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Are Inverse Agonists of the Histamine H3 Receptor Effective in Reducing Excessive Daytime Sleepiness (EDS) in Individuals with Sleep Disorders?

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Are Inverse Agonists of the Histamine H3 Receptor Effective in Reducing Excessive Daytime Sleepiness (EDS) in Individuals with Sleep Disorders?

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not "Are inverse agonists of the Histamine H3 receptor effective in reducing excessive daytime sleepiness (EDS) in individuals with sleep disorders?"

DESIGN: Review of two randomized controlled trials and one cross-sequential pilot study. All studies were primary sources, published in the English language and from 2008-2017.

DATA SOURCES: A single-blind, placebo controlled, cross-sequential study comparing an H3 inverse agonist to placebo in narcoleptics. Two randomized, double-blind, placebo controlled studies; one in narcoleptic patients and one in obstructive sleep apnea (OSA) patients. All studies found using PubMed and Cochrane databases.

OUTCOMES MEASURED: All three trials assessed the efficacy of using an H3 inverse agonist to reduce EDS symptoms in patients with either narcolepsy or obstructive sleep apnea. EDS severity was assessed using the Epworth Sleepiness Scale (ESS), an eight question self-administered questionnaire that assess an individual's likelihood of falling asleep in normal everyday settings. Scores range 0-24, with a higher score correlating with more severe EDS.

RESULTS: The pilot study done by Lin J-S et al. showed a significant reduction in ESS score of 4.86 (p =0.0006). The RCT done by Dauvilliers (2013) concluded with a significant ESS score reduction of -3.0 (p= 0.024) when compared to placebo. The final study involving OSA patients done by Herring et al. showed a larger reduction in ESS scores when treated with an H3 inverse agonist compared to treatment with a placebo. These results were not proven to be statistically significant.

CONCLUSIONS: These results suggest that H3 inverse agonists are effective at reducing EDS symptoms in patients with sleep disorders. All three studies provided evidence of reduced ESS scores, indicating a perceived improvement in EDS symptoms with the use of an H3 inverse agonist. Two of the three studies provided statistically significant reductions ESS scores when compared to placebo.

KEY WORDS: Narcolepsy, Sleep Apnea, Excessive Daytime Sleepiness (EDS)

Introduction

"I'm always tired" is one of the few complaints physicians and physician assistants dread to hear. Fatigue and excessive tiredness is a sensitive but also nonspecific indicator for many underlying conditions in a variety of medical settings. Determining the cause of a patient's fatigue can be a long and frustrating process for both the doctor and the patient. However, what is even more frustrating is knowing the source of the fatigue but not being able to adequately treat the patient. Unfortunately, this is the discouraging truth for many patients with sleep disorders who suffer from excessive daytime sleepiness (EDS).

EDS is a universal symptom of almost all sleep disorders. It is defined as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months. [1] EDS affects nearly 20% of the US population,[2] however it's true prevalence is difficult to estimate due to the subjective nature of the symptoms and inconsistencies in terminology (ie – fatigue, drowsiness, sluggishness). EDS can lead to cognitive impairment, immune suppression, and decreased quality of life. If not properly managed, EDS can lead to unnecessary health care costs and motor vehicle accidents. Narcolepsy and Obstructive Sleep Apnea (OSA) are two sleep disorders commonly recognized for severe EDS.

Narcolepsy is a sleep disorder that effects 1 out of every 2,000 Americans.[3] It is well known for its unique "sleep attacks" in which individuals suddenly fall into a deep sleep at a moment's notice. The etiology of narcolepsy is still not fully understood, but it is thought to be caused by a deficiency in hypocretin, a brain chemical that regulates sleep. It's most debilitating symptom is EDS, which occurs in 100% of individuals with the disorder.[4] Treatment involves the use of drugs to try to regulate the sleep-wake cycle. Modafinil is the current gold standard in

treating the symptoms of EDS in narcoleptic patients.[4] Additional CNS stimulants, such as methylphenidate and amphetamines, may also be used when modafinil is insufficient. Prior to modafinil, sodium oxybate was considered the first line treatment, and is still frequently used today.

It is estimated that 22 million Americans suffer from obstructive sleep apnea.[3] EDS is present in 70% of patients with OSA and is the most common daytime symptom.[5] The defining pathological event of OSA is the closure of the upper airway during sleep, resulting in apneic events, or pauses in breathing.[6] The closure of the airway is thought to occur due to the failure of the genioglossus and other upper airway dilator muscles. Failure of these muscles can be a result of several factors including obesity, neck circumference >17 inches, and tonsillar hypertrophy. [6] Apneic events are relieved by sudden brain activation and arousal. The cyclic nature of these apneic events and brain activation leads to fragmented sleep and poor sleep quality. Continuous positive airway pressure (CPAP) is considered the gold standard of treatment for OSA. With optimal adherence, CPAP improves sleep quality. However, one study showed that even with optimal adherence, 22% of patients reported residual symptoms of EDS.[7] This, in combination with already low adherence rates, EDS continues to be a major problem in this population.

The prevalence of sleep disorders comes with a high cost. In the US, it is estimated to be between $50 and $100 billion dollars. Patients with narcolepsy are often on full disability and annual medical costs are often twice as much as matched controls.[8] In the workplace, sleepiness results in the loss of $54 million/year due to reduced productivity[9] and individuals with EDS are three times more likely to be involved in a workplace accident.[10] Another study estimated that 810,000 automobile accidents resulting in 1400 fatalities are attributable to OSA in a single year.[11] By treating the same OSA patients with CPAP at 70% adherence, it was estimated that it

would prevent 500,000 collisions.[11] However, this means that even with treatment with the current gold standard, there would still be 310,000 collisions with 400 fatalities at the cost of $4.8 billion. It is clear that an adjunctive treatment to EDS is needed.

It has been well speculated that histamine plays a role in sleep and arousal ever since the sedating properties of antihistamines were first observed in the 1940's.[12] However, it hasn't been until recently that we have begun to fully understand the complexity of the histaminergic system. In 1983, histamine H3 receptors were discovered to provide negative feedback on the synthesis of histamine. While activation of H1 and H2 receptors via histamine excite and arouse various neurons, H3 receptor activation actually has the opposite effect. When histamine binds to an H3 receptor it triggers a negative feedback to restrict further histamine synthesis and release. An inverse agonist of this receptor would block the effects of the H3 receptor and exert the opposite effect by suppressing spontaneous receptor signaling.[13] In other words, it would promote the release of more histamine and arousal. The discovery if this new H3 receptor has become a potential target for the pharmaceutical treatment of EDS.

Objective:

The objective of this systematic review is to determine whether or not inverse agonists of the Histamine H3 receptor are effective in reducing excessive daytime sleepiness (EDS) in individuals with sleep disorders.

Methods:

A detailed search of the PubMed database was completed between November 2016 and January 2017 using the keywords "narcolepsy", "EDS", and "sleep apnea". Cochrane Systematic Reviews was also searched to rule out any previous systematic reviews or meta-analysis on the topic. Articles were selected based on publication date, relevance to practice and importance to

patient-oriented outcomes (POEMs). Inclusion criteria included placebo-controlled trials

comparing the efficacy of a H3 inverse agonist to that of a placebo. Two studies also compared

the efficacy of modafinil compared to H3 inverse agonists and placebo. All studies included

participants over the age of 18 with a clinically diagnosed sleep disorder published in an English

peer reviewed journal after 2006. All participants reported having an ESS score of at least 10 or

above prior to the start of the respected studies. Two double-blinded RCT's comparing the

pharmacological effects of a H3 inverse agonist were included in this review; one was a

crossover design and the other was a parallel design. Due to the sparsity of published

interventions involving H3 inverse agonists, a single-blind pilot study was also included in this

review.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria:	Exclusion Criteria:	W/D	Interventions:
Lin J-S (2008)	Cross Sequential Study Single blind	22 14 ♂ 8 ♀	28-54	Diagnosis of narcolepsy via the International Classifications of Sleep Disorders Presence of severe EDS for 3 months or greater	ESS Score < 10	1	1 week of daily: 40 mg capsule of tiprolisant (a histamine H3 inverse agonist) vs. Visually matched placebo
Dauvilliers (2013)	RCT Double blind/ parallel group design	95 51 ♂ 44 ♀	21-52	Age > 18 yo Must be diagnosed with narcolepsy and confirmed via polysomnogram. Self – reported EDS for more than 3 months. A ESS Score > 14	Women of child bearing age not on a birth control method Use of any investigational drug within 30 days of screening Any disorder that could be the main cause of EDS. Hx of substance abuse Cardiovascular, renal, hepatic disorders, or psychiatric disorder.	16	8 weeks of treatment. Pitolisant (Histamine H3 inverse agonist) vs. Visually matched placebo vs. Modafinil

Herring (2013)	RCT Double blind/ crossover design	125 100 ♂ 25 ♀	18-64	>18 yo Diagnosed OSA and managed with cont. positive airway pressure therapy Use of compliant CPAP treatment for > 2months ESS >10 Clinical global impressions-severity scale rating >4	History of sleep disorders other than OSA. Medical conditions other than OSA that would explain EDS. 6 MWT sessions performed at the end of placebo screening; pt's excluded if they stayed awake throughout the 30-min test for more than 2 of the 6 sessions.	22	2 weeks each of daily: Modafinil (200mg), Visually matched placebo, and MK-0249 (5, 8, 10, or 12mg) One week washout between intervention periods.

Outcomes Measured:

Reduction in EDS was measured in all three studies by using the Epworth Sleepiness Scale (ESS). The ESS is a self-administered questionnaire that assesses the likelihood of falling asleep in a variety of everyday situations. Respondents rate, on a 4-point scale (0-3), their probability of dozing off while engaged in eight different activities. The total ESS score is the sum of all 8 items, and can range from 0-24. The higher the score, the higher the person's sleep propensity in daily settings, or their 'daytime sleepiness'. The ESS questionnaire only takes 2-3 minutes to complete, and is the most widely used clinical instrument for evaluating sleepiness.[14]

Results:

The two RCTs, and one pilot study included in this review compared the efficacy of H3 receptor inverse agonists in reducing excessive daytime sleepiness when compared to placebo in individuals diagnosed with narcolepsy or obstructive sleep apnea.

The single-blind pilot trial by Lin J-S et al.[15] was one of the first studies that looked at the effects of a H3 inverse agonist in humans. The study consisted of 22 patients with diagnosed narcolepsy. All participants were recruited from the sleep medicine practices of 4 participating centers. All stimulant medications were stopped 3 days before the study. Participants consumed a

capsule daily containing a placebo for 1 week, followed by 1 week of daily consumption of 40

mg of tiprolisant, an H3 inverse agonist. The study concluded with 21 participants. One

participant failed to complete the study after experiencing adverse effects from the

discontinuation of her previous medications prior to the study. The principal end-point of the

study was changes in ESS scores at the end of each week. Each patient acted as his/her control.

All analyses were performed on the intention-to-treat population (n=22). The mean ESS score

after 1 week of placebo and 1 week of tiprolisant were 16.66 ($\pm$ 4.86) and 11.81 ($\pm$ 6.11)

respectively (Table 2).

The t-tests, which compared the variables measured during the tiprolisant period versus

placebo period, were performed only when both values were available (n=21). Significant

differences in ESS were seen with Tiprolisant when compared to baseline and placebo.

Specifically, the ESS score under tiprolisant treatment showed a 4.86 $\pm$ 5.12 point reduction

when compared to placebo, and a 5.86 $\pm$ 5.51 reduction when compared to baseline (Table 3).

Table 2: Mean ESS Score ($\pm$ SD)

	Mean ESS Score ($\pm$ SD)
Baseline	17.55 ($\pm$ 3.89)
After Placebo period	16.66 ($\pm$ 4.86)
After Tiprolisant period	11.81 ($\pm$ 6.11)

Table 3: Treatment Effect (Point Reduction [95% CI]; p-value)

Tiprolisant vs placebo	Tiprolisant vs Baseline
4.86 (2.22 to 7.56)	5.86 (3.42 to 8.34)
p= 0.0006	p < 0.0001

11 patients experienced 23 adverse events during tiprolisant treatment as compared to 7

patients experiencing 13 adverse events during placebo treatment. Among the 22 patients the

most significant adverse events during the tiprolisant period were headache (n=5), nausea (n=4),

insomnia (n=2), malaise (n=2), and sweating (n=2). The majority of the adverse events (95%)

occurred during the first 3 days of treatment. None of these adverse events led to treatment cessation and 21/22 fully complied with the prescribed treatments.

The conclusion of the pilot study led to a much larger study 5 years later. This double-blind RCT by Dauvillers et al. [16] involved 94 narcoleptic patients from 32 centers in five European countries. Eligible participants were at least 18 years old with self-reported EDS for more than 3 months. Participants were randomly assigned to a treatment group, in which they received either a placebo, Modafinil or Pitolisant, an H3 receptor inverse agonist. All psychostimulants were stopped 14 days prior to the start of the study. The study started with three weeks of flexible dosing based on the investigators discretion. Potential dosing amounts included 10mg/20mg/or 40mg a day of Pitolisant or 100mg/200mg/ or 400mg a day of Modafinil. This was followed by five weeks of stable dosing. ESS was used to score EDS at baseline and at completion of the trial. In the intention-to-treat analysis, all three treatment groups saw a decrease in ESS scores. Patients given the placebo saw the smallest improvement in their ESS scores, with reductions of -3.4. While those in the modafinil and pitolisant treatment groups saw greater improvements with reductions of –6.9 and -5.8 respectively (Table 4).

Pitolisant was determined to be superior compared to placebo and noninferior compared to modafinil (Table 5). The non-inferiotirty of pitolisant versus modafinil was tested based on a non-inferiority margin of 2 ESS points. This value was half the difference between modafinil and placebo in previous trials (Mean change of 4.02, 95% CI 0.14-7.09).

Table 4: ESS scores throughout the trial

	Baseline	Final	Change over Trial
Placebo Group (n=30)	18.9 (2.5)	15.6 (4.3)	-3.4 (4.2)
Pitolisant Group (n=31)	17.8 (2.5)	12.0 (6.2)	-5.8 (6.2)
Modafinil Group (n=33)	18.5 (2.7)	11.6 (6.0)	-6.9 (6.2)

Table 5: Treatment Effect (mean difference [95% CI]; p-value)

Pitolisant vs placebo	Pitolisant vs Modafinil
-3.0 (-5.6 to -0.4) p= 0.024	0.12 (-2.5 to 2.7) p=0.250

Nine severe adverse events occurred during the treatment period; 6 of these was regarded as treatment related. One with pitolisant (abdominal discomfort) and five with modafinil (abdominal pain, abnormal behavior, amphetamine-like withdrawal symptoms, lymphoadenopathy, and inner ear disorder).

Lastly, the study done by Herring et al.[17] was a RCT, double-blind, six sequence cross-over study consisting of 125 patients with obstructive sleep apnea and refractory EDS. The study was conducted at 26 sites across the United States. Participants were randomized into one of six treatment sequences. All sequences included three periods of 2 week treatments of MK-0249 (an H3 inverse agonist), Modafinil, and a placebo daily for 2 weeks. Periods 1 and 2 were followed by a single-blind wash out period in which participants received a placebo daily for 1 week before starting the next period in their respected sequence

Various doses of MK-0249 were used in the trial. Dosing options of MK-0249 included 3mg, 5mg, 8mg, 10mg and 12mg. An unblinded statistician determined the appropriate dose for each participant. A total of 125 patients were randomized and 103 completed the study.
At the end of each treatment period, reevaluation of each participants EDS was assessed via the ESS scale. All participants who had at least one end-point in at least one treatment period were included in the full analysis set.

Unlike the previously discussed studies, in this study ESS was considered a secondary end-point. A conditional approach was prespecified prior to the start of the study. Due to the conditional nature of this approach, failure of the primary hypothesis also lead to the failure of

the secondary hypotheses. Therefore, only descriptive results with a 95% CI for the treatment difference were provided and no p-values were given.

Efficacy was seen most with the top two doses of MK-0249 (10mg + 12mg). These dosages were combined into a single group for the analysis. All three groups displayed a decrease in average ESS scores. MK-0249 saw the largest improvement with a decrease of 3.99, while placebo and modafinil groups saw a smaller improvement with changes of -2.21 and -2.96, respectively (Table 6). When compared to placebo, MK-0149 (10mg + 12mg) saw an improvement of -1.78 in average ESS scores. This was a much larger improvement than the, -0.74 ESS difference, seen between modafinil and placebo (Table 7).

Change from baseline over 2 weeks	
Placebo Group (n=116)	-2.21 (±0.76)
MK-0249 (10mg + 12 mg) (n=74)	-3.99 (±1.01)
Modafinil Group (n=106)	-2.96 (±0.79)

Table 6: Least squares mean (95% CI) ESS change from baseline at week 2

MK 10+ 12 vs placebo	Modafinil vs placebo
-1.78 (-2.78 to -0.78)	-0.74 (-1.60 to 0.11)

Table 7: Treatment Efficacy: ESS differences from placebo in least squares mean (95% CI) change from baseline at week 2

Reasons for discontinuation in the 22 patients were AEs (N=12), withdrawal by patient (N=9) and protocol violation (N=1). Patient compliance was evaluated by capsule counts at each visit.

Discussion:

The Herring et al.[17] study was one of the first studies to be done assessing similar therapeutic effects on OSA patients. Treatment with the H3 inverse agonist, MK-0249, showed qualitative improvement in ESS scores when compared to baseline scores. However, while these results are meaningful and should not be negated, they are not statistically significant. It is

evident that more studies need to be done in order to appropriately assess the benefits of H3 inverse agonists in the OSA population.

The unique cross sequential design in the Lin J-S et al.[15] study allowed the direct comparison of the placebo and treatment effects on the same subject. One limitation of this study design is the potential "carry over" effects between treatments. In the Lin J-S et al. study, patients were asked to discontinue all stimulant medications, and receive one week of placebo followed by one week of tiprolisant. It is possible that patients felt more tired than expected while withdrawing from their stimulant medication. In addition, subject may have also perceived a greater treatment effect from tiprolisant after a not receiving a stimulant for an entire week prior. The study done by Herring et al.[17] allowed a one week washout period between interventions in order to try to eliminate this "carry over" effect.

The Dauvillers et al.[16] and Herring et al.[17] studies reported adverse events that resulted in participation discontinuation. Throughout this review, there was only one serious adverse event related to treatment with an H3 inverse agonist. The patient complained of abdominal pain and was in the Dauvillers et al.[16] study. The most common side effect noted in all three studies was headache and anxiety. The Herring et al. study also had reports of insomnia with treatments involving higher doses of the H3 inverse agonist. Further studies should be investigated to determine the continuation of these effects with continued treatment.

It is important to remember that while both narcolepsy and OSA present with clinical symptoms of EDS, the etiology of sleepiness is not the same in each condition. While narcolepsy occurs due to a deficiency in a neuropeptide in the brain, OSA occurs as a result of a physical obstruction of the airway. OSA patients have the physiological ability to regulate sleep-wake cycles, while narcoleptic patients do not. The efficacy of H3 inverse agonists may be different

between narcolepsy and OSA simply due to the nature of the conditions. Histamine may play a more primary role in helping to better regulate the dysfunctional sleep-wake cycle in narcolepsy. In contrast, the effects of additional histamine and arousal in OSA patients may just symptomatically treat residual EDS.

Conclusion:

Life with excessive daytime sleepiness (EDS) can be debilitating, expensive, and dangerous. All three studies discussed in this review, show promising results to suggest that histamine H3 inverse agonists are effective in treating patients with sleep disorders. The two studies involving narcoleptic participants provided the most promising evidence. Similar findings in ESS score reduction were also seen in a new study recently published in early 2017 investigating the effects of pitolisant in reducing daily cataplexy attacks in narcoleptic patients.[18] More studies should be done to prove the significance of H3 inverse agonist use in OSA patients. Currently, there is a study finalizing the results of the use of an H3 inverse agonist in 202 OSA patients; results are expected to be published in the near future.[19] Additional future studies should be done to investigate the long-term effects and/or tolerability to use of this new drug class. As more is learned about the histaminergic system and the effects of histamine on arousal, it is hopeful that more treatment options will become available for all patients suffering from EDS.

References

1. American Academy of Sleep Medicine. *The international classification of sleep disorders : diagnostic & coding manual.* 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

2. Carlton R, Lunacsek O, Regan T, Carroll CA. Healthcare Costs Among Patients with Excessive Sleepiness Associated with Obstructive Sleep Apnea, Shift Work Disorder, or Narcolepsy. *American Health & Drug Benefits.* 2014;7(6):334-339.

3. Ferri FF. *Ferri's Clinical Advisor 2018: 5 Books in 1.* Elsevier - Health Sciences Division; 2017.

4. Abbott SM, Reid KJ, Zee PC. Chapter 40: Circadian Disorders of the Sleep-Wake Cycle. *Principles and Practice of Sleep Medicine.* 2017:414-423.e415.

5. Ryan S. Obstructive Sleep Apnea A2 - Quah, Stella R. In: *International Encyclopedia of Public Health (Second Edition).* Oxford: Academic Press; 2017:308-314.

6. Khoury J, Doghramji K. Primary Sleep Disorders. *Psychiatric Clinics of North America.* 2015;38:683-704.

7. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proceedings of the American Thoracic Society.* 2008;5(2):173-178.

8. Thorpy MJ, Hiller G. The Medical and Economic Burden of Narcolepsy: Implications for Managed Care. *American Health & Drug Benefits.* 2017;10(5):233-240.

9. Rosekind MR, Gregory KB, Mallis MM, Brandt SL, Seal B, Lerner D. The Cost of Poor Sleep: Workplace Productivity Loss and Associated Costs. *Journal of Occupational and Environmental Medicine.* 2010;52(1):91-98.

10. Eva L, Ned C, Thorarinn G, Christer J. Role of Snoring and Daytime Sleepiness in Occupational Accidents. *American Journal of Respiratory and Critical Care Medicine.* 2001(11):2031.

11. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep.* 2004;27(3):453-458.

12. Emanuel MB. Histamine and the antiallergic antihistamines: a history of their discoveries. *Clin Exp Allergy.* 1999;29 Suppl 3:1-11; discussion 12.

13.   Merkestein M, Gispen WH, Adan RAH. Melanocortins: Brain Effects A2 - Squire, Larry R. In: *Encyclopedia of Neuroscience.* Oxford: Academic Press; 2009:713-719.

14.   Kryger MH, Roth T, Dement WC. *Principles and Practice of Sleep Medicine.* Elsevier; 2016.

15.   Lin J-S, 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.

16.   Dauvilliers Y, Bassetti C, Lammers GJ, et al. Articles: Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurology.* 2013;12:1068-1075.

17.   Herring WJ, Liu K, Hutzelmann J, et al. Alertness and psychomotor performance effects of the histamine-3 inverse agonist MK-0249 in obstructive sleep apnea patients on continuous positive airway pressure therapy with excessive daytime sleepiness: a randomized adaptive crossover study. *Sleep Medicine.* 2013;14(10):955-963.

18.   Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Articles: Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *The Lancet Neurology.* 2017;16:200-207.

19.   ClinicalTrials.gov. *Efficacy and safety of BF2.649 in treatment of excessive daytime sleepiness in patients with obstructive sleep apnea (OSA) refusing the nasal continuous positive airway pressure (nCPAP) therapy.* 2017.