Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial

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Summary

Background Histaminergic neurons are crucial to maintain wakefulness, but their role in cataplexy is unknown. We assessed the safety and efficacy of pitolisant, a histamine H3 receptor inverse agonist, for treatment of cataplexy in patients with narcolepsy.

Methods For this randomised, double-blind, placebo-controlled trial we recruited patients with narcolepsy from 16 sleep centres in nine countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine). Patients were eligible if they were aged 18 years or older, diagnosed with narcolepsy with cataplexy according to version two of the International Classification of Sleep Disorders criteria, experienced at least three cataplexies per week, and had excessive daytime sleepiness (defined as an Epworth Sleepiness Scale score ≥12). We used a computer-generated sequence via an interactive web response system to randomly assign patients to receive either pitolisant or placebo once per day (1:1 ratio). Randomisation was done in blocks of four. Participants and investigators were masked to treatment allocation. Treatment lasted for 7 weeks: 3 weeks of flexible dosing decided by investigators according to efficacy and tolerance (5 mg, 10 mg, or 20 mg oral pitolisant), followed by 4 weeks of stable dosing (5 mg, 10 mg, 20 mg, or 40 mg). The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (weekly cataplexy rate [WCR]) between the 2 weeks of baseline and the 4 weeks of stable dosing period. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01800045.

Findings The trial was done between April 19, 2013, and Jan 28, 2015. We screened 117 patients, 106 of whom were randomly assigned to treatment (54 to pitolisant and 52 to placebo) and, after dropout, 54 patients from the pitolisant group and 51 from the placebo group were included in the intention-to-treat analysis. The WCR during the stable dosing period compared with baseline was decreased by 75% (WCR_{final}=2·27; $WCR_{baseline}$=9·15; $WCR_{final/baseline}$=0·25) in patients who received pitolisant and 38% (WCR_{final}=4·52; $WCR_{baseline}$=7·31; $WCR_{final/baseline}$=0·62) in patients who received placebo (rate ratio 0·512; 95% CI 0·43–0·60, p<0·0001). Treatment-related adverse events were significantly more common in the pitolisant group than in the placebo group (15 [28%] of 54 *vs* 6 [12%] of 51; p=0·048). There were no serious adverse events, but one case of severe nausea in the pitolisant group. The most frequent adverse events in the pitolisant group (headache, irritability, anxiety, and nausea) were mild or moderate except one case of severe nausea. No withdrawal syndrome was detected following pitolisant treatment; one case was detected in the placebo group.

Interpretation Pitolisant was well tolerated and efficacious in reducing cataplexy. If confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom there are currently few therapeutic options.

Funding Bioprojet, France.

Introduction

Narcolepsy is characterised by excessive daytime sleepiness and abnormal rapid eye movement (REM) sleep manifestations including cataplexy and hallucinations.[1,2] Narcolepsy type 1 is a debilitating disorder attributable to loss of orexin (also known as hypocretin) producing neurons in the lateral hypothalamus,[1,2] and to an increase in the number of tuberomamillary histaminergic neurons,[3,4] although the concentration of histamine in the CSF appears normal.[5] Since the wake-promoting activity of orexin might depend, at least partly, on histaminergic transmissions,[6] We hypothesised that the orexin deficit could be circumvented by directly activating histaminergic transmissions pharmacologically. Pitolisant, an inverse agonist of the H3 autoreceptor that activates histaminergic transmissions, was shown to improve excessive daytime sleepiness in a previous study.[7]

Of the two types of drugs currently used to treat cataplexy, antidepressants are used off-label and systematic research evidence of their efficacy is unavailable,[1,2,8] whereas sodium oxybate appears efficacious but requires two successive nocturnal administrations and its safety profile comprises serious adverse events.[1,2,9] Although

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Research in context

Evidence before this study

We searched PubMed and Web of Science for articles published up to Aug 18, 2016, using the following search terms: "histamine H3 receptor antagonist clinical trial in cataplexy", "histamine H3 receptor antagonist clinical trial in narcolepsy with cataplexy", and "histamine H3 receptor inverse agonist clinical trial in narcolepsy with cataplexy". We applied no language restrictions. We retrieved two articles. The first reported data on the effect of pitolisant in patients with narcolepsy with or without cataplexy and the primary endpoint was excessive daytime sleepiness, cataplexy being a secondary endpoint in a fraction of patients. The second article was a short review of the discovery of the H3 receptor and preclinical data for pitolisant, and a summary of clinical data before start of the trial reported here.

Added value of this study

This randomised double-blind study versus placebo assesses the effect of pitolisant on cataplexy as a primary endpoint in a group of severely affected patients with narcolepsy with cataplexy. It shows that pitolisant, the first histamine H3 receptor antagonist–inverse agonist to be studied in this indication, given once a day for 7 weeks, was well tolerated and able to significantly reduce the frequency of cataplexies.

Implications of all available evidence

In narcolepsy, pitolisant appears to be active against not only excessive daytime sleepiness but also cataplexy, the two major manifestations of the disease. If these data are confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for narcoleptic patients with cataplexy (type 1 narcolepsy), for whom there are currently few therapeutic options.

histaminergic neurons seem to remain active during cataplexy[10] and, in a post-hoc analysis, pitolisant seemed to improve cataplexy,[7] no trial testing H3 receptor inverse agonists has definitively measured its effect on cataplexy.

In the HARMONY-CTP randomised trial, we assessed the safety and efficacy of pitolisant in comparison with placebo in patients with narcolepsy who had a high frequency of cataplexy attacks.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled trial with patients recruited from 16 sleep centres (referred by a local doctor) in nine countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine). Eligible patients were aged 18 years or older with a diagnosis of narcolepsy with cataplexy according to version two of the International Classification of Sleep Disorders (ICSD-2) criteria,[11] defined as complaint of excessive daytime sleepiness and a history of cataplexy (sudden and transient episodes of loss of muscle tone triggered by emotional factors). Diagnosis was confirmed in most patients (103 [97%] of 106 patients) by a polysomnography followed by a multiple sleep latency test done within the year before recruitment to the study, and showing two or more sleep onset REM periods (SOREMPs). Three or more cataplexies per week and an Epworth Sleepiness Scale (ESS) score of 12 or more were required for inclusion. Ongoing anticataplectic treatment with sodium oxybate or antidepressants was allowed if doses were stable at least 1 month before randomisation and throughout the trial. Psychostimulants and sedative medications were not permitted.

Exclusion criteria were participation in another trial within the month preceding screening, any other disorder with excessive daytime sleepiness (eg, sleep-related breathing disorder with apnoea index ≥10 events per h, apnoea–hypopnoea index ≥15 events per h of sleep, or periodic limb movement disorder with microarousal index ≥10 events per h), history of substance misuse, a serious cardiovascular disorder, severe hepatic or renal abnormalities, or a psychiatric disorder. Women of childbearing potential had to use a birth control method.

The study was approved by local ethics committees in each country. An independent board regularly monitored the trial safety, having access to masked study information. The study was monitored by national Contract Research Organisations in each country. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned to receive either pitolisant or placebo (1:1) by site investigators using an interactive web response system (Arone, France). The randomisation sequence was computer-generated by Amatsi (France) and balanced between centres in blocks of four. Unither Développement (Le Haillan, France) created the capsules with study drug and placebo and allocated the drugs to treatment numbers. Investigators provided the appropriate numbered drug packs to the patient, and both patients and investigators were masked to treatment. Pitolisant and placebo were given in sealed capsules, similar in appearance and taste, and containing a quarter, half, one, or two tablets of pitolisant 20 mg or lactose only (placebo). Amatsi tested the success of masking, which was found to be successful. The dose-escalation scheme (figure 1) was applied to both treatments with double-blinding maintained throughout the trial. All patients took one capsule daily before breakfast.

Procedures

Before randomisation, all potential participants entered a 3-week selection period consisting of a 1-week washout period during which forbidden treatments (eg,

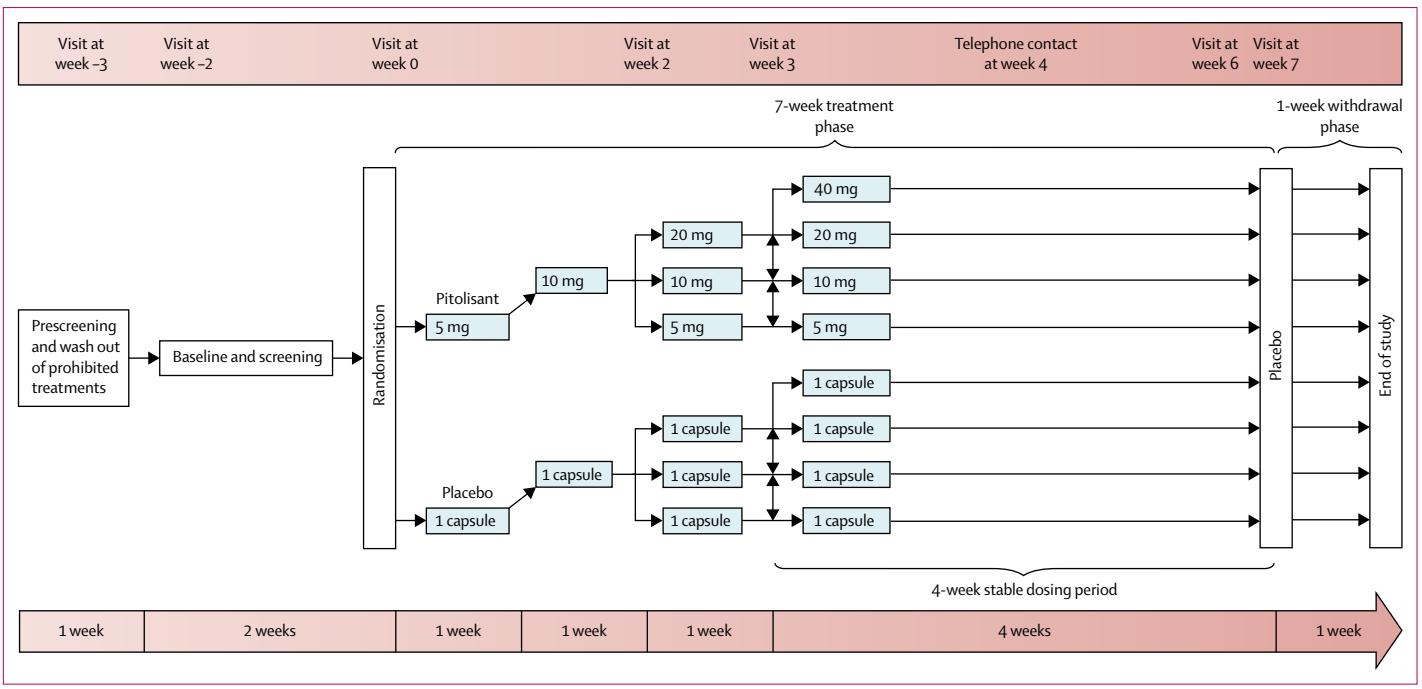

Figure 1: **Trial design**

psychostimulants, sedatives, or H1 antihistamines) were discontinued, and a 2-week baseline period during which investigators screened patients and did baseline cataplexy tests. Patients fulfilling all selection criteria were randomly assigned to treatment groups at day 0. Treatment lasted 7 weeks: 3 weeks of flexible dosing (5 mg, 10 mg, or 20 mg once daily) followed by 4 weeks of stable dosing (5 mg, 10 mg, 20 mg, or 40 mg once daily). During the flexible dosing period, patients took 5 mg of pitolisant or placebo once a day for the first 7 days, then 10 mg of pitolisant or placebo once a day for the next 7 days. During the visit at week 2, we assessed the dose, which could remain at 10 mg, be increased up to 20 mg, or decreased to 5 mg by the investigators on the basis of individual clinical efficacy and safety assessed by investigators; no specific recommendations were given to the investigators for this adjustment. On the visit at week 3, the investigators adjusted patient doses again to establish the final dose (5 mg, 10 mg, 20 mg, or 40 mg once daily) for the 4-week stable dosing period. At the end of the stable dosing period, all patients entered a 1-week withdrawal period during which time they received placebo. Assessments were regularly completed at visits (figure 1; appendix).

Outcome measures

The primary outcome for this study was the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing (weekly cataplexy rate [WCR]). Patients reported in individual diaries all cataplexy attacks defined as sudden and transient episodes (ranging from several seconds to a few minutes) of partial or generalised loss of muscle tone triggered by emotion. For each patient, we calculated the final weekly cataplexy rate (WCR_f) measured during week 4 of stable dose treatment, and the corresponding baseline rate (WCR_b) measured during the 2 weeks preceding randomisation. The cataplexy reduction was measured by the ratio $WCR_{f/b}=WCR_f/WCR_b$.

Secondary efficacy endpoints were WCR changes in patients maintained or not in their anticataplectic treatment, the mean change in ESS score, the proportion of patients with a final ESS score (ESS_f) of less than or equal to 10 (a validated cutoff),[7,10] the proportion of patients with abnormally high cataplexy rate (WCR >15, a non-validated cutoff corresponding to the median of the sample), the maintenance of wakefulness test (MWT; four 40-min sessions at visit 2 and visit 6), clinical global impressions of change (CGI-c) on cataplexy and excessive daytime sleepiness, patient global opinion on efficacy (PGO), European quality-of-life questionnaire (EQ-5D), and number of days with hallucinations (recorded in the patient's diary). Two additional secondary endpoints were the change in weekly cataplexy rate from the 2-week end of treatment period minus baseline and aggregate scores of secondary endpoints (z-scores), which are not reported in this Article since, although positive, do not add additional information to the outcome.

See Online for appendix

Safety endpoints assessed and recorded at each visit included adverse events, vital signs, physical examination, laboratory tests, electrocardiograms, and Beck Depression Inventory (BDI-13). A withdrawal syndrome defined

according to DSM-IV[21] as occurrence of dysphoria and two or more symptoms (among which are fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor retardation, or agitation) was assessed during the 1-week placebo period following end of treatment and registered at visit 7. The study was monitored by the following contract research organisations: Balkan-Trials (Sofia, Bulgaria; Skopje, Macedonia), Auxiliis Clinical Development (Budapest, Hungary), MedCoNet Group (Belgrade, Serbia), Kuantum CRO & Logistics (Cigli Izmir, Turkey), FGK Clinical Research (Prague, Czech Republic; Warsaw, Poland), and ZAO AMT (Moscow, Russia). Serious adverse events were based on patient outcome and were defined as events that are a threat to a patient's life or functioning. Individual adverse events were defined as mild, moderate, or severe depending on the intensity of the event.

Statistical analysis

For sample size calculation, we assumed a ratio $WCR_{f/b}$=0·5 in the placebo group and calculated that a WCR rate ratio of pitolisant to placebo of 0·75 or lower should be detected at a two-tailed 0·05 significance level with a power of 0·9 if we recruited at least 47 patients per group. This number was determined by analytical calculation and confirmed by simulation. In this calculation we did not account for the possible correlation between baseline and final WCR values.

WCR during the 4-week stable dosing period was assessed by a mixed model featuring Poisson regression, with treatment as a fixed factor, adjusted for WCR_b, treatment centre as a random factor, and exposure time as offset variables. In case of overdispersion, a negative binomial regression was used.

Efficacy and tolerance were assessed in all patients randomly assigned to treatment who received at least one treatment dose (intention–to-treat). Initial hypotheses were: pitolisant decreases the number of cataplexies compared with placebo; for patients treated with placebo, WCR is reduced by 50%; given the minimum value for inclusion (WCR_b=3), WCR_f in the placebo group is 3*0·5=1·5 cataplexies per week, thus six cataplexies per month (a month was the duration of exposure at fixed dose); the primary efficacy outcome is cataplexy reduction identified as the rate ratio (pitolisant

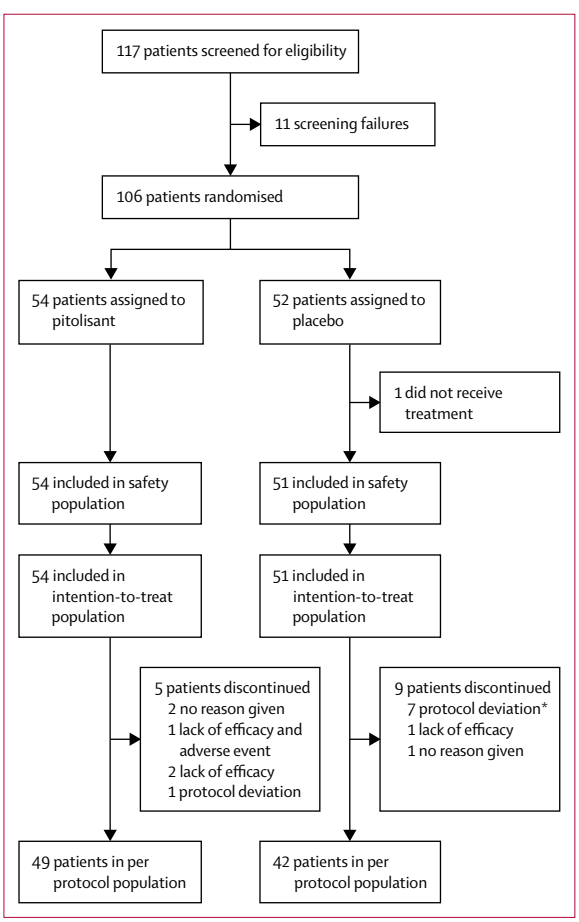

Figure 2: **Trial profile**
*One patient never took treatment and was prematurely withdrawn. All protocol deviations were defined as a lower than 80% compliance to protocol for the duration of the trial.

	Pitolisant group (n=54)	Placebo group (n=51)
Median age, years	34 (18–64)	39 (18–66)
Mean weight, kg	80·1 (17·8)	85 (18·3)
Mean height, cm	171·4 (9·1)	172 (10·7)
Mean body mass index, kg/m²	27·2 (5·2)	28·8 (6)
Men	26 (48%)	27 (53%)
Cataplexy episodes per week at prescreening	11 (8·9)	9·2 (8·8)
Mean sleep latency	4·2 (3·2)	4·7 (4·5)*
Mean ESS score at screening	17·3 (3·3)	17·1 (3·4)
History of associated symptoms		
Hallucinations	36 (67%)	32 (63%)
Ongoing hallucinations	32 (60%)	27 (53%)
Automatic behaviour	16 (30%)	14 (28%)
Ongoing automatic behaviour	13 (24%)	13 (26%)
Disturbed night sleep	37 (69%)	32 (63%)
Ongoing dyssomnia	33 (61%)	31 (61%)
Sleep paralysis	32 (59%)	32 (63%)
Ongoing sleep paralysis	24 (44%)	30 (59%)
Number of patients with at least one cataplexy medication in previous 3 months	22 (41%)	41 (80%)
Number of patients continuing cataplexy medications during the trial	4 (7%)	8 (16%)
Mean BDI–13 item score at screening	5·3 (4·1)	5·3 (4·3)

Data are median (range), mean (SD), or n (%). ESS=Epworth Sleepiness Scale. BDI=Beck Depression Inventory. *Mean sleep latency in the placebo group had 49 patients.

Table 1: **Demographics and baseline characteristics (intention-to-treat population)**

$WCR_{f/b}$/placebo $WCR_{f/b}$) between basal and final periods; the 1-month stable medication period is considered for final outcome assessment; and a centre effect, suggested by a previous study[7] is taken into account. All the reported analyses were done on an intention-to-treat basis. Per-protocol analyses were used as supportive results and provided similar results to the intention-to-treat population. The only post-hoc analysis assessed the treatment effect within each of the doses during the stable dose period compared with placebo, by use of the main statistical model.

We analysed secondary outcomes with a similar non-linear mixed model using treatment as fixed factor, centre as random factor, and baseline adjustment as a covariate. Instead of Poisson regression, we used a linear model for ESS (assumption of normal distribution and homoscedastic residuals). We assessed the number of hallucinations using the same model as the primary outcome. We used logistic regressions for binary endpoints, particularly for response to therapy. We imputed missing final values by the mean of the two previous values.[12] We tested the interaction between treatment and concomitant anticataplectic medication. We report the geometric means of WCR, MWT, and number of hallucinations because of their log-normal distributions whereas ESS is reported as arithmetic mean.

The statistical analysis was done by an independent external statistician. A third party statistician independently reviewed the Statistical Analysis Report and the structure and consistency of statistical charts. We used SAS statistical package (version 9.3) and a two-tailed 0·05 significance level. This trial is registered with ClinicalTrials.gov, number NTC01800045.

Role of the funding source

The protocol was developed by the funder (IL, J-ML, J-CS), with guidance from a steering committee of European academic experts (ZS, YD, and PL). The funder had no role in the collection, analysis, or interpretation of data. All the statisticians were commissioned by the funder. The paper was written by J-CS, with revisions made by the expert panel (ZS, YD, J-ML, and PL) and approved by all authors. All authors had full access to all data and ZS made the final decision to submit the paper for publication.

Results

The trial was done between April 19, 2013, and Jan 28, 2015. We screened 117 patients, 106 of whom were eligible and randomly assigned to treatment: 54 to pitolisant, and 52 to placebo (figure 2). 105 received at least one dose of the assigned treatment; one patient assigned to placebo withdrew from the trial because of an unrelated injury before receiving treatment and was not included in the analyses. Baseline demographics and narcolepsy characteristics of the two groups were similar (table 1). Five patients from the pitolisant group and nine patients from the placebo group withdrew from the study; eight patients did not comply (seven in the placebo group and one in the pitolisant group), four did not show efficacy of treatment (two in each group) and two patients from the pitolisant group changed their home address and were unable to continue visitations.

The reduction of cataplexy by 75% in the pitolisant group ($WCR_{f/b}$=0·25) was significantly higher than in the placebo group (38%; $WCR_{f/b}$=0·62; rate ratio [rR]=0·51, 95% CI 0·44–0·60, p<0·0001, table 2). In post-hoc analyses, this effect remained significant (all p<0·0001) for each subgroup of patients receiving

	Pitolisant (n=54)			Placebo (n=51)			Treatment effect	
	Baseline	Final	Change	Baseline	Final	Change	Effect (95% CI)	p value
WRC*	9·15	2·27	0·25	7·31	4·52	0·62	0·51 (0·43–0·60)	<0·0001
WRC >15 (n/N [%])	15/54 (28%)	4/54 (7%)	..	9/51 (18%)	12/51 (24%)	..	0·05 (0·01–0·40)	0·005
ESS score†	17·4	12·0	–5·4	17·3	15·4	–1·9	–3·48 (–5·03 to –1·92)	0·0001
ESS reponders (final score ≤10)	..	20/51 (39%)	..	..	9/50 (18%)	..	3·28 (1·08–9·92)	0·035
MWT (min)‡	3·54	6·91	1·95	4·08	4·32	1·06	1·85 (1·24–2·74)	0·003
Improvement in CGI cataplexy (n/N [%])	..	36/54 (67%)	..	..	17/51 (33%)	..	4·00 (1·54–10·38)	0·004
Improvement in CGI EDS	..	37/54 (69%)	..	..	12/51 (24%)	..	7·07 (2·55–19·59)	0·0002
Improvement in PGO (score <3, n/N [%])	..	43/54 (79%)	..	..	22/51 (43%)	..	..	..
EQ-5D sum score†	6·4	6·0	–0·4	6·5	6·4	–0·1	–0·33 (–0·70 to 0·03)	0·075
Number hallucinations per week*	0·41	0·16	0·39	0·57	0·32	0·57	0·50 (0·31–0·83)	0·007

WRC=weekly rate of cataplexies. ESS=Epworth Sleepiness Scale. MWT=maintenance of wakefulness test. CGI=clinical global impression of change. EDS=excessive daytime sleepiness. EQ-5D=European quality-of-life questionnaire. *WRC was the primary outcome; the geometric mean was calculated and 0 values replaced with 0·1; change calculated as the final value/baseline measurement; treatment effect analysed as a ratio rate derived from Poisson regression after adjusting to baseline. †Arithmetic mean; change calculated as final measurement–baseline measurement; treatment effect derived from a linear model adjusting for baseline. ‡Geometric means; change calculated as the final value/baseline measurement; treatment effect derived from linear model of log-transformed values and adjusted for baseline. Other statistical analyses used logistical regression to identify odds ratio.

Table 2: **Efficacy results (intention-to-treat population)**

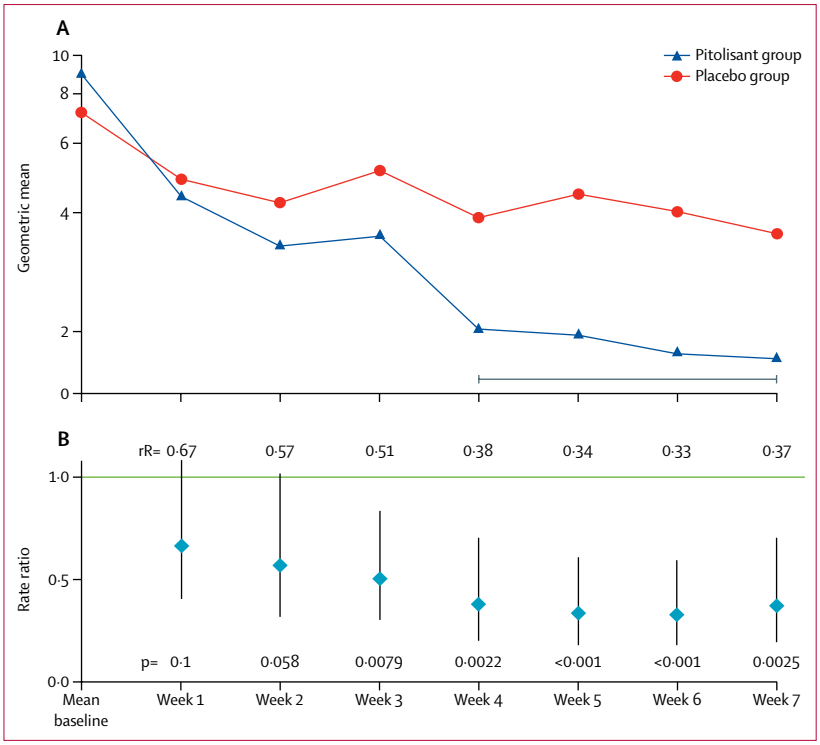

Figure 3: **Changes in weekly cataplexy rates during treatment**
(A) Geometric mean of weekly cataplexy rates. (B) Rate ratio (rR) of pitolisant or placebo adjusted for baseline (mean of weeks 1 and 2) with 95% CI and p values for each week. These are crude data, calculated without missing values imputation.

	Pitolisant group (n=54)	Placebo group (n=51)	p value
Adverse events	19 (35%)	16 (31%)	0·528
Headache	5 (9%)	5 (10%)	..
Somnolence	1 (2%)	3 (6%)	..
Irritability	3 (6%)	1 (2%)	..
Anxiety	3 (6%)	0	..
Nausea	3 (6%)	0	..
Apathy	1 (2%)	2 (4%)	..
Dizziness	0	2 (4%)	..
Treatment-related adverse events	15 (28%)	6 (12%)	0·048
Severe adverse events	1 (2%)	0	..
Amphetamine-like withdrawal syndrome	0	1 (2%)	0·305

Data are number of patients (%). p values are from χ^2 tests.

Table 3: **Adverse events**

10 mg (n=7), 20 mg (n=9), or 40 mg (n=35) as their stable dose. By comparing WCR in both groups at each week, a significant benefit of pitolisant was observed from week 5, enhancing until the last week (rR=0·37, 95% CI 0·07–0·69, figure 3). In a prespecified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0·49, 95% CI 0·31–0·82, n=12) or did not receive this medication (rR 0·51, 0·11–2·28, n=93) were not significantly different ($p_{interation}$=0·455).

For almost all the secondary endpoints (table 2) a significant superiority of pitolisant was observed (ie, proportion of patients with WCR >15 at the end of treatment, mean ESS decrease, patient proportion with final ESS≤10, MWT mean change, clinical and patient global impression [CGI and PGO], and frequency of hallucinations).

The number of patients reporting adverse events did not differ significantly between those receiving pitolisant and those receiving placebo (16 [31%] of 54 pitolisant group *vs* 19 [35%] of 51 in the placebo group; table 3). The most frequent adverse events were headache for both treatment groups, irritability, anxiety, and nausea for the pitolisant group, and somnolence for the placebo group. No clinically relevant differences were observed between groups in terms of intensity of symptoms and recovery (table 3). Nevertheless, double the number of adverse events were considered treatment-related with pitolisant compared with placebo (15 [28%] of 54 in the pitolisant group *vs* six [12%] of 51 in the placebo group; p=0·048), but all were of mild-to-moderate intensity, except for one case of severe nausea that resolved without sequelae after pitolisant discontinuation. BDI score decreased significantly between baseline and end of treatment in the pitolisant group compared with placebo (–1·8 *vs* –0·8; p=0·02; appendix). Duration of nocturnal awakenings also did not differ significantly between groups. No withdrawal syndrome was reported with pitolisant, although one was observed with placebo. Blood chemistry and haematological or cardiovascular parameters did not change in either group.

Discussion

In our study, once-daily treatment with pitolisant significantly improved cataplexy in patients with narcolepsy, in contrast with previous work, which only reported improvement in excessive daytime sleepiness.[7] Our trial recruited severely affected narcoleptic patients with cataplexy who experienced a high frequency of cataplexy episodes at baseline (7–9 per week; ie, considerably higher than the minimum required for inclusion), marked daytime sleepiness (mean ESS of 17, a low score on the multiple sleep latency test, and low MWT values), and high frequency of associated symptoms such as hallucinations (in 68 [65%] all 105 patients randomised to treatment). Pitolisant given once daily in the morning improved cataplexy; the frequency of episodes at end of treatment was reduced by 75% compared with baseline, and by half compared with placebo; confirming other trials.[9,13] A high placebo effect was found, which might reflect the well known role of

subjective and emotional factors in the triggering of cataplexy attacks. Similar cataplexy frequency decreases were found in previous trials with pitolisant[7] or with 6–9 g sodium oxybate.[9,13] From baseline, WCR progressively decreased with a maximum change observed after 1 month (figure 3). These results were unaffected by whether or not a pre-inclusion anti-cataplectic treatment was resumed during the trial.

Following the flexible dosing period, for each of the subgroups of patients receiving a stable dose of 10 mg, 20 mg, or 40 mg, WCR was reduced significantly compared with placebo, which underscores the potential advantage of the flexible dosing scheme and reduces unnecessary drug exposure. Results on secondary endpoints provide evidence of consistency across the various measures: as shown through CGI, cataplexy improved in twice as many patients treated with pitolisant than treated with placebo. Improvement of cataplexy with pitolisant treatment compared with placebo was also shown when considering the number of patients experiencing a large WCR (>15) at end of treatment. The improvement was also measured by a significant change in PGO.

Compared with modafinil and other psychostimulants, whose effects on cataplexy are unclear,[1,14,15] pitolisant reduces cataplexy, although by a mechanism that remains unknown. Its effect is, however, consistent with the decrease of direct transitions from wakefulness to REM sleep episodes it elicits in a mouse model of the disease.[16] Neurophysiological studies have identified pontine and amygdala nuclei that control REM sleep and cataplexy. Emotions seem to trigger enhanced activity in the amygdala from which GABA neurons project to ponto-medullary centres mediating the motoneuron atonia of cataplexy. Notably, the amygdala, which plays a critical role in cataplexy induction, receives heavy histaminergic inputs from the tuberomammillary nucleus and expresses a high density of H3 receptors.[17–20] The histamine-releasing effects of H3 receptor inverse agonists might be particularly prominent in narcoleptic patients with cataplexy in whom the number of tuberomamillary neurons is nearly doubled, presumably as a compensatory response to loss of excitatory drive from the orexin-producing neurons.[3] Since hallucinations might also be related to REM sleep features,[1,2] the significant anti-hallucinatory effect of pitolisant (p=0·007) might arise from similar mechanisms.

Similar to an earlier controlled trial with pitolisant,[7] this study showed an improvement in excessive daytime sleepiness in both subjective and objective assessments. Mean ESS decreased by over 5 units from baseline to final assessments and by over 3 units compared with placebo, values generally considered as clinically relevant, and the number of responders (ESS<10) was superior with pitolisant. This benefit in excessive daytime sleepiness was confirmed on MWT, a laboratory test measuring time to remain awake under a dim light. Both treatments were well tolerated, with one severe adverse event detected in the pitolisant group, and a similar frequency and intensity of adverse events; however, treatment-related adverse events were doubled with pitolisant than with placebo. As in the HARMONY I trial,[7] no withdrawal syndrome was detected after abrupt cessation of pitolisant, which is consistent with the decreased activation of accumbal dopaminergic neurons, psychomotor stimulation, and behavioural sensitisation it elicits, and its low addiction liability potential, thereby indicating that pitolisant does not function as a typical psychostimulant.[22–24]

Our study has limitations. Its short duration does not address whether tolerance to pitolisant will develop on continuation of treatment, and the effects of treatments with longer duration remain to be assessed in this chronic disorder. Also, the flexible dosage and multiple visits could have affected the treatment efficacy, with less responsive patients being more likely to be titrated to the highest dose. The exclusion of children, patients with unstable comorbidities, and those refusing a potential placebo treatment does not allow us to generalise our findings to these populations. The positive opinion of patients regarding their potential pitolisant treatment might have been biased by the drug identification via its subjective effects. Since the trial started before the publication of ICSD-3,[25] narcolepsy was diagnosed according to ICSD-2.[11] Low CSF orexin concentrations—which is the best criterion for narcolepsy type 1 diagnosis—was not an inclusion criterion; hence, although all tested patients had low latency values, and at least two sleep onset REM periods on MSLT, we cannot exclude the existence of a bias in the selection and enrolment of non-narcolepsy type 1 cases in this study, thus diagnoses must be interpreted with caution.

In spite of these limitations, the study suggests that pitolisant given once daily is well tolerated and could be useful to improve not only cataplexy but also excessive daytime sleepiness and hallucinations in narcolepsy. If confirmed in long-term studies, these features indicate that pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom well tolerated and effective therapeutic options are few.

Contributors

J-CS participated in the conception and design of the study, and wrote the first draft of the paper. ZS contributed to the conception and design of the study, data acquisition and interpretation, and revisions to the paper. YD contributed to the conception and design of the study, and revisions to the paper. IL participated in the study coordination and data acquisition. VM, IP, SK, SJ, and KS participated in data acquisition and interpretation and revised the paper. PL developed the statistical analysis plan and revised the paper. IL and JML participated in the conception, design, and organisation of the study.

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Declaration of interests

YD has received personal fees from and serves on the advisory board for UCB Pharma, Bioprojet, Flamel, Theranexus, Actalion, and Jazz. SJ reports personal fees from Bioprojet. KS reports personal fees from Boehringer Ingelheim, Novartis, Bioprojet, Berlin Chemie, Luitpold Pharmaceutical, and Eisai. VM, IP, and SK report grants from Bioprojet. IL, J-ML and J-CS are employees and shareholders of Bioprojet. All other authors have nothing to disclose. J-ML and J-CS also hold a patent for pitolisant (EP 1428820).

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Wide implications of a trial on pitolisant for cataplexy

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Narcolepsy type 1 is a neurological sleep-wake disorder with severe effects on daily life, not only because of incapacitating sleepiness during daytime but also because patients can experience cataplexy—ie, partial or even generalised loss of muscle tone triggered by emotion. The pathophysiological hallmark of the disease is an almost complete loss of wake-promoting hypothalamic neurons secreting orexin (also known as hypocretin). The choice of treatments for these patients is limited to a few stimulants, antidepressants, and sodium oxybate. Previously, it was reported that pitolisant, a histamine H3 receptor inverse agonist, improves subjective daytime sleepiness in patients with narcolepsy.[1] In *The Lancet Neurology*, Zoltan Szakacs and colleagues[2]—some of these researchers also did the previous study—did a well-designed randomised, double-blind, placebo-controlled trial in 106 patients with narcolepsy and found that pitolisant also reduces the average number of cataplexy attacks per week. Although it remains speculative how histaminergic neurotransmission modulates the expression of cataplexy, these results are interesting as they provide further clues that the histamine system might play an important role in narcolepsy.[3]

The main limitation of the study is that the diagnosis of narcolepsy was based on criteria that were not specific.[4] According to the inclusion criteria used in the study, subjective sleepiness and experience of cataplexy were sufficient for diagnosing narcolepsy, which is why the authors corroborated the diagnosis in most patients with multiple sleep latency tests. Still, the diagnostic value of standard multiple sleep latency tests is not optimal, since shift work and chronic sleep deprivation can produce similar findings,[5,6] and test-retest reliability in hypersomnia conditions is poor.[7] The fact that reported mean sleep latencies in the cohort of Szakacs and colleagues[2] (4·2–4·7 min) were higher than those reported in other cohorts, including ours (2·6–2·9 min),[8] leaves some uncertainty about patient inclusion.

However, despite this and other limitations, this study is important and deserves the attention of clinicians, scientists, and policymakers. First, this study will hopefully contribute to approval of this novel compound by national drug regulators. This is good news for clinicians, since we need more treatment options to better tailor individualised therapy for patients with narcolepsy. For instance, as a subset of these patients can experience side effects from treatment with modafinil, the observed tolerability of pitolisant makes it an attractive option.[1] The additional effect of pitolisant on cataplexy makes it a viable substitute for sodium oxybate, a nocturnal treatment option that also improves both sleepiness and cataplexy, but necessitates drug intake before and during night sleep, and closer monitoring for side effects.

Second, for policymakers, this study provides evidence that excellent collaboration between eastern and western European countries is not only possible, but also necessary if research goals need to be reached within a reasonable timeframe. The implementation of clinical trial procedures in western countries has become laborious, expensive, time-consuming, and even confusing, which reduces our competitiveness compared with other world regions. Keeping patient safety in mind, we must halt and reverse this development when possible, if we want to keep our competitive edge in research, particularly since more administrative oversight does not necessarily improve ethical handling of study procedures or care for patients.

Last but not least, this study is a good example that important findings deserve dissemination in a leading clinical journal, even if some methods are outdated at the time of publication. The new diagnostic criteria for narcolepsy, which were published after the present study started, are more specific, and ever since, additional studies have provided better insights into how to improve the diagnosis of narcolepsy based on sleep laboratory tests.[6,8–10] Thus, confirmatory studies on the effect of pitolisant on cataplexy shall be based on these new criteria. I still hold some hope that high-quality confirmatory—and also negative—studies will get similar attention. Today, negative and confirmatory studies are often difficult to publish. I have observed this *in extremis* some years ago when my colleagues and I finally found a journal to publish our report that we could not replicate a previous finding published in a leading journal, and subsequently received positive feedback from 14 other groups worldwide.[11] Together, these 14 other groups spent about USD$6·5 million trying to replicate the same findings, but found it too invidious to publish their negative results.

Let us wait for this promising compound to be available for patients, let us welcome confirmatory studies on the multiple effects of pitolisant, and let us engage our community to speak up for the swift publication of confirmatory and negative studies.

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