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G. Hajak · P. Clarenbach · W. Fischer · A. Rodenbeck
B. Bandelow · A. Broocks · E. Rüther

Rebound insomnia after hypnotic withdrawal in insomniac outpatients

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Abstract The effect of abrupt medication withdrawal (no-pill discontinuation) was investigated in 1507 insomniacs using the patients' self-ratings on visual analogue scales. Drug discontinuation followed a 28-day treatment period with either 7.5 mg zopiclone, 0.25 mg triazolam, 1.0 mg flunitrazepam, or placebo in a randomized, double-blind, parallel group, multicenter study in private practice. Deterioration below individual pretreatment values (no-pill baseline) in at least one of three subjective parameters of sleep quality (sleep latency, total sleep time, nocturnal awakenings) and three parameters of daytime well-being (morning freshness, daytime tiredness, anxiety) were defined as rebound. The number of patients with rebound (rebound rate) was analyzed for every day of a 2-week posttreatment period. The overall rebound rate was higher in the placebo group ($p \leq 0.001$) than in each group treated with active drugs. Rebound rates affecting sleep quality were higher for placebo than for zopiclone ($p \leq 0.001$) and for flunitrazepam ($p \leq 0.05$). Rebound rates were smaller for zopiclone ($p \leq 0.001$) and flunitrazepam ($p \leq 0.01$) than for triazolam. Rebound in at least one item per day appeared in 21.5% (sleep quality) and 25.5% (daytime well-being) of the patients. Rebound decreased with increasing numbers of items of sleep quality or daytime well-being. Patients who did not respond to treatment showed higher rebound rates than those who were treatment responders ($p \leq 0.001$). Concerning treatment nonresponders, highest rebound was seen in the placebo group, whereas rebound was lowest in placebo responders. These results show that pill discontinuation itself may worsen sleep and daytime well-being in the sense of a rebound phenomenon. Furthermore, the number of patients with rebound remained at a high and varying level during the whole posttreatment period. This result indicates that a deterioration of sleep after drug withdrawal is not apparent during a few days but may last for longer periods in some patients and is modified by marked night-to-night variations.

Key words Rebound · Withdrawal · Insomnia · Sleep · Hypnotics

G. Hajak (✉) · A. Rodenbeck · B. Bandelow · A. Broocks
E. Rüther
Department of Psychiatry, University of Göttingen,
von-Siebold-Strasse 5, D-37075 Göttingen, Germany

P. Clarenbach
Department of Neurology,
Evangelisches Johannes-Krankenhaus, Bielefeld, Germany

W. Fischer
Rhone-Poulenc Rorer GmbH, Köln, Germany

Introduction

Rebound insomnia is a serious problem arising with the use of commonly taken benzodiazepine hypnotics: Upon discontinuation, sleep worsens in comparison with pretreatment levels (Lader 1992). Rebound insomnia becomes apparent when a hypnotic is taken for at least several nights and then stopped (Kales et al. 1991). Some patients suffer one, two, and sometimes three or more nights of insomnia worse than that experienced before treatment (Kales et al. 1983; Gillin et al. 1989; Lader 1992). Rebound insomnia may be interpreted as a deterioration in insomnia by the patient (Lader 1992) and as the appearance of withdrawal symptoms related to physical dependence by the physician (Morgan 1990). This may lead both, the patient and physician, to restart hypnotic intake. It is logically apparent with such a connection (Roehrs et al. 1990) that resuming medication increases the risk of long-term use and may form an essential prerequisite in the cause of drug dependence. Thus, the existence or absence of rebound has become an important factor when judging the "benefit/risk ratio" of hypnotic drugs.

There is limited evidence from existing studies for a reduced rebound potential of the new nonbenzodiazepine hypnotics compared with benzodiazepine hypnotics of equivalent duration of action (Lader 1992). However, before accepting this claim, studies are required which consider the following aspects:

1. The initial definition of rebound insomnia was based on sleep laboratory recordings (Kales et al. 1978, 1979). Nevertheless, data on subjective rebound measured by questionnaires appear to be more relevant in explaining clinical consequences (Schneider-Helmert 1988).
2. Rebound symptoms are not only restricted to insomnia but also include anxiety. Since rebound anxiety has been found after discontinuation of benzodiazepines (Kales et al. 1983; Fontaine et al. 1984), parameters of anxiety and daytime well-being should be assessed during the withdrawal of hypnotics.
3. Sleep quality in general, intensity of sleep complaints, and type of insomnia vary over time in both, a day-by-day and a long-term pattern (Roth et al. 1977; Hohagen et al. 1994). Observation periods after withdrawal should therefore exceed the commonly used 1–3 days to differentiate between rebound and spontaneous variability.
4. With respect to variation, caution in interpreting rebound studies is appropriate because the number of subjects studied often has been insufficient, especially for the significant revelation of differences between treatment groups.
5. Sleep, whether in normal subjects or insomniacs, tends to improve spontaneously over time (Roth et al. 1977; Mamelak et al. 1989). Therefore, parallel placebo treatment is needed so that rebound insomnia can be assessed between verum and placebo treated groups.
6. A difference between pretreatment sleep and sleep during discontinuation of benzodiazepines has been found in one study, regardless of the type of treatment with active drug or placebo (Roehrs et al. 1992a). This suggests that pill discontinuation itself might cause rebound insomnia in the sense of a placebo effect.

The present study investigated rebound symptoms in patients with insomnia in an attempt to address the above-mentioned aspects. Patients were treated with the nonbenzodiazepine hypnotic zopiclone, the benzodiazepines triazolam and flunitrazepam, and placebo. The therapeutic effects have been presented in a previous paper (Hajak et al. 1994).

Materials and methods

A multicenter, randomized, double-blind study was performed with a total of 1507 outpatients (age range 18–71 years, mean age 51 ± 11 years), who were treated by 158 general practitioners, internists, psychiatrists, and neurologists. Written informed consent was obtained from all patients and the study was approved by the local ethics committee. All physicians serving as investigators attended a 1-day training course on the diagnosis of sleep disorders and the way to carry out double-blind studies. A semi-structred interview on sleep disorders, including a symptom checklist, was introduced. This procedure should guarantee valid and reliable diagnosing by the large and heterogenous group of physicians.

All the patients suffered from insomnia either due to difficulties in initiating and/or maintaining sleep, or due to non-refreshing sleep. Patients met the following criteria required for the study: insomnia of at least 4-week duration and the presence of at least two of the following as a mean of 3 days before starting treatment (no-pill baseline): (a) sleep latency ≥ 45 min, (b) total sleep time ≤ 6 h, and (c) nocturnal awakening ≥ 3 times. It is a consequence of carrying out this study with a heterogenous group of physicians that 216 (14.3%) of the included patients suffered from difficulties falling and staying asleep but did not meet the criteria of severity given in the study design. However, all 1507 patients received medication and were therefore included in the intent-to-treat analysis. Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded from this study. The only concurrent therapies permitted consisted mainly of cardiovascular agents, drugs

Table 1 Characteristics of the patients

	Total (n = 1507)	Zopiclone (n = 612)	Triazolam (n = 307)	Flunitrazepam (n = 307)	Placebo (n = 298)
Gender					
Male	566 (37.6)	223 (36.4)[a]	123 (40.1)	108 (37.2)	112 (37.6)[a]
Female	939 (62.3)	388 (63.4)	184 (59.9)	182 (62.8)	185 (62.1)
Age (years; mean ± SD)	51 ± 11	51 ± 11	51 ± 10	51 ± 10	51 ± 11
Height (cm; mean ± SD)	169 ± 8	169 ± 8	169 ± 8	169 ± 8	169 ± 8
Weight (kg; mean ± SD)	72 ± 12	72 ± 12	72 ± 12	72 ± 12	72 ± 12
Ethnic origin					
Caucasian	1497 (99.3)	606 (99.0)	306 (99.7)[a]	288 (99.3)	297 (99.7)[a]
Other	10 (0.9)	6 (1.0)	–	2 (0.7)	–
Insomnia[b]					
Total	1291 (85.7)	522 (85.3)	256 (83.4)	254 (87.6)	259 (86.9)
≤ 1 year	553 (36.7)	224 (36.7)	107 (34.8)	113 (39.1)	109 (36.5)
≥ 1 year	744 (49.3)	309 (50.5)	154 (50.1)	135 (46.5)	146 (49.0)
Work-related	328 (21.8)	135 (22.1)	62 (20.2)	64 (22.1)	67 (22.5)
Family-related	315 (20.9)	126 (20.6)	73 (23.8)	56 (19.3)	60 (20.1)
Drug pretreatment [no. (%)]					
Benzodiazepines	465 (30.9)	186 (30.4)	110 (35.8)	83 (28.6)	86 (28.9)
Other CNS drugs	188 (12.5)	73 (11.9)	38 (12.4)	39 (13.4)	38 (12.8)

Numbers in parentheses are percentages
[a] In 1 case data not given
[b] Multiple response possible

for metabolic disorders, and analgesics. Previous treatment with benzodiazepines had been undertaken in 30.9% of the subjects, whereas 12.5% had been treated with other centrally active drugs. The most frequent causes given for the insomnia were occupational stress or trouble with colleagues (21.8%), family problems (20.9%), partner problems (7.2%), or the death of a wife or husband (5.8%). The patients' characteristics were comparable in all four treatment groups regarding gender, age, height, weight, probable origin and duration of insomnia, and drug pretreatment (Table 1).

The statistically necessary sample size was determined to include 409 patients per group. In order to reduce the number of patients who had to be treated with benzodiazepine hypnotics, the random generator was adjusted according to a 2 (zopiclone):1 (triazolam):1 (flunitrazepam):1 (placebo) proportion in center-specific randomization blocks of 5 patients. Medication was applied in a double-blind manner using identical capsules for active drugs and placebo. All capsules were packed in blisters for daily intake during a 1-week treatment period. Following a 3-day washout phase, patients took their capsules containing the original preparations of either zopiclone (7.5 mg), flunitrazepam (1 mg), triazolam (0.25 mg), or placebo (1 capsule) every evening before going to bed for a period of 28 days. On day 29 the active drugs and placebo were abruptly withdrawn and the patients were observed for a further period of 14 days without medication.

Quality of sleep and daytime well-being were recorded daily by the patients using the Visual Analogue Scale (VIS-A for evening assessment and VIS-M for morning assessment) of Ott and colleagues (1986). A compliance check on study medication was done weekly by collecting the empty blisters. Checking on proper intake of study medication, concomitant medication, and alcohol consumption was performed at weekly intervals by investigator interviews using a checklist.

Treatment outcome was calculated as treatment response rates. Patients were defined as responders if they showed improvement in at least one sleep item (shortening of sleep latency by at least 15 min, or prolongation of total sleep time by at least 20%, or reduction of the number of nocturnal awakenings to three or less) and a fresh feeling upon waking up in the morning as well as no impairment in daytime well-being as a result of tiredness or anxiety at the end of the 4-week treatment period. (Daytime anxiousness and tiredness as well as not being refreshed when awakening was assumed when the visual analogue scale score exceeded 25 mm.)

The quantitative assessment for the determination of rebound was a deterioration below individual mean pretreatment values of the scores given on the visual analogue scales during the discontinuation period. A patient was counted as having rebound according to the following: deterioration in at least one of the three sleep quality parameters (a) sleep latency, (b) total sleep time, or (c) number of nocturnal awakenings; or deterioration in at least one parameter of daytime well-being defined as (d) a feeling of being refreshed on awakening in the morning, or as an impairment in daytime well-being as a result of (e) tiredness or (f) anxiety.

Rebound based on individual subject data was analyzed for the occurrence of rebound criteria for sleep quality and daytime well-being. Rebound values are given as percentage of patients with rebound from the treatment groups (rebound rate) for each day of measurement during the 2 weeks of the posttreatment period (days 29–42). Rebound rates were analyzed for the whole patient group, treatment responders, and treatment nonresponders, and are presented as overall rebound rates, rebound rates for items of sleep quality, rebound rates for items of daytime well-being, and rebound rates for different numbers of rebound items.

Statistical data analysis was performed with the multifactor analysis of variance with repeated measures (MANOVA) to determine whether there were differences between treatment groups, number of items, or days of rebound. If the overall F-values for differences were significant, subsequent post hoc analysis was performed using Scheffés' test.

Results

A total of 1507 patients received treatment: 612 patients received zopiclone, 290 flunitrazepam, 307 triazolam, and 298 placebo.

Treatment outcome and overall rebound rates

At the end of the 4-week treatment, total response, including improved sleep quality and daytime well-being, was significantly higher with zopiclone (37.4%) than with placebo (26.8%; $p \leq 0.0017$) and showed a tendency to be higher than that with triazolam (32.2%) or flunitrazepam (30.0%). This response was mainly due to response in daytime well-being, since parameters of sleep quality were markedly improved in all treatment groups including placebo (zopiclone 94.0%, flunitrazepam 95.5%, triazo-

Table 2 Overall rebound rates (percentages of patients with rebound per treatment group; mean ± SD) and rebound rates of patients who met the criteria for total treatment response (responders) and of nonresponders. For significant differences see text

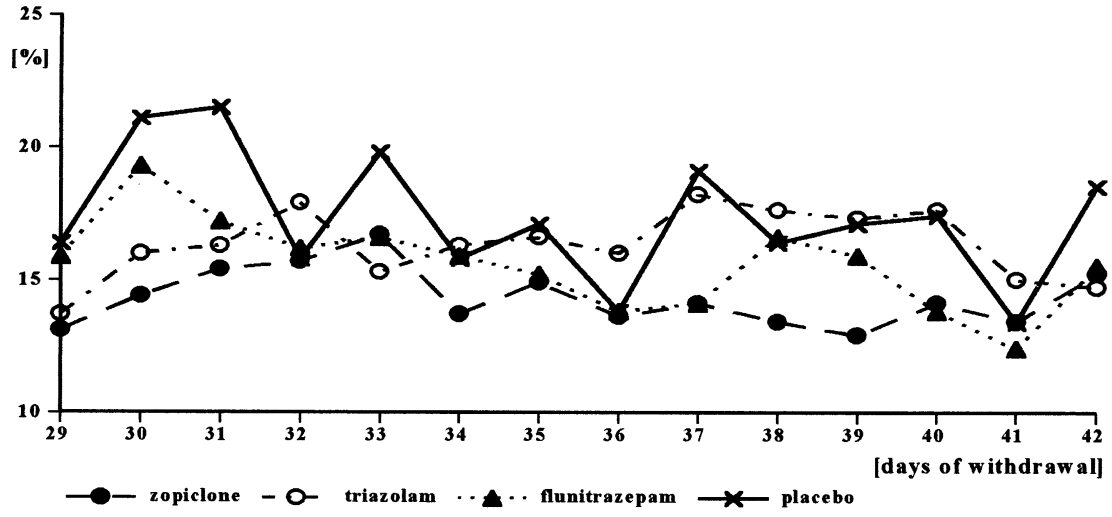
	Overall rebound	Responder	Nonresponder
Zopiclone	46.07 ± 1.42	9.05 ± 1.16	36.02 ± 1.35
Triazolam	46.63 ± 1.93	7.70 ± 0.88	38.93 ± 1.45
Flunitrazepam	46.36 ± 2.30	5.59 ± 0.88	40.76 ± 1.61
Placebo	48.56 ± 3.28	4.92 ± 1.20	43.65 ± 2.49

Table 3 Rebound rates (percentages of patients with rebound per treatment group; mean ± SD) for one up to three items of sleep quality (sleep latency, total sleep time, nocturnal awakenings) and three items of daytime well-being (morning freshness, daytime tiredness, anxiety). For significant differences see text

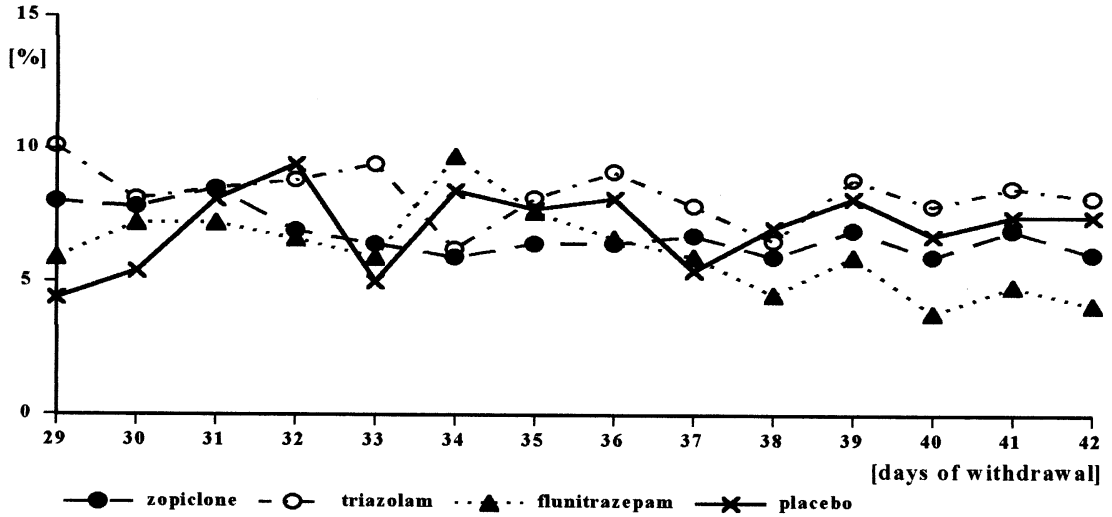
Rebound in items of sleep quality			
	1 item	2 items	3 items
Zopiclone	14.33 ± 1.11	6.76 ± 0.83	2.36 ± 0.47
Triazolam	16.32 ± 1.33	8.27 ± 1.04	2.39 ± 0.85
Flunitrazepam	15.60 ± 1.71	6.12 ± 1.57	2.84 ± 0.67
Placebo	17.37 ± 2.43	7.04 ± 1.47	2.22 ± 0.92
Rebound in items of daytime well-being			
	1 item	2 items	3 items
Zopiclone	18.52 ± 1.44	14.09 ± 1.11	7.89 ± 0.82
Triazolam	190.4 ± 2.00	13.10 ± 1.91	7.73 ± 1.33
Flunitrazepam	19.09 ± 1.54	14.04 ± 2.78	6.89 ± 1.14
Placebo	22.06 ± 2.49	11.41 ± 2.13	6.91 ± 0.86

Fig. 1 Rebound rates (percentages of patients with rebound per ▶ treatment group) of sleep quality (sleep latency, total sleep time, nocturnal awakenings) with rebound affecting **a** one item, **b** two items, or **c** three items during the course of the posttreatment period. $N_{total} = 1507$; $N_{zopiclone} = 612$; $N_{triazolam} = 307$; $N_{flunitrazepam} = 290$; $N_{placebo} = 298$

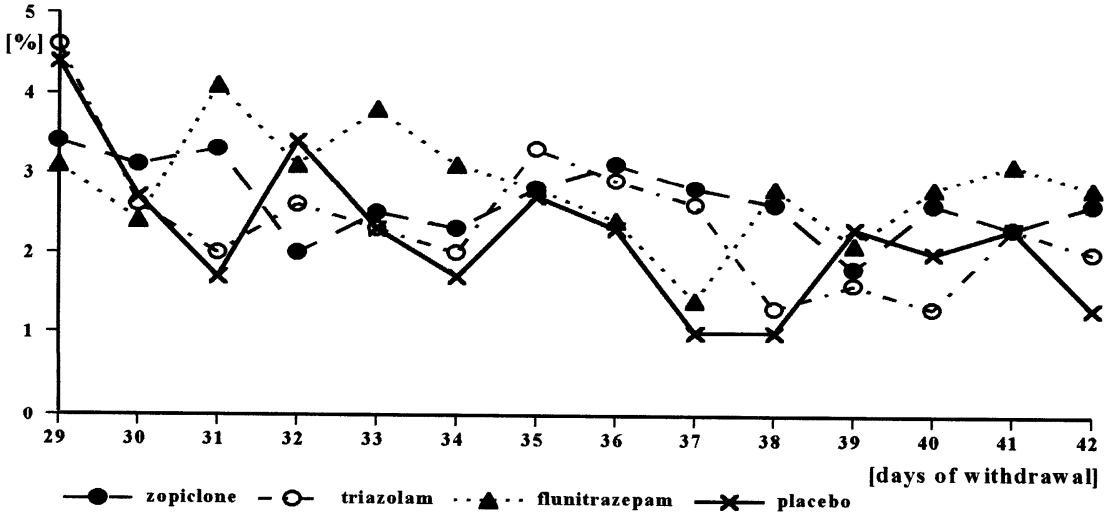
a rebound in 1 item of sleep quality



b rebound in 2 items of sleep quality



c rebound in 3 items of sleep quality



lam 93.8%, and placebo 85.9%; for details see Hajak et al. 1994).

Rebound criteria were met by patients from all treatment groups, including the placebo group. Two-factor ANOVA with repeated measures for overall rebound including all items of sleep quality and daytime well-being (treatment groups, days of withdrawal) revealed significant differences between treatment groups (F = 4.345; df = 3; $p \leq 0.01$) and days of withdrawal (F = 4.88; df = 13; $p \leq 0.05$). Post hoc Scheffés' test shows that the number of patients with rebound (rebound rate) was significantly higher in the placebo group than in the groups treated with active drugs ($p \leq 0.01$ for comparison of each drug to placebo), whereas there were no differences between active drugs (Table 2). The rebound rates were lower on the first day of drug discontinuation (day 29) than on day 31 ($p \leq 0.05$).

Rebound rates in treatment responders versus nonresponders

Three-factor ANOVA for rebound depending on treatment outcome (treatment groups, treatment outcome divided into responders and nonresponders, days of withdrawal) showed significant differences between groups and days of withdrawal (see above), but also between treatment responders and nonresponders (F = 31192.7; df = 1; $p \leq 0.001$). Moreover, MANOVA revealed a significant group-x treatment outcome interaction (F = 33.09; df = 3; $p \leq 0.001$). In the post hoc analysis with Scheffés' test, the rebound rate was lower in placebo responders compared with responders of all other groups ($p \leq 0.01$ for each comparison). Flunitrazepam responders showed a lower rebound rate than zopiclone ($p \leq 0.01$) or triazolam ($p \leq 0.01$) responders, whereas zopiclone responders showed higher rebound rates than triazolam responders ($p \leq 0.01$) (Table 2). In all treatment groups rebound rates were significantly higher in treatment nonresponders than in responders. Although the lowest rebound rate was seen in placebo responders, placebo nonresponders showed the highest rebound rate of all treatment groups ($p \leq 0.01$ for the comparison with each active drug). Comparing rebound in nonresponders following active drugs, the rebound rate was higher in flunitrazepam nonresponders than in triazolam nonresponders ($p \leq 0.01$) or zopiclone nonresponders ($p \leq 0.01$). Triazolam nonresponders showed a higher rebound rate than zopiclone nonresponders ($p \leq 0.01$; Table 2).

Rebound rates for varying numbers of rebound items

Rebound rates for one, two, and three rebound items for both, rebound in sleep quality and daytime well-being, are shown for each day of the study in Figs. 1 and 2. A deterioration in sleep quality concerning one rebound item for at least 1 day of the posttreatment period was experienced by 12.4–21.5% of the patients (Fig. 1a), whereas 15.6–25.5% of patients experienced a deterioration in daytime well-being (Fig. 2a). Rebound rates decreased with increasing number of rebound items. With the maximum of three rebound items, rebound rates ranged between 1.0 and 4.6% (sleep quality; Fig. 1c), and 5.4% and 10.1% (daytime well-being; Fig. 2c). Figures 1 and 2 show that the rebound rates for sleep quality were highest during the first days of withdrawal, but only slightly higher than the range of variation in the rebound rate which was measured during the posttreatment period.

Rebound rates for items of sleep quality

Three-factor ANOVA (treatment groups, number of items, days of withdrawal) for items of sleep quality revealed significant differences between treatment groups (F = 11.2; df = 3; $p \leq 0.001$), number of items (F = 2506.7; df = 2; $p \leq 0.001$), and days of withdrawal (F = 3.1; df = 13; $p \leq 0.001$). Post hoc analysis with Scheffés' test shows that rebound rates were significantly lower for zopiclone than for triazolam ($p \leq 0.001$) and placebo ($p \leq 0.001$). Rebound rates were also lower for flunitrazepam than for triazolam ($p \leq 0.01$) and for placebo ($p \leq 0.05$). The number of patients with rebound decreased with increasing number of rebound items ($p \leq 0.001$) and showed a marked variabilty during the posttreatment period (Fig. 1).

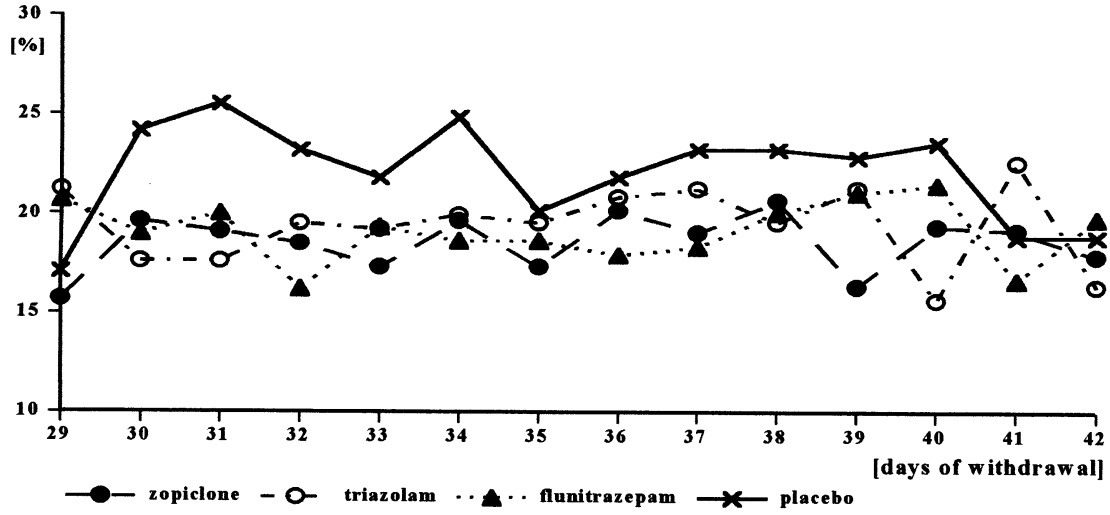
Same MANOVA revealed a significant group-x number of items interaction (F = 11.5; df = 6; $p \leq 0.001$). Subsequent post hoc Scheffés' test showed that the number of patients having a rebound in one item was significantly lower for zopiclone than for triazolam ($p \leq 0.001$) and placebo ($p \leq 0.001$). Patients treated with flunitrazepam showed a lower rebound rate in one item than patients of the placebo group ($p \leq 0.01$). Concerning two items triazolam rebound rate was higher than for zopiclone ($p \leq 0.05$) and for flunitrazepam ($p \leq 0.001$), whereas there were no differences comparing the treatment groups for three rebound items.

Rebound rates for items of daytime well-being

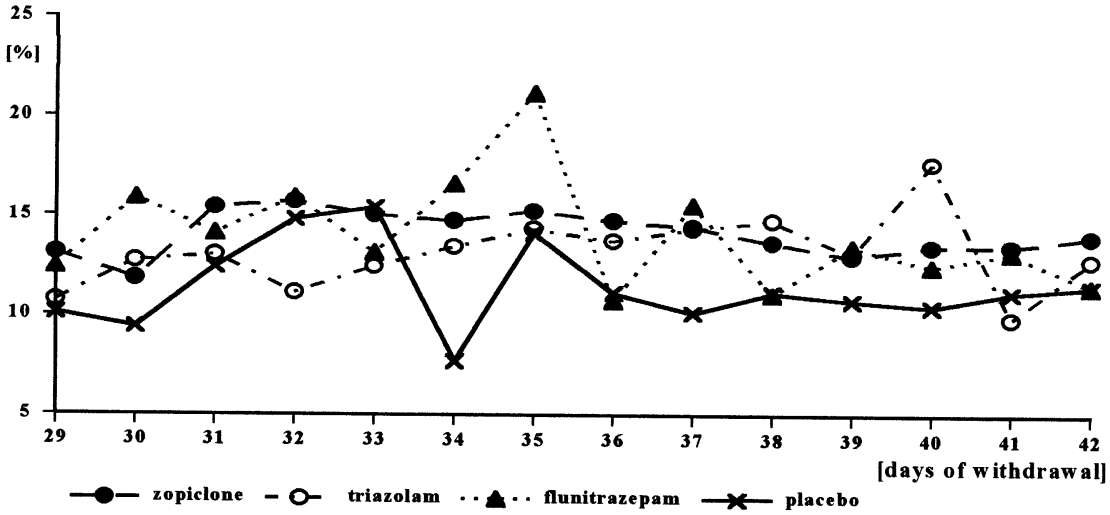
The MANOVA for rebound items of daytime well-being revealed a significant difference for number of items (F = 860.1; df = 2; $p \leq 0.001$), but not for treatment groups and days with rebound. Thus, in the Scheffé test the number of patients with rebound decreased with increasing number of rebound items (Fig. 2). Furthermore, MANOVA revealed a significant group-x number of items interaction (F = 12.2; df = 6; $p \leq 0.001$). Subsequent post hoc Schef-

Fig. 2 Rebound rates (percentages of patients with rebound per ▶ treatment group) of daytime well-being (morning freshness, daytime tiredness, anxiety) with rebound of **a** one item, **b** two items, or **c** three items during the course of the posttreatment period. N_{total} = 1507; $N_{zopiclone}$ = 612; $N_{triazolam}$ = 307; $N_{flunitrazepam}$ = 290; $N_{placebo}$ = 298

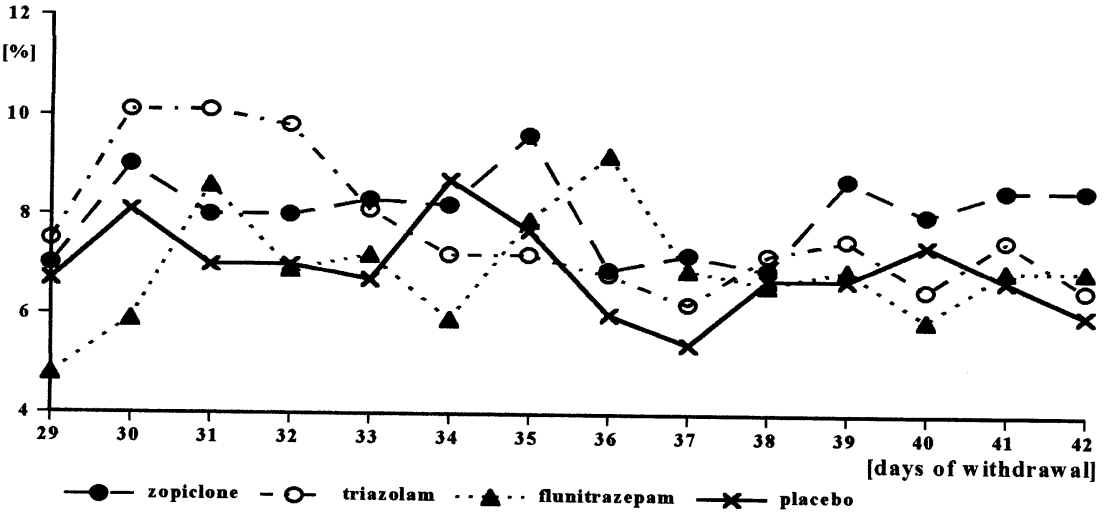
a rebound in 1 item of daytime well-being



b rebound in 2 items of daytime well-being



c rebound in 3 items of daytime well-being



fés' test showed that the rebound rate was significantly lower in patients treated with zopiclone than patients of the placebo group concerning one item only ($p \leq 0.05$). There were no differences between any treatment group regarding two or three items.

Discussion

This study shows that not only a remarkable number of patients treated with active drugs, but also patients treated with placebo, experience a deterioration in subjective sleep parameters after drug discontinuation in comparison with pretreatment levels. The number of patients with rebound in the placebo group was even higher than in those patients treated with either zopiclone, triazolam, or flunitrazepam. These results correspond to a study on rebound in a small group of 21 insomniacs and controls which reported that the average values of polysomnographic sleep parameters were significantly disturbed on the discontinuation night compared with the baseline night, regardless of treatment with triazolam or placebo (Roehrs et al. 1992a). To the best of our knowledge, all other existing studies on rebound insomnia have compared a placebo baseline or parallel placebo condition to a placebo discontinuation. These investigations, therefore, were not able to detect rebound phenomena related to withdrawal of pills not containing active drugs. The presented study compared a no-pill baseline to a no-pill discontinuation after 28 consecutive nights of pill administration. Although rebound phenomena undoubtedly have a pharmacological basis and may be related to some disregulation of central nervous receptor binding (Miller et al. 1988), our results indicate that pill discontinuation itself may worsen sleep in the form of rebound insomnia with impaired daytime well-being.

The analysis of rebound in the present study differed from the way rebound has been analyzed in other studies. Rebound was initially defined as a statistically significant increase or an increase of 40% or greater in the mean group value for total wake time for a single withdrawal night or for the entire withdrawal condition as compared with baseline (Kales et al. 1983). Later, rebound was also measured in terms of other sleep parameters such as sleep latency, sleep efficiency, or wake time after sleep onset (Gillin et al. 1989). Ample evidence exists for the occurrence of rebound phenomena when using this definition, particularly with benzodiazepines with short half-lives and with administration at high doses over long periods (Kales et al. 1983; Lader and Lawson 1987; Gillin et al. 1989). Therefore, rebound was detected by analyzing averaged sleep parameters of treatment groups after drug withdrawal, not only in the above-mentioned articles but also in most studies done in this field. However, no or at most only a few rebound phenomena were observed using these criteria under normal dosing regimes in a numerous studies on flunitrazepam (e.g., Bixler et al. 1977; Lingjaerde et al. 1983), triazolam (e.g., Pegram et al. 1980; Spinweber and Johnson 1982; Borbély et al. 1983), and zopiclone (for reviews see Bianchi and Musch 1990; Wadworth and MacTavish 1993). Individual characteristics of patients might be suspected as one reason, since there is considerable interindividual variation in the occurrence of rebound symptoms. Some subjects consistently experience rebound insomnia, whereas others consistently do not (Merlotti et al. 1991). On the basis of the available evidence, it is clear that rebound symptoms may occur in isolated cases, which particularly are not evident from the statistical analyses of mean values of sleep parameters obtained in large studies, such as the present investigation. Consequently, and in contrast to former investigations, in this study rebound was analyzed by counting the number of patients with rebound per treatment group ("rebound rates"). Only those patients who rated a decline in subjective sleep or daytime well-being on their visual analogue scales after drug withdrawal as compared with their mean baseline values were considered to fulfill the criteria of rebound.

The reasons for placebo rebound as found in this study are not clear but are most probably psychological. The expectation of difficulties in initiating or maintaining sleep after drug withdrawal might be one reason (Roehrs et al. 1992a). The role of expectation in alcohol effects has been well documented (Hull and Bond 1986). Expectation of discontinuing diazepam has also been shown to be associated with symptoms of a pseudo-withdrawal (Winokur and Rickels 1981). Since in this study the number of patients per group who did not fulfill the criteria of treatment response, but those for rebound increased with decreasing treatment outcome, it could be speculated that worse treatment outcome might predict a patient to expect a deterioration of sleep following drug discontinuation. This expectation may be an important factor in rebound insomnia found in this study and in general. Indeed, there might be an interaction between treatment outcome and the occurrence of rebound, since healthy subjects with rebound were shown to have a greater treatment effect than subjects without rebound (Merlotti et al. 1991).

When analyzing single rebound items, an enhanced placebo rebound compared to active drugs was only seen for the rebound in one item, whereas rebound rates for placebo did not differ from active drugs in two or three rebound items. This was found to be true for items of sleep quality and daytime well-being. If an increased number of items in which rebound occurred were a reliable tool for the severity of rebound, it could be concluded that discontinuation of placebo treatment was followed by a high rebound rate but combined with a mild quality of rebound.

The special interest in the rebound evident in the present investigation arose from the suspicion that rebound predisposes the patient to long-term use of hypnotics, and that it may be an indicator of incipient dependence. The small amount of existing data regarding clinical implications of rebound are somewhat controversial. Most studies strongly suggest that rebound insomnia is a relevant clinical factor in the routine use of hypnotics for a longer term (Oswald et al. 1982). It has also been stated that rebound insomnia is a frequently cited reason for patients

restarting their hypnotic drugs (Morgan 1990). One study on 21 subjects, which addressed this issue controversially, found that the experience of rebound insomnia after a short treatment period of 7 days did not increase the likelihood of self-administration of a benzodiazepine hypnotic (Roehrs et al. 1992b). Regardless of these contradictions, the present study shows that not only the pharmacological substance, but also the psychological aspect of medication intake and treatment outcome, has to be taken into account when judging the rebound-related risk of restarting hypnotic treatment.

Despite the placebo rebound and the dependence on treatment outcome, differences in rebound rates between patients who responded to active drugs indicate that there is an indisputable pharmacological component influencing rebound phenomena. In this study rebound rates were higher in the triazolam group than in the flunitrazepam group. Elimination half-life of a drug has been suspected to be an important determinant of the occurrence of rebound symptoms (Gillin et al. 1989; Roth and Roehrs 1991), and it has been claimed that short-acting hypnotics show rebound insomnia more frequently (Lader and Lawson 1987; Gillin et al. 1989). This was proven to be true in our study for the two benzodiazepine hypnotics tested. However, rebound rates of treatment responders were higher in patients treated with zopiclone (elimination half-life 5–7 h) than in patients treated with triazolam (elimination half-life 3–5 h) or flunitrazepam (elimination half-life 15 h). In contrast, rebound rates regarding rebound in items of sleep quality were smaller in patients treated with zopiclone than in patients treated with triazolam. These somewhat inconsistent results do not totally support the existing, though limited, evidence that nonbenzodiazepine hypnotics, e.g., zopiclone, have less rebound potential than benzodiazepine hypnotics (Bianchi and Musch 1990; Lader 1992; Shapiro et al. 1993).

The detection of rebound in this study was also dependent on whether the rebound was rated using items of sleep quality or items of daytime well-being. Rebound rates were higher concerning the chosen items of daytime well-being than items of sleep quality. Rebound anxiety or depression, as well as other symptoms of daytime impairment, are well known to be related to the discontinuation of benzodiazepines (Kales et al. 1983; Fontaine et al. 1984; Lader 1994; Petursson 1994). It has been discussed recently that the impaired daytime well-being resulting from insomnia deeply interferes with the quality of life as well as daytime performance (Partinen 1993; Billiard and Guelfi 1995). As a direct consequence of the interdependence of impaired daytime performance and vigilance with an increased risk of morbidity, accident, and injury (Kripke et al. 1991; Klink et al. 1992; Martikainen et al. 1992), analysis of rebound symptoms needs to take account of the whole 24-h cycle and not just concentrate on sleep. Thus, it appears to be highly important for further studies on rebound to discriminate more precisely between rebound items related to sleep or daytime condition.

Both, a deterioration in sleep quality and in daytime well-being compared with baseline, were not only found during the first days after drug discontinuation but also during the whole posttreatment period. With regard to the longer-lasting problems of drug withdrawal, some authors distinguish between different patterns of discontinuation syndromes. Withdrawal from hypnotics can result in a short-lived rebound developing within 1–4 days of discontinuation, a full-blown withdrawal syndrome usually lasting 10–14 days (Petursson 1994) and combined with physical withdrawal symptoms (Lader 1994), or a return of the initial symptoms of the disease (Petursson 1994). The present study shows, on the basis of the rebound criteria used, that there is a considerable overlap between these discontinuation patterns. A deterioration of sleep quality and daytime well-being compared with baseline was present during the whole posttreatment period, with rebound rates varying between all the days observed. A pronounced deterioration of daytime well-being was present during the first 6 days after withdrawal. There was a wide range of fluctuations in the rebound rates during the 2 weeks of posttreatment observation. This underlines that a marked night-to-night variation in sleep (Roth et al. 1977; Mamelak et al. 1989) influences rebound analyses. Indeed, data from other studies show clearly that a poor night of sleep on withdrawal may be followed by a very good night in compensation (Mamelak et al. 1984), and such cycles may even be repeated (Scharf and Jacoby 1982). Thus, older recommendations to investigate only the first 3 days after drug withdrawal (Federal Drug Administration 1977) are outdated. Long posttreatment observation periods as performed in this study are desirable to discriminate between short-lasting rebound, delayed rebound, withdrawal syndrome, longer-lasting deterioration of complaints, reappearance of the disease, and the spontaneous fluctuations in sleep quality.

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