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Withdrawal from long-term use of zopiclone, zolpidem and temazepam may improve perceived sleep and quality of life in older adults with primary insomnia

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Abstract

Long-term use of benzodiazepines or benzodiazepine receptor agonists is widespread, although guidelines recommend short-term use. Only few controlled studies have characterized the effect of discontinuation of their chronic use on sleep and quality of life. We studied perceived sleep and quality of life in 92 older (age 55-91 years) outpatients with primary insomnia before and after withdrawal from long-term use of zopiclone, zolpidem or temazepam (BZDA). BZDA was withdrawn during 1 month, during which the participants received psychosocial support and blindly melatonin or placebo. A questionnaire was used to study perceived sleep and quality of life before withdrawal, and 1 month and 6 months later. 89 participants completed the 6-month follow-up. As melatonin did not improve withdrawal, all participants were pooled and then separated based solely on the withdrawal results at 6 months (34 Withdrawers. 55 Nonwithdrawers) for this secondary analysis. At 6 months, the Withdrawers had significantly ($P < 0.05$) shorter sleep-onset latency and less difficulty in initiating sleep than at baseline and when compared to Nonwithdrawers. Compared to baseline, both Withdrawers and Nonwithdrawers had at 6 months significantly ($P < 0.05$) less fatigue during the morning and daytime. Stress was alleviated more in Withdrawers than in Nonwithdrawers ($P < 0.05$). Satisfaction with life and expected health 1 year later improved ($P < 0.05$) in Withdrawers. In conclusion, sleep disturbances, daytime fatigue and impaired quality of life may resolve within 6 months of BZDA withdrawal. These results encourage withdrawal from chronic use of benzodiazepine-type hypnotics, particularly in older subjects.

KEYWORDS

benzodiazepine agonists, older outpatients, perceived sleep, primary insomnia, quality of life, withdrawal from chronic use, Z-drugs

1 | INTRODUCTION

Insomnia is a frequent problem among older individuals. Benzodiazepines and related drugs (here BZDA) are recommended for short-term treatment of insomnia only, but their long-term use is widespread.[1-4] Chronic BZDA use in older adults is associated with an increased risk of adverse outcome such as balance difficulties, falling, cognitive impairment, dementia and increased mortality.[5-13]

Various strategies have been applied to improve the quality of hypnotic prescription and to withdraw BZDA hypnotics from their chronic users.[14-19] In Finland in 2009, that

is, when this study was started, sales of BZDA hypnotics were 51.4 defined daily doses (DDD)/1000 inhabitants, and zopiclone and zolpidem together with temazepam accounted for over 90% of the total hypnotic sales.[20]

Rebound symptoms, such as exacerbation of insomnia and anxiety, are usual after discontinuation of prolonged BZDA use. However, interindividual variation in sensitivity to rebound symptoms is large and may depend, for example, on pharmacokinetic properties and doses of the BZDAs used, duration of use, as well as on personality and concomitant diseases. Psychotherapeutic interventions and gradual BZDA dose reduction can alleviate rebound symptoms and improve withdrawal success.[15-19]

Only very few controlled studies have involved the effect of withdrawal from the long-term use of BZDA hypnotics on sleep and the quality of life in older people.[21,22] Our purpose was to investigate, as a part of our Satauni-BZDA withdrawal trial,[23] how older chronic BZDA users perceive their sleep and their quality of life before and after successful withdrawal. Accordingly, we compared the subjective sleep, freshness, and quality-of-life parameters at months 1 and 6 after start of dose-tapering to their baseline value within those participants who totally withdrew from BZDAs, and within those who continued their BZDA use as hypnotics. Furthermore, we compared these parameters between the Withdrawer- and Nonwithdrawers groups.

2 | MATERIALS AND METHODS

2.1 | Study design

The details of study design, the participants and the BZDA withdrawal results of our Satauni study have appeared earlier,[23] but no results on the effects of the BZDA withdrawal on the sleep and quality of life have been reported previously. In short, we performed during the years 2009-2010 a randomized, double-blind, placebo-controlled, parallel-group study on the efficacy of daily melatonin (2 mg) in BZDA withdrawal during a 1-month period and a double-blind 5-month follow-up (Figure 1). Randomization codes were decoded only at the end of follow-up. As melatonin did not improve withdrawal, the groups were pooled and then separated solely based on the BZDA withdrawal results at 6 months (34 Withdrawers vs 55 Nonwithdrawers) for this secondary analysis. The study protocol was approved by the Ethics Committee of Satakunta Hospital District (2§/7/2008) and by the National Agency for Medicines of Finland (218/2008; EudraCT 2008–0006795-30).

2.2 | Study population

Participants were primary healthcare outpatients who voluntarily entered our BZDA withdrawal study. A physician met the potential participants for screening and recruitment. Written informed consent came from each participant before the study began.

The participants, men and women, had to be at least 55 years old and be chronic users of zopiclone, zolpidem or temazepam as hypnotics, defined as 1 month or longer regular night-time use. The hypnotics must have been prescribed according to DSM-IV criteria for primary insomnia. The key exclusion criteria were concurrent use of other benzodiazepines or antipsychotic or anti-epileptic medications, a history of alcohol or drug abuse, severe anxiety disorder, or other severe psychiatric or neurological diseases, cancer or smoking of more than 10 cigarettes daily. Of the 92 initially recruited participants, two dropped out during the BZDA withdrawal period and one during the follow-up. We report here the sleep and quality-of-life data of those 89 individuals who were followed up for 6 months (Figure 1).

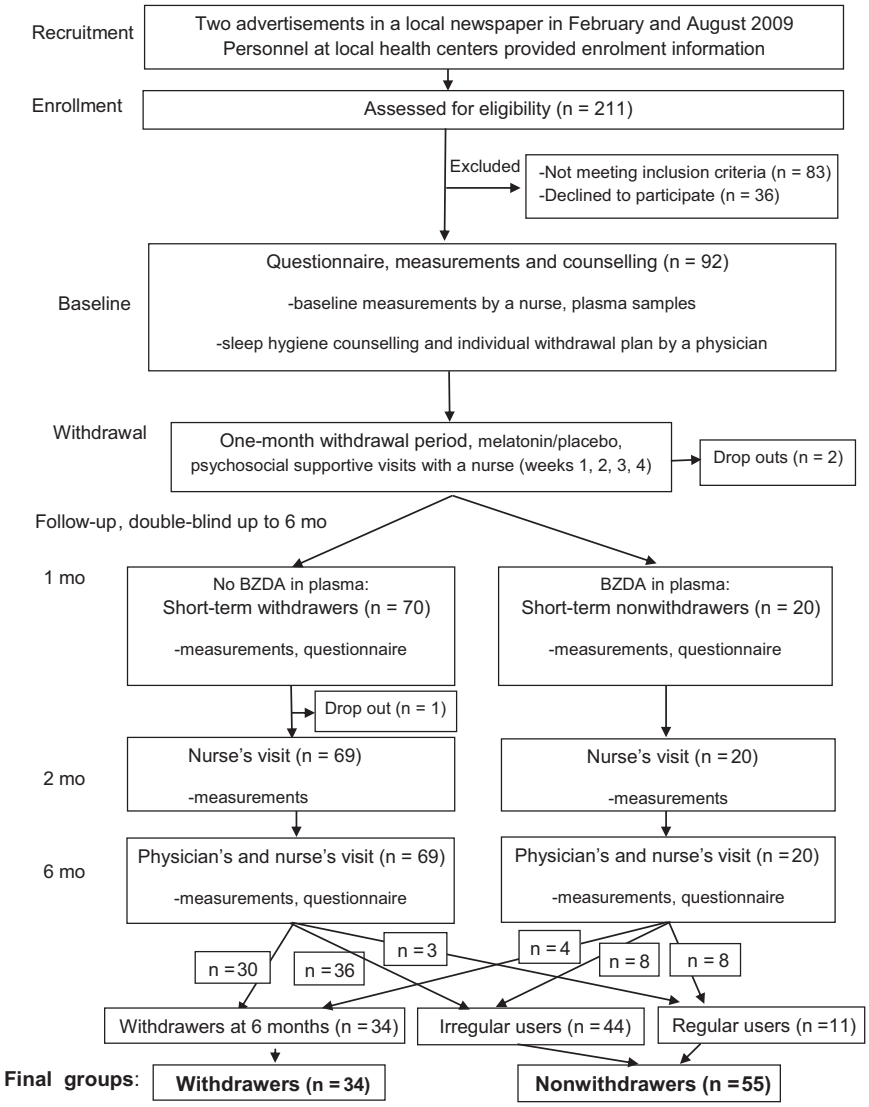
2.3 | Interventions

At baseline, a physician provided psychosocial support and individual sleep-hygiene counselling, including discussions with participants about regular sleep rhythm and the influence of the following on sleep: normal changes in sleep patterns related to ageing, the situation regarding the bedroom and bed, exercise, diet and alcohol use, coffee and stimulants prior to sleeping, deep and calm breathing, and psychological and physical relaxation in bed. If they were not asleep within 15 min., they were counselled to rise and do something relaxing.[23]

The physician performed a clinical examination and, in agreement with the participant, determined an individual withdrawal schedule which aimed to complete discontinuation of BZDA use within 1 month. Most often, the recommended reduction from the initial BZDA daily dose was 50% per week. The initial dose reduction was 25% per week among those eleven participants with the highest BZDA dose, that is, more than twice the age-related defined daily dose (DDD), and among some other participants who were afraid of withdrawal symptoms. Length of BZDA use was not used as a criterion for dose-tapering rate; only two of the participants had used BZDA less than for 1 year. The physician informed each participant as to possible withdrawal symptoms, especially rebound insomnia. The psychosocial support was further continued by a nurse who provided supportive visits once a week during the withdrawal period and was available by phone.

2.4 | Measurements and data collection

Interviews completed by questionnaire took place at baseline, after the 1-month withdrawal period, and



Nurse's visit = A participant's visit at the Health Centre for individual psychosocial support and follow-up measurements performed by the nurse. BZDA = benzodiazepine agonist

FIGURE 1 Flow of participants and formation of the groups Withdrawers and Nonwithdrawers

6 months after withdrawal initiation (Figure 1). At baseline, we collected socio-demographic data and data on health and disease, including mood measurement by the Geriatric Depression Scale 15 (GDS-15).[24] We scrutinized BZDA use by interview at baseline and at months 1 and 6. In addition, we measured concentrations of zopiclone, zolpidem, temazepam, diazepam, desmethyldiazepam and oxazepam in plasma samples drawn at baseline and at month 1.[23]

The nurse performed baseline measurements. Subsequent contacts with the nurse consisted of interviews, measurements and psychosocial support (at weeks 1, 2, 3 and 4 from baseline). Participants also had the option during the withdrawal period for psychosocial support sessions with the physician. The nurse's follow-up re-assessments occurred at months 2 and 6 after withdrawal initiation, and the physician's follow-up examination was at month 6 after withdrawal initiation (Figure 1).

The structured questionnaire included questions derived mainly from the Basic Nordic Sleep Questionnaire (BNSQ), which is a valid tool as a quantitated measure of subjective sleep complaints.[25] These questions assessed the insomnia-related symptoms, such as length of sleep-onset latency in the evening, frequency of difficulty in initiating sleep, frequency of awakenings during night and use of additional medicine (hypnotic) at any nightly awakening (Table 2). Questions regarding following-day freshness mapped too-early-morning awakenings, fatigue in the morning and during daytime, sleepiness during daytime and compulsive sleepiness on weekdays (Table 2). The quality-of-life questions assessed the life quality in general, and self-perceived stress, satisfaction with life, self-reported

health, and expected health 1 year later (Table 3). Quality of life was mapped by the visual analogue scale (VAS) at 0 to 100 mm (0 = worst, 100 best). Other questions included three to six alternative answers. The answers represented the situation from the 3-month period before the beginning of BZDA withdrawal ("baseline"), from the 1-month period after beginning of withdrawal ("month 1"), and from the 3-month period before the end of the follow-up ("month 6"). Because some of the questionnaires had been fulfilled incompletely, the number of participants (n) answering to all questions was not 89 at each time-point.

2.5 | Final study groups and statistical analyses

At month 6, the physician (RL) and two research nurses determined the withdrawal status by interview using a structured questionnaire (26) and by checking carefully the participants' medical and prescription records in the Finnish health system for potential refills as described earlier (23). All the 89 participants who had completed the 6-month follow-up were assigned into one of the two groups solely based on the BZDA use at month 6, independent of whether they had been double-blindly on melatonin or placebo during the actual 1-month withdrawal. The two groups formed were those 34 participants who had completely withdrawn from use of BZDA at month 6 (Withdrawers) and those 55 participants who still used a BZDA at month 6 (Nonwithdrawers). Distribution of the melatonin and placebo users during the first withdrawal month did not differ between the groups ($P = 0.220$). Of note, also 44 of the Nonwithdrawers had reduced their BZDA doses or had been without them for some time after the withdrawal, but at month 6, they failed to totally abstain from BZDA.

Categorical variables are described as number of participants (n), and continuous variables by medians and ranges or by means and standard deviations (SD). Differences between the Withdrawers and Nonwithdrawers underwent testing by Student's *t* test, the Tukey-Kramer test, the Wilcoxon signed-rank test or by the Mann-Whitney *U* test, when appropriate. Variables measured with ordinal or nominal scales between the groups were tested by the chi-square or Fisher's exact test. The differences in changes between and within the Withdrawer and Nonwithdrawer groups were analysed by cumulative logistic regression using generalized estimating equations with an independent correlation structure and described as cumulative odds ratios (COR) with 95% confidence intervals (CI). In general, COR ≥ 1 values for categorical variables suggest improvement in parameter within the group of Withdrawers and Nonwithdrawers compared to baseline. COR is statistically significant ($P < 0.05$; bolded in Tables 2 and 3) when its CI does not include 1.0. For continuous variables, mean changes within groups are statistically significant (bolded) when CI does not include 0.0. None of the group × time interactions were significant ($P \geq 0.05$), which suggests that the changes (baseline vs other time-points) between the groups were not statistically different. Continuous variables were calculated by least squares means with SD. Significant differences between the Withdrawer- and Nonwithdrawer groups are indicated by asterisk (*) in Tables 2 and 3. Due to multiple comparisons, *P*-values were adjusted by the Dunnett-Hsu test. *P*-values < 0.05 were considered statistically significant. For clarity, only *P*-values, without COR and 95% CI, are given in the text. The statistical analyses were by SAS version 9.2 and Enterprise Guide version 4.1 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

The groups differed significantly only by age (Table 1). Withdrawers were somewhat younger (median 63 years) than Nonwithdrawers (median 67 years; $P = 0.041$). At baseline, the groups did not differ in number of medications, in duration of regular sedative hypnotic use or in percentage of participants using antidepressants.

3.2 | Sleep and freshness variables

3.2.1 | Sleep-onset latency

The sleep-onset latency was similar in both groups at baseline (Figure 2). At month 6, the latency in the Withdrawers was shorter than at baseline ($P = 0.006$) or in the Nonwithdrawers ($P = 0.017$). (Tables 2 and 4). In the Withdrawers, the percentage of those participants with the longest sleep-onset latency (>30 minutes) decreased from 52% at baseline to 24% at month 6 but remained unchanged (51%) in the Nonwithdrawers (Figure 2).

3.2.2 | Difficulties in initiating sleep

At baseline, most of the participants in both groups every night had difficulties in initiating sleep (Table 2). At month 6, the Withdrawers had fewer difficulties than at baseline ($P = 0.002$) or compared to the Nonwithdrawers ($P = 0.042$).

3.2.3 | Nocturnal awakenings

The Nonwithdrawers had at month 6 slightly less nocturnal awakenings than at baseline. However, no significant differences emerged in nocturnal awakenings between the Withdrawers and Nonwithdrawers at any time-point (Tables 2).

TABLE 1 Characteristics of 89 long-term hypnotic users at baseline grouped according to withdrawal results at month 6. Withdrawers (n = 34) totally discontinued, Nonwithdrawers (n = 55) continued their sedative hypnotic use

Variable	Withdrawers Median [Range]	Nonwithdrawers Median [Range]	*P*
Age (y)	63.0 [55-78]	67.0 [55-91]	0.041
Body mass index (kg/m²)	26.4 [18.8-37.1]	27.3 [21.3-41.6]	0.440
Doses of alcohol per week	1.5 [0-25.5]	0 [0-13.3]	0.242
Number of medications	4 [1-10]	4 [1-11]	0.983
Regular sedative hypnotic use (y)	8.0 [0.42-35]	10.0 [2-26]	1.000
	n (%)	**n (%)**	
Women	19 (56)	40 (73)	0.102
Exercise in a week (h)			1.000
Not at all	2 (6)	4 (7)	
½-3 h	31 (91)	49 (89)	
>3 h	1 (3)	2 (4)	
Smokers	2 (6)	4 (7)	1.000
Living alone	6 (18)	19 (35)	0.085
Antidepressive medication	6 (18)	11 (20)	0.784
Participants with more than 5 points in GDS-15	2 (6)	7 (13)	0.473
Occupation			
Retired	24 (71)	48 (87)	0.062
Daytime work	6 (18)	6 (11)	
Shift work	4 (12)	1 (2)	

GDS-15, Geriatric Depression Scale.
P = Statistical significance of difference between Withdrawers and Nonwithdrawers.

3.2.4 | Additional medicines at nocturnal awakenings

At baseline, 26% of the Withdrawers and 18% of the Nonwithdrawers nightly used additional sleep medicines, but both groups had markedly reduced their use of additional medicines at month 1 (Figure 3, Table 2). At month 6, none of the Withdrawers used additional medicines ($P < 0.0001$ vs baseline), with a significant difference in their use between the Withdrawers and Nonwithdrawers ($P = 0.034$). The Nonwithdrawers also used additional medicines at month 6 less often than at baseline ($P = 0.003$) (Table 2).

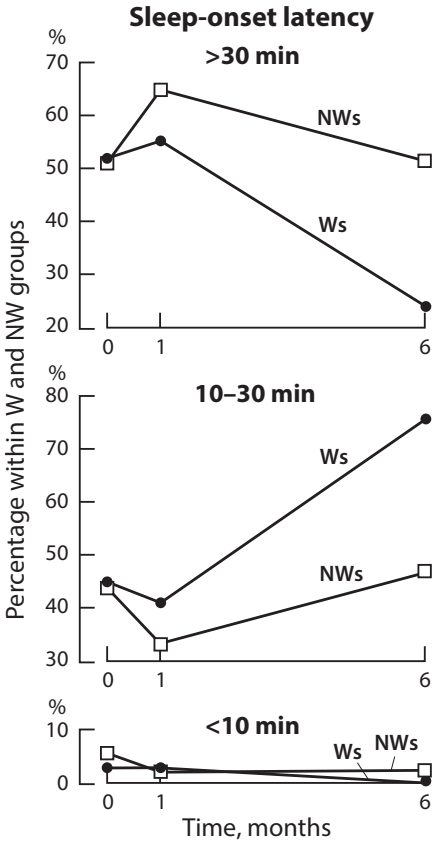


FIGURE 2 Sleep-onset latency. Percentage of participants within groups of Withdrawers (Ws) and Nonwithdrawers (NWs) according to sleep-onset latency (>30 minutes, 10-30 minutes or <10 minutes) at baseline (0 month), and at 1 month and at 6 months after beginning of withdrawal from chronic hypnotic use. The participants were classified as Ws (n = 34) or NWs (n = 55) based on their withdrawal results at month 6

3.2.5 | Early-morning awakenings

At baseline, most of the participants in both groups suffered from too-early-morning awakenings once a week or more frequently (Table 2). At month 6, compared to baseline, early-morning awakenings were significantly less frequent in both groups ($P < 0.05$).

3.2.6 | Fatigue in mornings and during days

At baseline, many of the participants had in the mornings a feeling of non-restorative sleep (Table 2). Compared to baseline, their morning fatigue and daytime fatigue were diminished in both groups at month 6 ($P < 0.05$-$P < 0.001$).

3.2.7 | Compulsive sleepiness on weekdays

At baseline, the Withdrawers group suffered from compulsive sleepiness on weekdays more than did the

TABLE 2 Sleep and freshness parameters at baseline and at month 1 and 6. Withdrawers (Ws; n = 34) had discontinued, but Nonwithdrawers (NWs; n = 55) continued their hypnotic use at 6 months after start of withdrawal. Data are number of participants and odds ratios (COR) for categorical variables, and mean values and changes for continuous variables

Parameter and group	At baseline n	At month 1 vs baseline COR (95% CI)		At month 6 vs baseline COR (95% CI)	
Sleep-onset latency (min)	**<10, 10-30, >30**				
Withdrawers	1, 15, 17	1.2 (0.5, 2.6)		**2.9 (1.3, 6.2)***	
Nonwithdrawers	3, 24, 28	1.9 (0.97, 3.5)		0.9 (0.5, 1.7)	
Difficulties initiating sleep (nights/wk)	**<1, 1-5, ≥6**				
Withdrawers	4, 11, 19	2.3 (0.9, 5.8)		**5.6 (1.8,17.0)***	
Nonwithdrawers	2, 10, 43	**6.7 (3.2, 14.1)**		**8.6 (3.9, 18.8)**	
Awakenings during night (nights/week)	**<1, 1-5, ≥6**				
Withdrawers	2, 8, 24	**1.1 (0.5, 2.6)**		1.1 (0.6, 2.2)	
Nonwithdrawers	3, 10, 42	1.0 (0.6, 1.8)		**2.4 (1.2, 5.0)**	
Additional night medicine (nights/wk)	**<1, 1-5, ≥6**				
Withdrawers	23, 2, 9	**17 (2, 142)**		**NA***	
Nonwithdrawers	37, 8, 10	**4.5 (2.0, 9.9)**		**2.7 (1.4, 5.2)**	
Too-early-morning awakenings/wk	**<1, 1-5, ≥6**				
Withdrawers	8, 21, 5	1.0 (0.5, 2.0)		**2.7 (1.1, 6.5)**	
Nonwithdrawers	15, 29, 11	1.6 (0.4, 1.1)		**3.8 (2.0, 7.3)**	
Morning fatigue, sleep didn't refresh; how often? **I** never; **II** < 1; **III** ≥1/mo	**I, II, III**				
Withdrawers	11, 3, 20	0.5 (0.2, 1.2)		**0.2 (0.1, 0.5)**	
Nonwithdrawers	24, 4, 27	0.6 (0.4, 1.1)		**0.4 (0.2, 0.8)**	
Daytime fatigue (d/week)	**<1, 1-5, ≥6**				
Withdrawers	10, 16, 7	1.1 (0.5, 2.4)		**3.4 (1.7, 6.8)**	
Nonwithdrawers	20, 22, 13	1.3 (0.8, 2.1)		**1.8 (1.1, 3.2)**	
Sleepy during d (d/wk)	**<1, 1-5, ≥6**				
Withdrawers	16, 13, 5	1.5 (0.7, 3.1)		1.7 (0.9, 3.3)	
Nonwithdrawers	34, 14, 7	0.8 (0.5, 1.3)		0.96 (0.5, 1.8)	
Compulsive sleepiness (d/wk)	**<1, 1-5, ≥6***				
Withdrawers	26, 8, 0	1.7 (0.6, 4.5)		**2.9 (1.04, 7.9)**	
Nonwithdrawers	51, 3, 1	0.6 (0.2, 1.9)		0.5 (0.2, 1.6)	
Total sleep time (h)	**Mean (SD)**	**Mean (SD)**	**Change (95% CI)**	**Mean (SD)**	**Change (95% CI)**
Withdrawers	6.7 (1.1)	6.1 (1.6)	**−0.6 (−1.1, −0.0)**	7.1 (1.2)	0.4 (−0.1, 1.0)
Nonwithdrawers	6.7 (1.2)	6.1 (1.1)	**−0.5 (−0.9, −0.2)**	6.7 (1.2)	−0.1 (−0.4, 0.3)
Sleep during nights (h)					
Withdrawers	6.4 (0.9)	6.0 (1.7)	−0.4 (−1.0, 0.2)	7.0 (1.1)	0.5 (−0.0, 1.1)
Nonwithdrawers	6.5 (1.1)	6.1 (1.2)	**−0.4 (−0.8, −0.1)**	6.6 (1.2)	0.1 (−0.3, 0.4)

COR, Cumulative Odds Ratio compared to baseline within the group; CI, Confidence Interval; SD, standard deviation; COR > 1 suggests improvement in other sleep and freshness parameters but in morning fatigue COR < 1 means improvement; COR is statistically significant (bolded; $P < 0.05$) when CI does not include 1.0; NA, COR not available due to zero frequencies, $P < 0.0001$ (Wilcoxon signed rank test); Mean change from baseline within the group is statistically significant when CI does not include 0.0; n, number of participants; *Asterisk indicates significant difference *between* the Ws and NWs groups at the time. Group x time interaction effects (= changes from baseline) between groups were not significant ($P > 0.05$).

Nonwithdrawers. Compared to baseline, compulsive sleepiness was diminished only in the Withdrawers group ($P = 0.043$) at month 6 (Table 2).

3.2.8 | Length of sleep time

No significant differences emerged in the length of total sleep time or sleep during nights between the Withdrawers

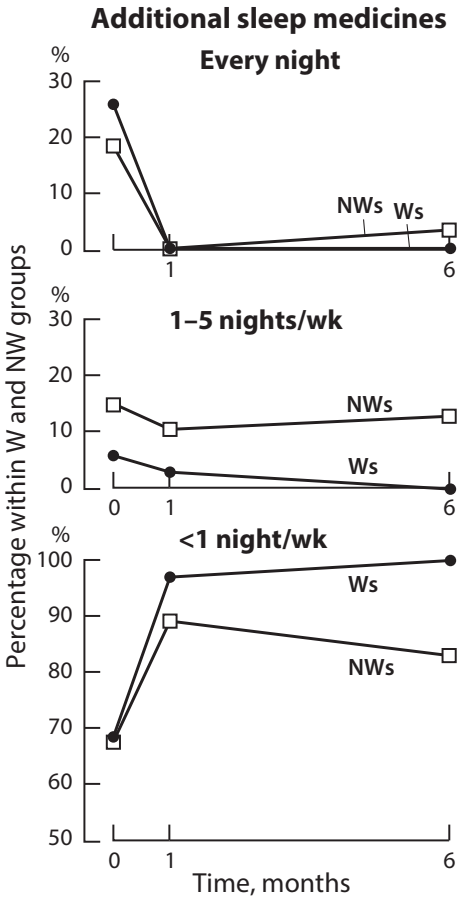


FIGURE 3 Additional sleep medicines. Percentage of participants within groups of Withdrawers (Ws) and Nonwithdrawers (NWs) according to use of additional sleep medicines at nocturnal awakenings (on every night, on 1-5 nights/week, <1 night/week) at baseline (0 month), and at 1 month and at 6 months after beginning of withdrawal from chronic hypnotic use. The participants were classified as Ws (n = 34) or NWs (n = 55) based on their withdrawal results at month 6

and Nonwithdrawers (Table 2). Compared to baseline, the total sleep time was at month 1 significantly shorter in both groups, but sleep during nights was significantly shortened only in Nonwithdrawers ($P = 0.007$). At month 6, both the total and nocturnal sleep times were significantly longer than at month 1 in both groups.

3.3 | Quality-of-life parameters

3.3.1 | Quality of Life (QOL)

The groups did not differ from each other in QOL at any time-point as assessed by the visual analogue scale. However, in the Withdrawers group, QOL was improved at month 1 ($P = 0.013$) and at month 6 ($P = 0.015$) compared to baseline (Table 4), and Nonwithdrawers had an improved QOL at month 6 ($P = 0.003$) compared to baseline (Figure 4).

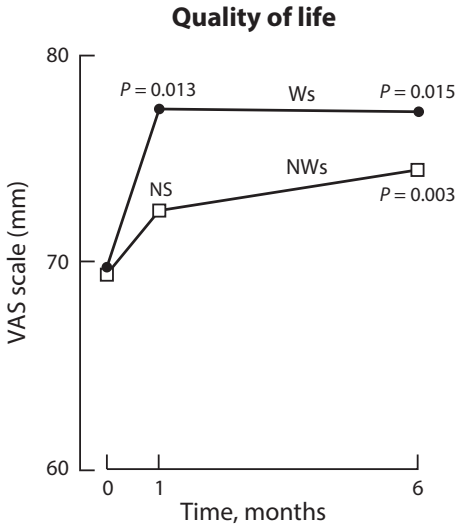


FIGURE 4 Quality of life, measured using visual analogue scale (VAS 0-100 mm; 0 = worst, 100 = best), of Withdrawers (Ws) and Nonwithdrawers (NWs) at baseline (0 month), and at 1 month and at 6 months after beginning of withdrawal from chronic hypnotic use. The participants were classified as Ws (n = 34) or NWs (n = 55) based on their withdrawal results at month 6. For clarity, only mean values are shown. *P*-values refer to statistically significant differences compared to baseline values (NS, not significant)

3.3.2 | Geriatric Depression Scale

Differences in the Geriatric Depression Scale between or within the groups at any time-points (Table 3) failed to reach significance.

3.3.3 | Self-perceived stress

At month 6, the self-perceived stress was in the Withdrawers group less than at baseline ($P = 0.029$) or than in the Nonwithdrawers group ($P = 0.039$) (Table 4).

3.3.4 | Satisfaction with life

At month 6, satisfaction with life was improved compared to baseline only in the Withdrawers group ($P = 0.012$ (Table 4), but with no significant differences between the groups at any time-point (Table 3).

3.3.5 | Self-reported health

No significant differences in the self-reported health existed between the groups at any time (Table 4).

3.3.6 | Expected health 1 year later

This parameter was in the Withdrawers better at month 6 than at baseline ($P = 0.003$), but it did not differ significantly between the groups (Table 3).

TABLE 3 Quality of life parameters at baseline and at month 1 and 6. Withdrawers (Ws; n = 34) had discontinued but Nonwithdrawers (NWs; n = 55) continued hypnotic use at 6 months after start of withdrawal. Data are mean values and their changes for continuous variables, and number of participants (n) and odds ratios for categorical variables. Statistically significant differences from baseline within group are bolded, and difference between groups indicated by asterisk

Parameter and group	At baseline	At month 1 vs. baseline		At month 6 vs. baseline	
	Mean (SD)	Mean (SD)	Change (95% CI)	Mean (SD)	Change (95% CI)
Quality of life (VAS 0-100 mm; 0 = worst;100 = best)					
Withdrawers (mm)	69.7 (19.7)	77.5 (13.0)	**7.8 (1.5, 14.0)**	77.4 (19.2)	**7.6 (1.4, 13.9)**
Nonwithdrawers (mm)	69.3 (14.5)	72.5 (12.5)	3.2 (−0.1, 6.5)	74.3 (12.3)	**4.8 (1.5, 8.2)**
	n	COR (95% CI)		COR (95% CI)	
Depression (GDS-15)					
(scores; 0-5, no depression = **I**; 6-15, depressed = **II**)	**I**, **II**				
Withdrawers (n)	32, 2	1.0 (0.2, 4.4)		2.1 (0.5, 8.6)	
Nonwithdrawers (n)	47, 7	1.2 (0.5, 3.0)		1.5 (0.6, 3.7)	
Self-perceived stress					
(mild = **I**, moderate **II**, severe = **III**)	**I**, **II**, **III**				
Withdrawers (n)	27, 6, 1	**8.5 (1.3, 57)**		**4.0 (1.2, 14)***	
Nonwithdrawers (n)	45, 6, 4	**1.6 (1.04, 2.5)**		1.2 (0.7, 2.0)	
Satisfaction with life					
(good = **I**, moderate = **II**, bad =**III**)	**I**, **II**, **III**				
Withdrawers (n)	24, 8, 2	1.9 (0.9, 4.2)		**3.1 (1.3, 7.4)**	
Nonwithdrawers (n)	38, 14, 3	1.6 (0.9, 2.9)		1.7 (0.9, 3.2)	
Self-reported health					
(good = **I**, fair = **II**, bad =**III**)	**I**, **II**, **III**				
Withdrawers (n)	9, 24, 1	1.6 (0.9, 2.8)		2.1 (0.9, 5.2)	
Nonwithdrawers (n)	9, 46, 0	1.6 (0.9, 2.8)		**2.0 (1.04, 3.9)**	
Expected health 1 year later					
(good = **I**, fair = **II**, bad = **III**)	**I**, **II**, **III**				
Withdrawers (n)	5, 29, 0	1.8 (0.8, 4.1)		**3.6 (1.6, 8.2)**	
Nonwithdrawers (n)	13, 42, 0	0.9 (0.6, 1.4)		1.2 (0.7, 2.3)	

COR, Cumulative Odds Ratio compared to baseline within the group; Change, mean change from baseline; CI, 95% Confidence Interval; SD, Standard deviation; COR > 1 suggests improvement in parameter compared to baseline; COR is statistically significant (**bolded**; $p < 0.05$) when CI does not include 1.0. Change is significant when CI does not include 0.0; n, number of participants. *The only significant difference *between* the groups was in Self-perceived stress at month 6. Group × time interaction effects (=changes from baseline) were not significant ($p > 0.05$).

3.4 | Summary of results

Effects of the complete BZDA discontinuation on insomnia-related parameters 6 months after start of the withdrawal are summarized in Table 4.

4 | DISCUSSION

4.1 | General discussion

Our results indicate that withdrawal from long-term use of BZDA hypnotics may markedly improve the sleep and quality of life of older adults with primary insomnia. Some of the parameters were improved also in the Nonwithdrawers, probably because most of them also managed from time to time without BZDAs, or they had reduced their BZDA dose, or both. All participants had used zopiclone, zolpidem or temazepam nightly for a long time until they entered the withdrawal.

Studies on perceived sleep and objective sleep are known to produce somewhat differing results.[27] To investigate prospectively the perceived effects of withdrawal under natural home conditions, we assessed all participants thrice using the same structured questionnaire. The questionnaire assessed the main manifestations of insomnia, freshness and quality of life.[24-28] Thus, our results also offer some hints as to their time-course after discontinuation of BZDAs.

TABLE 4 Summary of results of sleep-related parameters in elderly outpatients at month 6 after start of withdrawal from zopiclone, zolpidem and temazepam. These chronic hypnotic users had volunteered in dose tapering during the first study month. At 6 months, the Withdrawers (n = 34) had totally discontinued but Nonwithdrawers (n = 55) continued hypnotic use

Parameter	Within Withdrawers, month 6 vs baseline	In Withdrawers vs Nonwithdrawers at month 6
Perceived sleep and next day freshness		
Sleep-onset latency	Shortened, $P = 0.006$	Shortened, $P = 0.017$
Difficulties initiating sleep	Less, $P = 0.002$	Less, $P = 0.042$
Awakenings during night	NS	NS
Additional sleep medicine during night	Less, $P = 0.0001$	Less, $P = 0.034$
Total sleep time	NS	NS
Sleep time during nights	NS	NS
Too-early-morning awakening	Less, $P = 0.031$	NS ($P = 0.058$)
Morning fatigue, sleep didn′t refresh	Less, $P = 0.0003$	NS
Daytime fatigue	Less, $P = 0.0007$	NS
Sleepy during d	NS	NS
Compulsive sleepiness on weekdays	Less, $P = 0.043$	NS
Quality of life		
Quality of life (VAS)	Better, $P = 0.015$	NS
Self-perceived stress	Less, $P = 0.029$	Less, $P = 0.039$
Satisfaction with life	Better, $P = 0.012$	NS
Self-reported health	NS	NS
Expected health 1 y later	Better, $P = 0.003$	NS

NS, no significant difference; VAS, Visual analogue scale.
Baseline = before start of withdrawal.
P, difference within withdrawers, or between withdrawers and nonwithdrawers at 6 mo.

Rebound insomnia is usual in chronic BZDA users after discontinuation.[29,30] Anxiety, nightmares and concentration impairments may also occur. As could be expected, many of our participants reported rebound insomnia lasting a night or two after each BZDA dose reduction. Accordingly, the total sleep time remained shortened at the end of the withdrawal period, 1 month after start of the gradual dose reductions. The dose-tapering period in our study was shorter than that usually recommended.[29] It is likely that sleep physiology was not fully normalized by 1 month. Self-perceived stress had, however, already diminished within 1 month. In Nonwithdrawers, also sleep during nights was significantly shortened at month 1, which may have contributed to their poorer withdrawal success. At month 6 in the Withdrawers group, several of the perceived sleep parameters had recovered, suggesting improved sleep physiology and that sleep had become more restorative.

The rate of BZDA dose tapering is a somewhat contentious issue.[29] Although some long-term users may require withdrawal over years, some chronic users can discontinue rapidly with little upset.[29] For example, withdrawal over 2-3 months but slower if the symptoms become too severe, or 1-month of withdrawal for each year of use, has been recommended (15,18,19,21,29). The 1-month dose tapering used in our study was relatively short. However, the participants had used BZDAs as hypnotics, mainly in therapeutic doses, and the short-term withdrawal results were good; about 75% were BZDA-free after the first month. This may be explained by intensive psychosocial support during the withdrawal and patients motivated to participate in the study. They had received both written and oral guidelines about insomnia and its treatment without medicines (23). When the participants were told that withdrawal symptoms are temporary and would pass, many of them even accepted being awake for 2 or 3 nights during the withdrawal period. Most of the participants were satisfied with the short withdrawal when they were interviewed at 6 months. However, it is possible that many participants could have benefitted from a longer withdrawal period or more psychosocial support after the withdrawal to accomplish healthier sleep patterns without BZDAs.

In general, our results agree with those of Belleville and Morin (2008), who reported overall improvement in insomnia, anxiety and distress symptoms in 15 chronic hypnotic users after successful discontinuation of sedative hypnotics.[21] In the study of Curran et al., in chronic users of temazepam, nitrazepam and loprazalam, withdrawers had higher health-related quality-of-life scores compared to

continuers but their sleep ratings did not differ when assessed 12 and 24 weeks after beginning of the withdrawal trial.[22] In our study, most of the 89 evaluable participants had been long-term users of the Z-drugs (zopiclone, 50 participants; zolpidem, 26 participants) and only 13 had used temazepam before the withdrawal trail. Thus, our results likely reflect the effects of Z-drug withdrawal, whereas the previous follow-up studies[21,22] have included no or very few chronic users of zopiclone and zolpidem.

We have found previously that muscle strength and balance of these same Withdrawer participants improved within some weeks after discontinuation of BZDAs.[7] On the other hand, no significant improvement was evident in their attentional or psychomotor cognitive functioning, not even within 6 months after BZDA withdrawal.[9] In some other studies, minor improvement in cognitive functions occurred during longer periods after BZDA discontinuation.[22,30]

4.2 | Clinical implications

Clinical relevance of the present findings seems obvious provided that BZDA withdrawal can be implemented into primary health care. In our study, the percentage of successful withdrawers was 37% (34/92) of the long-term BZDA users, who voluntarily participated in this study. As the withdrawal improved several sleep, freshness and quality-of-life parameters in our cohort, it is likely that significant number of chronic BZDA users would benefit from discontinuation. Moreover, even a reduction in BZDA use may have positive effects on sleep. As BZDA withdrawal improves also muscle strength and balance,[7] it can be suggested that risk of falls and some other adverse events could be reduced after BZDA withdrawal.

4.3 | Strengths and limitations of the study

4.3.1 | Strengths

The present investigation is the largest follow-up study in the chronic BZDA users on the effects of BZDA discontinuation on several insomnia-related subjective symptoms up to 6 months after withdrawal. All participants had suffered from primary insomnia, and for a lengthy time, nightly, they had used zopiclone, zolpidem or temazepam as hypnotics, as confirmed by interviews, medical and pharmacy records, as well as by plasma BZDA measurements.[23] Of the 92 participants, a high percentage (97%) were followed for up to 6 months.

4.3.2 | Limitations

Firstly, our patient material was somewhat selected: individuals with clear misuse of drugs or alcohol, and those with significant psychiatric diseases were excluded. Yet, our participants were typically older outpatient insomniacs who had chronically used therapeutic doses of BZDAs as hypnotics.

Secondly, although baseline characteristics of participants in the Withdrawer and Nonwithdrawers groups were rather similar, potential differences between the groups could have influenced the results. The slightly higher age of the Nonwithdrawers could explain their higher proportion living alone and being retired. These factors might have influenced withdrawal success, but they cannot explain the observed effects of withdrawal on sleep-related parameters within the groups when the 6-month data of the Withdrawers or Nonwithdrawers are compared to their own baseline data.

Thirdly, we did not use polysomnography, actigraphy or any other objective laboratory methods for sleep measurements, because we sought to discover possible changes in perceived sleep under everyday home conditions.

4.3.3 | Conclusions

In conclusion, successful withdrawal from BZDAs can improve perceived sleep, freshness and quality of life of older chronic users of zopiclone, zolpidem and temazepam. After a rebound worsening of some insomnia symptoms during dose tapering, improvement began, with positive effects on several sleep-related parameters, effects significant at 6 months after beginning of withdrawal. Some parameters improved within 1 month. The results encourage a gradual BZDA withdrawal, in chronic users.

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CONFLICT OF INTEREST

The authors have nothing relevant to disclose regarding this study.

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