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Is Pitolisant Effective in Reducing Excessive Daytime Sleepiness and Cataplexy in Adults with Narcolepsy?

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Is pitolisant effective in reducing excessive daytime sleepiness and cataplexy in adults with narcolepsy?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not pitolisant is effective in reducing excessive daytime sleepiness and cataplexy in adults with narcolepsy.

Study Design: Review of two randomized control trials (RCTs) published in 2013 and 2017, and one prospective, placebo-controlled, single-blind study published in 2008.

Data Sources: All articles were published in English and taken from peer-reviewed journals, which were found using the PubMed database.

Outcomes Measured: The outcomes of investigation measured include excessive daytime sleepiness (EDS) assessed by change in Epworth Sleepiness Scale (ESS) score, and cataplexy rate calculated from recorded cataplexy attacks in patients' sleep diaries.

Results: Dauvilliers, et al. found pitolisant was more effective in reducing mean ESS scores from baseline compared to placebo (-5.8 *vs* -3.4; p=0.024). A decrease in ESS score indicates improved EDS. Also, in post-hoc analyses, Dauvilliers et al. found that pitolisant was superior to placebo in reducing daily cataplexy rate from baseline (0.38 *vs* 0.92; p=0.034). Szakacs, et al. found pitolisant to be effective in reducing weekly cataplexy rate (WCR) by 75% from baseline compared to placebo (38% decrease in WCR), p <0.0001; they also report a significant decrease in ESS score from baseline in the pitolisant group compared with placebo (-5.4 *vs* -1.9; p= 0.0001). In a single-blind, placebo-controlled, prospective study, Lin et al. found that tiprolisant (currently called pitolisant) showed a significant reduction in ESS score from baseline compared to placebo (5.9 *vs* 1.0; p<0.001).

Conclusions: Pitolisant was shown to be efficacious in reducing EDS and cataplexy in adults with narcolepsy.

Key Words: Narcolepsy, pitolisant, tiprolisant

INTRODUCTION

Narcolepsy is a rare, chronic neurological disorder characterized by excessive daytime sleepiness (EDS) causing an individual to fall asleep at inappropriate times throughout the day, which can disrupt work, school, and social life. According to DSM-5 criteria, EDS occurs at least three times per week for at least three months with at least one of the following: cataplexy (at least a few times per month), shortened rapid eye movement (REM) latency of ≤15 minutes on polysomnography (or a multiple sleep latency test (MSLT) showing a mean sleep latency of ≤8 minutes and ≥2 sleep-onset REM periods), and hypocretin deficiency in CSF.[1] Cataplexy is defined as a sudden, brief loss of muscle tone associated with intense emotions (may have global hypotonia without emotional triggers, which is seen in children or when onset of disease is within six months), without loss of consciousness.

Narcolepsy usually presents in the teens or early twenties and has two peak onsets: ages 15-25 and 30-35 years.[1] It affects 1 in 2,000 people in the US.[2] Cataplexy often occurs within a year in 50% of those diagnosed and affects 0.02 – 0.04% of the general population worldwide.[1] Unfortunately, more than 80% of individuals with sleep disorders remain undiagnosed, which costs the US economy over $400 billion per year in medical costs, decreased/lost productivity, injuries, and screening programs.[2] Literature reports a mean delay in diagnosis of narcolepsy of up to 15 years, consequentially impacting the burden of disease.[3] Individuals with narcolepsy have a two to three-fold higher annual rate of inpatient admissions, and visits to the ED, hospital outpatient centers, neurologist, pulmonologist, and PCP.[4, 5] Studies have shown that the annual average cost per patient for medical services and medications is more than double the amount for patients with narcolepsy compared to matched controls ($11,702 *vs* $5261; $p < 0.0001$).[4]

The exact etiology and pathogenesis of narcolepsy remain unclear, but a few causes have been identified: genetics, decreases in hypocretin (orexin) neuropeptides, and destruction/loss of

orexin neurons. Orexins are excitatory neuropeptides that project to histaminergic or noradrenergic neurons known to play a key role in wakefulness.[6] All patients with narcolepsy suffer from EDS; other symptoms include abnormal REM sleep manifestations such as cataplexy (most common and most debilitating), hallucinations and sleep paralysis, which intrude into their wakefulness and vice versa, greatly impairing the person's quality of life.[2, 5]

The usual method of treating narcolepsy combines lifestyle changes plus stimulants or CNS depressants. Lifestyle changes include improving sleep hygiene by establishing a regular sleep schedule, getting at least seven hours of sleep per night, taking short naps throughout the day, daily exercise, and avoiding shift work. Psychostimulants such as modafinil, methylphenidate, or amphetamine/dextroamphetamine are commonly used as wake-promoting therapies to treat EDS.[2, 7] CNS depressants such as sodium oxybate is currently the only drug that is FDA approved for both cataplexy and EDS in adults.[7, 8] Antidepressants such as SSRIs, SNRIs, and TCAs are used off-label for cataplexy, however supporting evidence is scarce.[7]

Narcolepsy is a lifelong, debilitating disorder with no cure currently available. EDS and cataplexy are the two most commonly reported symptoms and known to significantly impact daily living. Since only one drug is FDA approved to treat both EDS and cataplexy, some patients must manage their symptoms with multiple medications. Sodium oxybate, while effective at treating both EDS and cataplexy, can however cause serious adverse effects and requires an inconvenient nightly dosing administration, in which the patient needs to set an alarm 2.5 to 4 hours later to take the second dose. Thus, a need exists for more safe and convenient drugs that can treat both EDS and cataplexy. Studies have shown that histamine neurons play a significant role in maintaining wakefulness[9] and patients with the most severe loss of orexin neurons tend to show the highest increase in histaminergic neurons in narcolepsy,[10] providing a targeted area of study in which to activate histaminergic transmissions for arousal. Research

demonstrates H1 and H3 histamine receptors in the brain are important in mediating the wake-promoting effects of histamine.[9] Studies suggest pitolisant, a histamine H3-receptor inverse agonist, activates these histaminergic neurons to release histamine and in turn increase wakefulness, thereby treating EDS and cataplexy in adults with narcolepsy. This review evaluates two randomized controlled trials (RCTs) and a prospective, single-blind, placebo-controlled trial comparing the efficacy of pitolisant in reducing EDS and cataplexy in adult patients with narcolepsy.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not pitolisant is effective in reducing excessive daytime sleepiness and cataplexy in adults with narcolepsy.

METHODS

All selected articles were published in English, in peer-reviewed journals, and found on the PubMed database using the following search terms: “Narcolepsy”, “pitolisant”, and “tiprolisant.” Articles were selected based on relevance to the stated clinical question and whether or not the outcomes mattered to patients. The inclusion criteria were placebo-controlled, single or double-blind primary resource studies, with at least two being RCTs, published no more than 10 years ago. Studies with patients younger than 18 years of age and initial/baseline ESS scores of less than 10 were excluded. Statistics reported in this review include mean change from baseline, confidence intervals, p-values, relative benefit increase (RBI), relative risk reduction (RRR), absolute risk reduction (ARR), absolute benefit increase (ABI), and numbers needed to treat (NNT). Demographics and characteristics of each study are provided in Table 1.

This review examines two double-blind, placebo-controlled RCTs and one prospective, sequential placebo-controlled, single-blind trial. The patient population selected for this review included individuals at least 18 years of age diagnosed with narcolepsy with or without

cataplexy. The intervention under study was pitolisant (formerly called tiprolisant and BF2.649), a selective histamine H3 receptor inverse agonist. Comparisons were made against a control group receiving a placebo. Outcomes measured were patient oriented and included EDS (assessed by Epworth Sleepiness Scale (ESS) score) and cataplexy rate based on those reported in patients' sleep dairies.

Table 1: Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dauvilliers (2013)[11]	Double-blind, placebo-controlled, parallel-group RCT	95	≥18	● Pts ≥18yo with narcolepsy +/- cataplexy, no psychostimulants for ≥14 days ● have EDS (ESS score ≥14) ● Self-reported EDS for >3mo ● Narcolepsy confirmed by polysomnogram ● multiple sleep latency test (MSLT) within 5yrs – mean sleep latency (MSL) of ≤ 8min with ≥2 REM periods	● Use of IND within 30 days before screening ● any disorder (d/o) that could cause EDS in those without cataplexy ● history of substance abuse, CVD, liver or renal abnormalities, or psych disorders	1	Pitolisant (10mg, 20mg, or 40mg/day), 4 cap, po once daily in AM x 8wks (3wks flexible dosing followed by 5wks stable dosing)
Szakacs (2017)[12]	Double-blind, placebo-controlled RCT	106	≥18	● Pts ≥18yo with narcolepsy with cataplexy (≥3/wk) ● have EDS (ESS score ≥12) ● Narcolepsy confirmed by polysomnogram ● MSLT within 1yr and ≥2 REM periods	● Use of any psychostimulant or sedative meds ● Participation in another trial within a month before screening ● History of any other d/o with EDS, substance abuse, CVD, liver/renal abnormalities, or a psych d/o	1	Pitolisant (5mg, 10 mg, 20 mg, or 40mg), 1cap po once daily in AM x 7wks (3wks flexible dosing followed by 4wks stable dosing)
Lin (2008)[13]	Pilot, prospective, comparative, sequential placebo-controlled, single-blind	22	≥28	● Adults with narcolepsy with cataplexy ● EDS with 2≤ direct onset REM periods and a MSL <8mins during an MSLT	● ESS score <10	0	Tiprolisant 40mg, 1 cap po once daily in AM x 1week

OUTCOMES MEASURED

The outcomes measured were change in EDS and cataplexy rate with pitolisant versus placebo. In all three articles, EDS was assessed by change in mean ESS score from baseline.[11-13] The ESS is a self-administered questionnaire that subjectively measures and screens for EDS by assessing the chance of falling asleep in eight ordinary life situations. Each item on the scale is graded from 0 – 3; thus, the score can range from 0 (normal, with no chance of falling sleep) to a max of 24 (severe EDS). A decrease in ESS score indicates improved EDS and an ESS score of 10 or lower is considered normal.[14] Dauvilliers et al. and Szakacs et al. also gave additional post-hoc analysis and secondary endpoint analysis, respectively, of dichotomous data on ESS responder rates, defined as patients with a final ESS (ESS_f) score of 10 or lower.[11, 12] Cataplexy rates were calculated from the mean number of attacks reported in patients' individual sleep diaries. Szakacs et al. and Dauvilliers et al. report weekly and daily (defined as ≥1 cataplexy attacks during baseline or treatment period) cataplexy rate reduction from baseline, respectively, as the ratio of final weekly cataplexy rate divided by the corresponding baseline ($WCR_{f/b}$). In a secondary analysis, Szakacs et al. also gave dichotomous data on the proportion of patients who had a weekly cataplexy rate (WCR) >15 at the end of the treatment study.[12] The post-hoc and secondary assessments were completed in order to confirm differences between the pitolisant and placebo groups.

RESULTS

All three studies used in this review aim to demonstrate the efficacy of pitolisant on EDS and/or number of cataplexy attacks by verifying whether the results of pitolisant are superior to those of placebo. Two double-blinded RCTs assessed both reduction of EDS and cataplexy, while one single-blinded trial assessed only reduction in EDS. All studies consisted of participants from multiple sleep centers in Europe. The inclusion and exclusion criteria of all

three articles are comparable (Table 1), and all patients who received at least one study dose were included in the intention-to-treat analysis. Prior to baseline (preceding randomization) patients discontinued psychostimulants, but were permitted to continue anticataplectic agents (sodium oxybate or antidepressants, except TCAs due to effect on H1 receptors in the brain and drug interactions with pitolisant) throughout the trial. In each of the studies, change in arithmetic mean ESS score was calculated. To test the superiority of pitolisant over placebo, they then adjusted for baseline values to show treatment effect between the groups.

In Dauvilliers et al.[11] 95 patients were randomly assigned to treatment: 30 to placebo, 32 to pitolisant, and 33 to modafinil. However, comparisons with modafinil are not included in this EBM review. One patient was lost from the pitolisant group due to withdrawal of consent (before receiving any treatment), leaving 94 patients in the intention-to-treat analysis, and 57 (61%) of which who had cataplexy. Double-blinding was maintained throughout the eight-week treatment phase and all patients were given four capsules per day, matched to placebo in taste and appearance, despite their assigned treatment or dose. The treatment period consisted of 3 weeks of flexible dosing (10mg, 20mg, or 40mg/day of pitolisant adjusted for individual clinical efficacy and safety) followed by 5 weeks of stable, assigned dosing.[11] Change in mean ESS score from baseline was the primary analysis of this study. They found pitolisant was more effective in reducing mean ESS scores from baseline compared to placebo (-5.8 *vs* -3.4; p=0.024; table 2).

In a double-blinded, RCT conducted by Szakacs et al.,[12] 106 patients with cataplexy were randomly assigned to treatment: 54 to pitolisant and 52 to placebo. One patient was lost from the placebo group due to injury unrelated to the trial; since they never received a dose they were not included in the intention-to-treat analysis. The treatment phase lasted 7 weeks: 3 weeks of flexible dosing (5mg, 10mg, or 20mg/day of pitolisant) followed by 4 weeks of stable, assigned

dosing (5mg, 10mg, 20mg, or 40mg pitolisant). Change in mean WCR from baseline was the principle outcome of this study.

Lin et al.[13] conducted a pilot, prospective, single-blinded two-week study of 22 patients (21 with cataplexy), all whom were included in the intention-to-treat analysis. Without knowing the sequence, patients were given 1 week of placebo followed by 1 week of a fixed dose of tiprolisant 40mg/day. Unlike the other two trials, each participant acted as their own control. The principle outcome of this study was change in mean ESS score from baseline (Table 2).

P-values of less than 0.05 indicate that there is a less than 5% chance that improvement in ESS scores occurred by chance and that there is a statistically significant difference in change in ESS score from baseline compared to placebo. The researchers used continuous data to present these findings, which is provided in Table 2. Despite change in ESS scores being negative or positive, all values indicate reduction of points from baseline. In each study reviewed, patients given pitolisant had a greater reduction in mean change of ESS score from baseline compared to placebo, indicating statistically significant improvement (reduction) in EDS.

Table 2: Comparison of change in mean ESS score from baseline compared to placebo

Study	Pitolisant	Placebo	Treatment effect (95% CI)	P-Value
Dauvilliers, et al. [11]	-5.8 (SD 6.2)	-3.4 (SD 4.2)	-3.0 (-5.6 to -0.4)	0.024
Szakacs, et al. [12]	-5.4	-1.9	-3.48 (-5.03 to -1.92)	0.0001
Lin, et al. [13]	5.9 (SD 5.5)	1.0 (SD 4.9)	4.9 (2.22 to 7.56)	0.0006

In the two double-blinded RCTs[11,12] additional dichotomous data on the percentage of ESS responders (defined as patients with final ESS scores (ESS_f) ≤ 10 after the treatment study) were used to further determine efficacy of pitolisant. An ESS score of ≤ 10 is considered within normal range. In a post-hoc analysis conducted by Dauvilliers et al.[11] 45% (14/31 patients) of patients given pitolisant have reported an $ESS_f \leq 10$, compared to 13% (4/30 patients) of those given placebo ($p<0.0006$, 95% CI: 4.4 (2.1–9.2)). Similarly, in a secondary efficacy assessment

conducted by Szakacs et al.[12] 39% (20/51 patients) of patients given pitolisant reported an ESS_f ≤10, compared to 18% (9/50 patients) given placebo (p = 0.035, 95% CI: 3.28 (1.08–9.92)). Determining the numbers needed to treat (NNT) value establishes clinical significance of the intervention. The NNT values of 3 and 5 mean that for every 3 or 5 patients with narcolepsy treated with pitolisant, one more patient will report an $ESS_f \leq 10$ (improved EDS) compared to those receiving a placebo (Table 3).

Table 3: Comparison of ESS responders (final ESS ≤ 10) between pitolisant and placebo

Study	Control Event Rate (CER)	Experimental event rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	P-Value
Dauvilliers, et al. [11]	0.13	0.45	2.46	0.32	3	<0.0006
Szakacs, et al. [12]	0.18	0.39	1.17	0.21	5	0.035

In the RCT conducted by Szakacs et al.[12] the primary outcome was change in geometric mean of WCR from baseline, which is reported as the ratio of final weekly cataplexy rate divided by the corresponding baseline ($WCR_{f/b}$). These results are recorded as continuous data and provided in Table 4. This study found pitolisant to be effective in reducing WCR by 75% ($WCR_{f/b}$ = 0.25) from baseline compared to placebo (38% decrease in WCR, $WCR_{f/b}$ = 0.62, p <0.0001, Table 4). The p-value listed in Table 4 indicates that WCR was reduced significantly with pitolisant compared to placebo.

Table 4: Change in mean WCR from baseline of the Szakacs, et al.[12] RCT

Treatment	Baseline	Final	Change (Final/Baseline)	Treatment effect (95% CI)	P-Value
Pitolisant (n=54)	9.15	2.27	0.25	0.51 (0.43–0.60)	< 0.0001
Placebo (n=51)	7.31	4.52	0.62		

Dauvilliers et al.[11] gave additional post-hoc analysis on the change in geometric mean of daily cataplexy rate from baseline. These results are recorded as continuous data and provided in Table 5 below. This analysis included only the patients who reported in their sleep diaries at least

one cataplexy attack during baseline or during the 8-week treatment phase. Pitolisant reduced daily cataplexy rate by 62% (0.38) from baseline versus 8% in those taking placebo (0.92). Pitolisant was effective and superior to placebo in reducing mean cataplexy rate from baseline (p= 0.034, Table 5).

Table 5: Change in mean daily cataplexy rate from baseline of the Dauvilliers, et al.[11] RCT

Treatment	Baseline (SD)	Final (SD)	Change (Final/Baseline)	Treatment effect (95% CI)	P-Value
Pitolisant (n=20)	0.52 (0.6)	0.18 (0.4)	0.38	0.38 (0.16–0.93)	0.034
Placebo (n=14)	0.43 (0.7)	0.39 (0.6)	0.92		

Szakacs et al.[12] conducted a secondary analysis on the proportion of patients with a final WCR greater than 15. This dichotomous data showed 7% (4/54 patients) of patients given pitolisant reported a final WCR >15, compared to 24% (12/51 patients) of those given placebo. The percentage of patients reporting high cataplexy rate was significantly decreased with pitolisant versus placebo, with p-value = 0.005. The NNT value of -6 means that for every 6 patients with narcolepsy and cataplexy treated with pitolisant, one less patient will report severely high WCR (WCR>15) compared to those taking placebo (Table 6).

Table 6: Proportion of patients with final WCR >15 between pitolisant and placebo

Study	Control Event Rate (CER)	Experimental event rate (EER)	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)	P-Value
Szakacs, et al.[12]	0.24	0.07	- 0.71	- 0.17	- 6	0.005

DISCUSSION

Pitolisant (formerly tiprolisant and BF2.649) is a selective histamine H3-receptor inverse agonist that inhibits H3-autoreceptors, activating histaminergic neurons in the brain to release histamine and thereby promote wakefulness.[9,13] It is not yet FDA approved and therefore not currently available in the US. Pitolisant (brand name Wakix, in EU) was approved by the EMA (European Medicines Agency) in 2016 and available for use in some countries in Europe only

for the treatment of adults with narcolepsy with or without cataplexy.[9,15] At this moment, pitolisant is not used for anything else other than to treat EDS and cataplexy in adults with narcolepsy. Pitolisant is well tolerated, with minor adverse effects such as: headaches (most common), nausea, insomnia, anxiety, and irritability.[11-13] The contraindications of pitolisant include: pregnancy, severe allergic reaction to pitolisant, and severe hepatic impairment (Child-Pugh class C).[16] No known black box warnings exist at this time. Pitolisant was shown to be effective in reducing EDS and cataplexy with once daily dosing in the morning.

Since pitolisant is a new drug of its class, and the first H3-receptor inverse agonist to be utilized in clinical trials with patients, the availability of completed primary research is scarce, rendering limited search results for this review. Regarding limitations of the studies themselves, all three articles consisted of a short duration of treatment, which may hinder pitolisant from reaching its maximum effectiveness and not allow assessment of tolerance of the drug. Another potential limitation in all three trials is that they took place in Europe, where their standards and regulations may be different from those followed in the US. Also, exclusion of children or those younger than 18 years old, patients with severe comorbidities, and those refusing placebo limit the ability to generalize findings to these populations.

The phase II study by Lin et al[13] was the first clinical trial done on this drug class. Limitations of this study included: a short-term duration of two weeks, a small sample size of 22 patients, single-blinding, and fixed dosing. The small sample size may not be indicative of the population at large. Giving each patient the same dose (40mg tiprolisant) may not have allowed for individual efficacy of the drug. Also, with the trial being single-blinded and sequentially placebo-controlled, this could have invited bias into the analysis of results and patient response to treatment.

CONCLUSION

After reviewing the data of all three articles and despite the limitations previously mentioned, it is conclusive that pitolisant is an effective treatment to significantly reduce both EDS and cataplexy in adults with narcolepsy.[11-13] Each study in this review was limited to narcoleptic patients in Europe, warranting future study to evaluate the effects of pitolisant on EDS and cataplexy on adults with narcolepsy in the US. Ongoing studies include assessing long-term evaluation of safety and efficacy of pitolisant in narcoleptic patients.[17] Also, the studies included in this review do not use DSM-5 criteria to define their inclusion/exclusion criteria, thus they did not consider the orexin levels in CSF, which is now an important diagnostic feature of those with narcolepsy with cataplexy. Thus, these results must be analyzed carefully because of possible bias in their selection of patients. Therefore, future research should diagnose according to DSM-5 and include its criteria in their inclusion/exclusion process. Furthermore, patients with narcolepsy often times complain of decreased attention and memory. H3-receptors and histamine are known to play a key role in learning and memory.[18,19] Further research should determine the efficacy of pitolisant on improvement of attention and memory in patients with narcolepsy.

REFERENCES

1. American Psychiatric Association. Sleep-wake disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: APA; 2013:361-422.

2. Scammell TE, Saper CB, Czeisler CA. Sleep Disorders. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill; 2018. http://accessmedicine.mhmedical.com.ezproxy.pcom.edu:2048/content.aspx?bookid=2129&sectionid=192344545. Accessed October 06, 2018.

3. Thorpy MJ, Krieger AC. Review Article: Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. 2014;15:502-507. doi:10.1016/j.sleep.2014.01.015.

4. Black J, Reaven NL, Funk SE, et al. The burden of narcolepsy disease (BOND) study: Health-care utilization and cost findings. *Sleep Med*. 2014;15(5):522-529. doi:10.1016/j.sleep.2014.02.001.

5. Flores NM, Villa KF, Black J, Chervin RD, Witt EA. The Humanistic and Economic Burden of Narcolepsy. *J Clin Sleep Med*. 2016;12(3):401-7. doi: 10.5664/jcsm.5594.

6. Ling S, Yves D, Jerome M. S. Interactions of the histamine and hypocretin systems in CNS disorders. *Nature Reviews Neurology*. 2015;(7):401. doi:10.1038/nrneurol.2015.99.

7. Thorpy MJ, Dauvilliers Y. Review Article: Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med*. 2015;16: 9-18. doi:10.1016/j.sleep.2014.10.002.

8. Drakatos P, Lykouras D, D'Ancona G, et al. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. *Sleep Med*. 2017;35:80-84. doi: 10.1016/j.sleep.2017.03.028.

9. Scammell TE, Jackson AC, Franks NP, Wisden W, Dauvilliers Y. Histamine: neural circuits and new medications. *SleepJ*. 2018: 1-8. doi: 10.1093/sleep/zsy183.

10. Valko PO, Gavrilov YV, Yamamoto M, et al. Increase of histaminergic tuberomammillary neurons in narcolepsy. *Ann Neurol*. 2013;74(6):794-804. doi:10.1002/ana.24019.

11. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol*. 2013;12(11):1068-75. doi:10.1016/S1474-4422(13)70225-4.

12. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(3):200-207. doi: 10.1016/S1474-4422(16)30333-7.

13. Lin J, Dauvilliers Y, Arnulf I, et al. An inverse agonist of the histamine H_3 receptor improves wakefulness in narcolepsy: Studies in orexin$^{-/-}$ mice and patients. *Neurobiology of Disease*. 2008;30(1):74-83. doi: 10.1016/j.nbd.2007.12.003.

14. Kallweit U, Schmidt M, Bassetti CL. Patient-Reported Measures of Narcolepsy: The Need for Better Assessment. *J Clin Sleep Med*. 2017;13(5):737-744. doi:10.5664/jcsm.6596.

15. European Medicines Agency. Wakix: European public assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/wakix. Published April 13, 2016. Last Updated April 13, 2016. Accessed Dec 3, 2018.

16. Pitolisant. DynaMed Plus. https://www-dynamed-com.ezproxy.pcom.edu/topics/dmp~AN~T910760/Pitolisant#References. Published 2015. Last Updated Nov 06, 2018. Accessed Dec 3, 2016.

17. Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term evaluation of safety and efficacy of pitolisant (wakix®), an histamine H3R antagonist, in narcolepsy. *Sleep Med*. 2017;40:e75. doi:10.1016/j.sleep.2017.11.215.

18. Alachkar A, Łażewska D, Kieć-Kononowicz K, Sadek B. The Histamine H3 Receptor Antagonist E159 Reverses Memory Deficits Induced by Dizocilpine in Passive Avoidance and Novel Object Recognition Paradigm in Rats. *Front Pharmacol*. 2017;8 (709):1-12. doi:10.3389/fphar.2017.00709.

19. Brabant C, Charlier Y, Tirelli E. The histamine H_3-receptor inverse agonist Pitolisant improves fear memory in mice. *Behavioural Brain Research*. 2013; 243:199-204. doi:10.1016/j.bbr.2012.12.063.