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Pitolisant-supported bridging during drug holidays to deal with tolerance to modafinil in patients with narcolepsy

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ABSTRACT

Study objectives: Modafinil is a common treatment for excessive daytime sleepiness (EDS) in narcolepsy. The long-term use of modafinil can lead to tolerance with the loss of efficacy and the continuous increase of its dose. Pharmacological strategies to deal with the tolerance to modafinil are lacking. We investigated the efficacy and safety of pitolisant-supported bridging during drug holidays in patients with tolerance to modafinil.

Methods: Narcolepsy patients on monotherapy with modafinil who developed symptoms of tolerance were eligible. The following alternating therapy regimen was established: Monday to Friday patients continued on modafinil whereas Saturday and Sunday they switched to pitolisant to "bridge" the EDS symptoms. Patients were assessed at baseline and after three months with the Epworth Sleepiness Scale (ESS) and the Ullanlinna Narcolepsy Scale (UNS). Health-related quality of life (HrQol) was evaluated by EuroQol5D. Adverse events were documented in the patients' diaries.

Results: 41 patients aged 30.9 ± 5.6 years were included. After three months of the alternating therapy regimen, the symptoms of tolerance decreased and the modafinil dose could be reduced by 41% ($p < 0.01$) resulting in better safety. The EDS improved on ESS (baseline: 18.2 ± 4.2, follow-up: 12.6 ± 4.0, $p < 0.0001$) and UNS (baseline: 25.8 ± 7.9, follow-up: 18.9 ± 5.9, $p < 0.0001$). The HrQol increased significantly.

Conclusion: Patients with tolerance to modafinil could benefit from pitolisant-supported bridging during drug holidays. This alternating pharmacological strategy proved to be safe and helped to reduce EDS and to decrease the modafinil dose. Further randomized controlled studies are required to evaluate the different strategies to deal with the tolerance to modafinil.

Clinical trial registration number: Clinical Trials.gov Identifier NCT05321355.

1. Introduction

Narcolepsy is a chronic neurological disorder with impaired sleep-wake regulation, which is mainly caused by a deficiency of orexin-producing neurons in the lateral hypothalamus [1,2]. Its main symptom is excessive daytime sleepiness (EDS), which is common for both types of narcolepsy (narcolepsy type 1, NT1 and narcolepsy type 2, NT2). Psychostimulants (modafinil/armodafinil, methylphenidate, solriamfetol), the wake promoting agent pitolisant and sodium oxybate are approved for the treatment of EDS in NT1 and NT2 by both the European Medicine Agency (EMA) (except for armodafinil) and the United States

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Abbreviations

BL – baseline
BMI – Body Mass Index
EDS – excessive daytime sleepiness
EMA – European Medicine Agency
ESS – Epworth Sleepiness Scale
EQ5D – EuroQol5D
FDA – Food and Drug administration
FU – follow-up (after 3 months in this study)
HrQol – health related quality of life
IQR – interquartile range
MS – multiple sclerosis
MSLT – multiple sleep latency test
NT1/2 – Narcolepsy Type 1 or 2
REM – rapid eye movement
SD – standard deviation
SOREM – sleep onset REM
UNS – Ullanlinna Narcolepsy Scale
US – United States

(US) Food and Drug Administration (FDA) [3,4].

Modafinil is the most frequently prescribed wake-promoting agent worldwide. Only in the US does the number of its annual prescriptions exceed one million [5]. Discovered by the French neuroscientist Michel Jouvet of Lafon Laboratories, it has been available on the European pharmaceutical market since 1994 and was approved for medical use in the US in 1998 [6]. It has a good efficacy in the treatment of EDS in NT1 and NT2 and is among the first-line of drugs in the current narcolepsy guidelines [7]. The approved daily dosage is 400 mg per day, but in narcolepsy, also due to tolerance development, often higher dosages are used (e.g. 600 mg) off-label. However, there is a risk of developing tolerance with long-term use, resulting in the loss of modafinil's efficacy and thus requiring patients to continuously elevate the daily dose in order to reach the same level of wakefulness [8–12]. There are no official recommendations on how to deal with modafinil tolerance, but most of the narcolepsy specialists either switch from modafinil to another wake-promoting agent or they establish regular drug holidays for modafinil on weekends in order to reduce the tolerance [9]. Drug holidays are a well-known practice used in many disorders, including narcolepsy, where a long-term use of stimulants leads to a development of drug tolerance [13]. However, no studies on drug holidays in modafinil are available until now [8]. The disadvantage of drug holidays is that the patients experience an increased EDS on the days without modafinil, which impairs both their activities of daily living and life quality.

Pitolisant is an antagonist and inverse agonist of histamine-3 receptors, which has been proven to be both effective and safe in narcolepsy and does not show development of tolerance in its long-term use [14]. Since the introduction of pitolisant, this drug has often been added to the current medication by sleep medicine specialists, but could also be administered during the drug holidays in order to "bridge" the modafinil-free days and avoid the worsening of EDS in those narcolepsy patients. This clinical approach has not been systemically evaluated until now [14].

In this observational register-based study, we evaluated the effect of pitolisant-supported bridging during a drug holiday in narcolepsy patients with tolerance to modafinil.

2. Methods

2.1. Design

We performed an observational study of patients with NT1 or 2 on modafinil monotherapy, who developed clinical signs of tolerance to this medication. They were assigned to drug holidays (two days on weekends without modafinil) bridged by pitolisant. These patients were taking modafinil from Monday till Friday and having a drug holiday on Saturday and Sunday. Prior to introduction to this alternating therapy regime, patients had already experienced drug holidays without "bridging". They could not withstand medication-free days as evidenced by an increase in their EDS by at least 30% as measured by the Epworth Sleepiness Scale (ESS). Therefore, during modafinil-free days pitolisant was administered. There were no fixed doses of modafinil or pitolisant during the observational period of three months. The "bridging" was started in the very first week after the assignment to drug holidays.

NT1 and 2 were diagnosed based on the International Classification of Sleep Disorders – third edition [15]. The diagnosis was confirmed by polysomnography and a multiple sleep latency test (MSLT). The value on the ESS exceeded 10 in all of the included patients. All of the patients were on modafinil monotherapy and showed an initial EDS-improvement (response) on this medication, which lasted for at least 12 months before they developed tolerance. The tolerance was defined as a continuous increase in EDS as measured by ESS during a period of at least 12 months despite modafinil therapy with a need to increase the dose of modafinil [16].

The data collection was performed in terms of the Mainz Sleep Register (MAINZ-SLEEPREG), which is an on-going observational data collection in patients with sleep disorders initiated by the Mainz Comprehensive Epilepsy and Sleep Medicine Center integrated within the Department of Neurology of the University Medical Center of the Johannes Gutenberg University Mainz, Germany. In order to exclude selection bias we have included all consecutive patients treated in our population-based register with a reference area of approximately 5 million inhabitants.

All of the study participants gave their informed consent for participation in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee.

2.2. Clinical parameters and health-related quality of life (HrQol)

The following data were collected at the baseline (BL) (time point before the initiation of drug holidays) and at the three month follow-up (FU) after the initiation of drug holidays: demographics, disease duration, medication, clinical symptoms of NT1 and 2, ESS, Ullanlinna Narcolepsy Scale (UNS) and EuroQol-5D (EQ5D and EQ VAS).

The ESS is a validated scale to measure a patient's daytime sleepiness [17]. It has eight items referring to different life situations, which can be scored from 0 to 3. Higher values express a higher level of sleepiness with a range of the total score between 0 and 24.

The UNS is a validated questionnaire-based scale, which is applied to measure the symptoms of the NT1 and NT2 (EDS and cataplexies) [18]. It consists of 11 items with a range of the total score between 0 and 44.

The questionnaire EuroQol-5D is a validated tool for the assessment of the subjective HrQoL. It describes the health status of the patients in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three levels for each (1 = no problems, 2 = moderate problems, 3 = severe problems) and includes a visual analogue scale (EQ VAS) with values from 0 ("worst conceivable health status") to 100 ("best conceivable health status") [19].

2.3. Statistical analysis

The IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were presented as mean and

standard deviation (SD) or median and range.

The differences in demographical and clinical parameters between the groups at BL and FU were estimated by applying a paired *t*-test or a non-parametric test if not normally distributed. For contingency analysis, a chi-square test was used. Statistical significance was assumed at a p-value of <0.05. The estimated effect size for an at least 30% change on ESS was 40 patients (study power of 80% and $p < 0.05$). No missing data or lost to follow-up issues were present in our study.

3. Results

3.1. Demographical and clinical data

The patients with narcolepsy (n = 41) were on average 31 years old (mean ± SD, 30.93 ± 5.61) and had a disease duration of approximately ten years (mean ± SD, 9.78 ± 1.17, see Table 1). Patients had already taken modafinil for a considerably long time of 34 months (mean ± SD, 34.22 ± 9.53) before they developed symptoms of tolerance (see definition in methods). They reported a loss of therapeutic efficacy and had to increase the dose of modafinil. They spent, on average, 16 months (mean ± SD, 15.78 ± 1.80) with the symptoms of tolerance before they switched to the new therapy regimen (alternation with pitolisant). Both types of narcolepsy (NT1, n = 25 and NT2, n = 16) were represented by patients in the study. There were no statistically significant differences in demographical and clinical parameters between participants with NT1 and NT2 (Table 1). Concerning the co-medication, there was only a significant difference in the use of antidepressants to treat cataplexies. In comparison to NT2 patients, patients with NT1 were more often using venlafaxine (48%, n = 12), citalopram (32%, n = 8) and clomipramine (20%, n = 5). Two patients with NT2 (12.5%) were on a stable dose of citalopram to treat depression.

3.2. Clinical effects and safety

After finishing three months of the alternating therapy regimen (Monday – Friday: modafinil, Saturday – Sunday: pitolisant), the symptoms of modafinil tolerance decreased and patients could reduce doses of modafinil by approximately 41% (mean ± SD, BL: 490 mg ± 94 mg, FU: 290 mg ± 118 mg, ****$p < 0.0001$, Table 2, Fig. 1) compared to BL doses. There was not a standard scheme to reduce the dosage of modafinil. The reduction was made individually, depending on the improvement of EDS. Whereas at BL, most patients took 400–600 mg modafinil per day (corresponds to the interquartile range (IQR), median = 500 mg), after three months most patients only took 200–400 mg (corresponds to the IQR, median = 300 mg). The median daily dosage of pitolisant was 18 mg (mean 23.05 ± 9.87) to bridge the modafinil-free days (Table 2).

The EDS, measured by the ESS was reduced by 31% at follow-up (mean ± SD, BL: 18.24 ± 4.16, FU 12.56 ± 4.03, ****$p < 0.0001$). This remarkable effect on EDS was also registered on the UNS; the total score was reduced by 27% (Table 2). Thus, in addition to a reduction of the modafinil dose, a significant reduction of EDS could be achieved in our cohort.

Additionally, the side effects of modafinil therapy were ameliorated (Table 3). Significant improvement was observed in form of the normalization of blood pressure and less frequent occurrence of insomnia.

Table 1
Demographic and clinical data of patients with narcolepsy.

	All patients	NT1	NT2
	n = 41	n = 25	n = 16
Age, years			
mean ± SD (range)	30.93 ± 5.61 (22–46)	30.12 ± 5.69 (22–41)	32.19 ± 5.42 (24–46)
Gender, n (%)			
female	21 (51)	12 (48)	9 (56)
male	20 (49)	13 (52)	7 (44)
Duration of narcolepsy, years			
mean ± SD (range)	9.78 ± 1.17 (7–12)	9.84 ± 1.11 (8–12)	9.69 ± 1.30 (7–11)
Duration on modafinil till tolerance development, months			
mean ± SD (range)	34.22 ± 9.53 (14–47)	34.28 ± 9.67 (14–47)	34.13 ± 9.63 (14–46)
Duration of tolerance, months			
mean ± SD (range)	15.78 ± 1.80 (13–18)	15.92 ± 1.73 (13–18)	15.56 ± 1.93 (13–18)
BMI			
mean ± SD (range)	26.02 ± 3.82 (19–32)	25.92 ± 3.99 (19–32)	26.19 ± 3.67 (19–32)

Abbreviations: NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; BMI, body mass index.

3.3. Health related quality of life

In line with these favorable results of EDS-improvement, self-reported HrQol increased under the alternating therapy regime after the treatment period of 3 months. Both, the EQ5D index score and the EQ VAS significantly improved compared to baseline (Table 2).

4. Discussion

In this observational study, we address an important therapeutic issue, which is the tolerance to modafinil in the long-term use. Patients treated with modafinil often report symptoms of tolerance and need increasing doses [8–12]. The risk of adverse effects, such as elevated blood pressure, sleep difficulties, gastrointestinal disturbances and headaches, increases on higher doses of modafinil [20]. Therefore, also a reduction of the modafinil dose is important in cases of tolerance. Generally, drug holidays are a common practice to deal with the tolerance independently from a substance [21] and they are also applied in cases of tolerance to modafinil. No standardized protocols are established for this practice, so the regimes for drug holidays vary from doctor to doctor and are usually individually agreed upon with the patient. In case of CNS drugs, drug holidays can lead to withdrawal symptoms, especially if patients are using higher dosages than recommended by the manufacturer. That is why future studies have to focus more on safety of drug holidays in different therapeutic settings. In our study, no withdrawal symptoms were reported.

In this paper, we provide the evaluation of a structural approach to the therapy regimen, which is established in our center to deal with the tolerance to modafinil. The weekend was chosen for modafinil-free days because most of patients do not work during this time and can better deal with the possible increase of EDS. At the same time, participants of our study were those, who could not withstand modafinil-free days without any pharmacological support. These patients are well-known in the clinical practice and reported a significant increase in EDS (30% as measured by ESS in our cohort). As a consequence, a pharmacologically supported drug holiday from modafinil is favorable in such cases. The choice of pitolisant for bridging the modafinil-free days was based on its mechanism of action, good safety and efficacy profile [22]. It does not cause elevation of blood pressure and is also approved to treat cataplexies in NT1 [23].

The implementation of the alternating therapy regimen with pitolisant-supported drug holiday from modafinil over the weekend significantly improved the EDS symptoms. Also remarkable is the fact that the doses of modafinil could be significantly reduced. In line with this clinical improvement, an increase in HrQol was registered. To the best of our knowledge, it is the first study evaluating strategies to deal with the tolerance to modafinil in narcolepsy.

Modafinil is very effective in the treatment of EDS in patients with NT1 and NT2 [6]. It has also been also tested in other indications such as fatigue in multiple sclerosis (MS) [24]. Although a tendency towards an

Table 2
Changes in modafinil dose, EDS and HrQol scores over time.

		NT1 n = 25	NT2 n = 16	All patients n = 41	% change	P-value
Pitolisant dose, mg		25 ± 10	20 ± 8	23 ± 10		
Modafinil dose, mg	**baseline**	492 ± 95	488 ± 96	490 ± 94		<0.0001****
	after 3 months	296 ± 124	281 ± 111	290 ± 118	−40.82%	
ESS	**baseline**	18.80 ± 3.42	17.38 ± 5.12	18.24 ± 4.16		
	after 3 months	12.76 ± 3.61	12.25 ± 4.73	12.56 ± 4.03	−31.14%	<0.0001****
UNS	**baseline**	26.16 ± 6.93	25.25 ± 9.40	25.80 ± 7.88		<0.0001****
	after 3 months	19.44 ± 5.39	18.19 ± 6.85	18.95 ± 5.95	−26.55%	
EQ5D index score	**baseline**	0.63 ± 0.11	0.67 ± 0.16	0.64 ± 0.13		<0.001***
	after 3 months	0.70 ± 0.13	0.76 ± 0.19	0.72 ± 0.16	+12.50%	
EQ VAS	**baseline**	58.60 ± 10.95	61.88 ± 16.01	59.88 ± 13.06		<0.001***
	after 3 months	66.00 ± 13.77	70.94 ± 19.25	67.93 ± 16.08	+13.44%	

% Change for all narcolepsy patients, all results displayed as mean ± SD (standard deviation), P-Value for all narcolepsy patients.
Abbreviations: EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; EQ5D, EuroQol5D; EQ VAS, EuroQol visual analogue scale; HrQol, health-related quality of life; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; UNS, Ullanlinna Narcolepsy Scale.

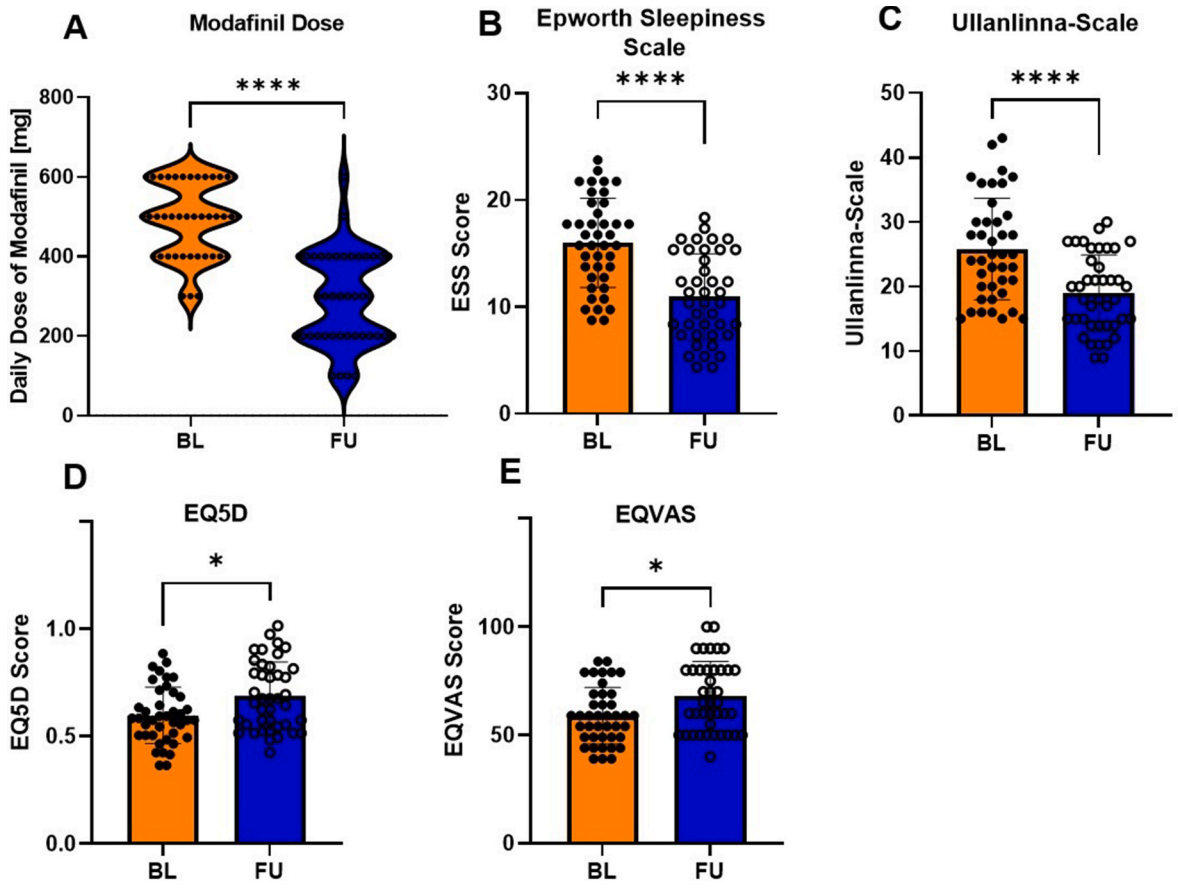

Fig. 1. Changes of scores between baseline (BL) and follow-up (FU).
A: Modafinil dosage was significantly reduced following three months of drug alternation with pitolisant. Similarly, ESS score (**B**) and Ullanlinna narcolepsy scale (**C**) were significantly reduced, whereas EQ5D (**D**) and EQ VAS (**E**) were increased. Results displayed as mean ± SD (standard deviation). ***p < 0.001, ****p < 0.0001.
Abbreviations: BL – baseline, FU – follow-up, ESS – Epworth Sleepiness Scale, EQ5D - European quality-of-life questionnaire.

improvement of fatigue was suggested, relevant side effects of higher doses force the physician to an individualized prescription [24]. Tolerance to modafinil is a commonly seen phenomenon. In our study, this was reflected in the high doses, which most of patients in our cohort were taking at baseline. Unfortunately, despite this well-known clinical phenomenon, published data on modafinil tolerance is very limited [20]. The mechanism of the tolerance of this substance is not fully understood. Modafinil has a plethora of impacts on neurotransmitters in the central nervous system, which has been investigated and reviewed extensively [25]. The increase of dopamine levels by modafinil [26,27] could be one mechanism accounting for tolerance of modafinil, possibly due to desensitization of receptors during the treatment. Pitolisant on the other hand does not show development of a tolerance in the long-term treatment of NT1 and NT2, probably due to its mechanism of action via the histaminergic system [28]. Apparently, in case of the modafinil tolerance, it could be favorable to use a wake promoting agent with another mechanism of action. In a randomized controlled trial, pitolisant has been proven to have a similar effectiveness as modafinil

Table 3
Side effects of treatment at baseline and after three months.

	Baseline	After 3 months	change	P-value
Headache, % (n)	17.1% (7)	9.8% (4)	−7.3%	0.33
Insomnia, % (n)	24.4% (10)	7.3% (3)	−17.1%	0.034*
Gastrointestinal disturbances, % (n)	17.1% (7)	9.8% (4)	−7.3%	0.33
Dizziness, % (n)	12.2% (5)	4.9% (2)	−7.3%	0.24
Tachycardia, % (n)	21.9% (9)	7.3% (3)	−14.6%	0.06
Systolic blood pressure, mmHg mean (±SD)	145 ± 23	125 ± 12	−20 (±19)	<0.0001****
Diastolic blood pressure, mmHg mean (±SD)	91 ± 12	82 ± 6	−9 (±10)	<0.0001****

Abbreviations: SD, standard deviation.

and a clear superiority to placebo [29]. The demographics and clinical parameters of our study population were comparable with pitolisant studies, which were considered in the approval process by FDA and EMA [23,29]. The alternating therapy regime in the current study led to a significant improvement of the ESS, comparable to treatment-naïve patients treated with modafinil or pitolisant in clinical randomized controlled trials [23,29]. Thus, the proposed approach rescues and reestablishes the effectiveness of modafinil.

HrQol is an important issue in NT1 and NT2 [30]. It is lower than in the general population and is comparable to other chronic neurological diseases, such as Parkinson's disease or epilepsy [31–34]. In our study, an improvement of HrQol was similar to other therapy studies in narcolepsy [23,29] and further corroborates our findings. As long as both of the wake promoters, modafinil and pitolisant are approved for the treatment for EDS in NT1 and NT2, their combination is not an off-label approach and can be easily implemented in different therapy regimes. Moreover, the possibility to reduce a high modafinil dose in cases of tolerance by using an alternating regime is a way to avoid off-label prescriptions of increased modafinil doses. It is also a way to avoid an elevated risk of side effects, in particular psychiatric and cardiovascular side effects, occurring in higher doses [29].

Although the mechanism of action of modafinil is not completely understood, it is known that it is a dopamine reuptake inhibitor [8]. Acting via histamine-3 receptors, pitolisant has a distinct mechanism of action, which is completely different from that of modafinil [14,35]. In comparison, the mechanism of action of solriamfetol includes dopaminergic effects in addition to its inhibition of norepinephrine reuptake [36]. Therefore, pitolisant is a better candidate to facilitate dopamine desensitization during a drug holiday, when used to "bridge" modafinil-free days. In addition to pharmacological reasons, pitolisant was chosen as a "bridging" agent because of its safety profile [14,35]. Hypertension was present in 58.5% of patients in our study. Among other wake-promoting agents, pitolisant shows the best safety profile in regards to hypertension.

Our study has the following limitations: First, it was performed in observational design and is, therefore, inferior to the evidence from randomized controlled studies. Unfortunately, no studies of a higher evidence addressing the strategies to deal with modafinil tolerance are available today. Second, no other regimes were compared in this study. Consequently, we could not conclude on the optimal time-span for modafinil-free days. Third, we did not compare pharmacologically-supported drug holidays to other strategies to deal with the tolerance, such as a switch to another wake promoting agent. For such comparisons, multicenter studies are required in order to recruit much higher numbers of patients in this orphan disease. Fourth, longer follow-ups than three months were not evaluated. Fifth, differentiation of tolerance-related dose increase from possible abuse can be difficult. Patients in our study did not report any voluntary elevations of modafinil dose, which were not approved by their managing doctor. However, substance abuse could not be completely excluded in participants of our study.

5. Conclusion

Our study provides the evidence that pitolisant-supported bridging during a drug holiday in narcolepsy patients with tolerance to modafinil is safe, can help to reduce the modafinil dose and favors both the improvement of EDS and increase of HrQol. Further randomized controlled studies are required to evaluate different strategies to deal with the tolerance to modafinil.

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Ethics

This study was approved by the local ethics committee (State medical association Rheinland-Pfalz, Reference number: 2022–16287).

Informed consent

All of the study participants gave their informed consent for participation in accordance with the Declaration of Helsinki.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

CRediT authorship contribution statement

Yaroslav Winter: contributed to the, Conceptualization, design of the study, Funding acquisition, Formal analysis, Writing – original draft. **Christina Lang:** contributed to interpretation of data, Writing – original draft, preparing the figures and tables. **Ulf Kallweit:** contributed to interpretation of data, Writing – original draft, preparing the figures and tables. **David Apel:** contributed to interpretation of data, Writing – original draft, preparing the figures and tables. **Vinzenz Fleischer:** contributed to interpretation of data, Writing – original draft, preparing the figures and tables. **Erik Ellwardt:** contributed to the, Conceptualization, design of the study, Funding acquisition, Formal analysis, Writing – original draft. **Sergiu Groppa:** contributed to the, Conceptualization, design of the study, Funding acquisition, Formal analysis, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YW reports honoraria for educational presentations and consultations from Angelini Pharma, Arvelle Therapeutics, Bayer AG, BIAL, Bioprojet, Bristol-Myers Squibb, JAZZ pharmaceuticals, Eisai, LivaNova, Novartis, Precisis and UCB Pharma. SG received compensation for professional services from Abbott, Abbvie, Bial, Medtronic, UCB and Zambon; research grants from Abbott, Boston Scientific, MagVenture, German Research Council and German Ministry of Education and Health. UK received honoraria for consulting from AOP Health, Bioprojet Pharma, Jazz Pharmaceuticals and Takeda Pharma. CL received honoraria for

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