiety. Am J Med 84:1041–1052

Vogel G, Poirrier R (1996) Studies of effects following discontinuation of zolpidem treatment. In: Freeman H, Puech AJ, Roth T (Eds) Zolpidem: an Update of Its Pharmacological Properties and Therapeutic Place in the Management of Insomnia. Elsevier, Amsterdam, Oxford, Paris, New York, Tokyo, pp 149–160

Wadworth AN, McTavish D (1993) Zopiclone. A review of its pharmacological properties and therapeutic efficacy as an hypnotic. Drugs & Aging 3:441–459

Walsh JK, Vogel GW, Scharf M, Erman M, Erwin CW, Schweitzer PK, Mangano RM, Roth T (2000) A five week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Med 1:41–49

Ware JC, Walsh JK, Scharf MB, Roehrs T, Roth T, Vogel GW (1997) Minimal rebound insomnia after treatment with 10-mg zolpidem. Clin Neuropharmacol 20:116–125