International Journal of Medical and Pharmaceutical Case Reports

14(1): 1-5, 2021; Article no.IJMPCR.64040
ISSN: 2394-109X, NLM ID: 101648033

New Kid on the Block: A First Look at the Clinical Use of Pitolisant for Narcolepsy

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Authors' contributions

This work was carried out in collaboration among all authors. Author ACC wrote the first and final draft of the manuscript, performed literature search and patient chart reviews. Authors VS, LB, KM and MS managed the clinical care of the patients described. Author CD reviewed the manuscript. Author PC co-wrote the first and final manuscript draft, revised the manuscript for important intellectual content and approved final version of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2021/v14i130120
Editor(s):
(1) Dr. Hayrettin Ozturk, Abant Izzet Baysal University, Turkey.
Reviewers:
(1) Siti Nor Fadhlina binti Misron, Kuala Lumpur Hospital, Malaysia.
(2) Dilara Mermi Dibek, Dokuz Eylul University, Turkey.
(3) Shatrughan Pareek, Indian Railway Health services, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/64040

Case Study

Received 06 November 2020
Accepted 12 January 2021
Published 01 February 2021

ABSTRACT

Aims: Highlight pitolisant as an effective treatment for narcolepsy.
Case Report: We describe two patients treated with pitolisant. Patient A showed decreased daytime sleepiness and improved social functioning. Patient B struggled to find a dose that kept side effects at a minimum.
Discussion: This orphan drug has a unique mechanism of action, that combined with dosing flexibility allows for a treatment option that can better attend to individual differences in patient needs.
Conclusion: The use of pitolisant presents some benefits and challenges, nonetheless offering a promising treatment for narcolepsy.

Keywords: Narcolepsy; pitolisant; excessive daytime sleepiness; histamine; histamine 3 receptor.

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ABBREVIATIONS

EAP : Expanded Access Program
EDS : Excessive Daytime Sleepiness
ESS : Epworth Sleepiness Scale
KQOL : Kemp Quality of Life
mg : Milligrams
MSLT : Multiple Sleep Latency Test
SOREM : Sleep Onset Rapid Eye Movement

1. INTRODUCTION

Despite being a rare sleep disorder, narcolepsy can be extremely debilitating. Narcolepsy is characterized by excessive daytime sleepiness (EDS) and while onset occurs during early life, impairments often compound over time. For example, EDS significantly impairs attention and memory in school, resulting in curtailed educational attainment. Maintaining employment can also be challenging for those with severe EDS. Over time, these impairments often lead to feelings of low self-worth and depression [1].

There is no cure for narcolepsy and until recently treatment options were limited to a handful of scheduled drugs that confer abuse potential, tolerance build-up and cardiovascular adverse events. Finally, patients who do not find symptom relief with existing medications are left with no alternative options. Together, this demonstrates how underserved the narcolepsy patient community is, and the critical need for novel interventions.

Last year pitolisant was approved for the treatment of EDS in narcolepsy in the United States. Unlike existing treatments, pitolisant targets EDS via histamine-releasing neurons, which are part of the hypothalamic arousal systems activated by hypocretin [2]. Pitolisant acts as a selective H3-receptor antagonist/inverse agonist, increasing brain levels of histamine and leading to enhanced wakefulness [3]. Studies demonstrated pitolisant's efficacy in treating EDS when compared to placebo or modafinil [4-6]. Adverse events include insomnia, anxiety, depression, and irritability [3]. Importantly, pitolisant is an unscheduled drug given its lack of abuse potential [7]. We present two cases to illustrate some benefits and challenges associated with the use of pitolisant in a real-world clinical practice.

2. REPORT OF CASE

2.1 Methods

Minor details were altered to represent a range of experiences. Patients in this study were enrolled in the Expanded Access Program (EAP) for pitolisant which provided medication free of cost.

2.2 Treatment Protocol

The indication was to take pitolisant first thing in the morning with or without food. Subjects were titrated for three weeks (see Fig. 1).

2.2.1 Patient A

A 44-year-old Caucasian male with Narcolepsy type 2 (see Table 1).

2.2.1.1 Treatment history

Diagnosis occurred following a primary complaint of memory loss. He started modafinil (10 mg) without improvement. Clinician added methylphenidate (5 mg) but it caused headaches. This was replaced initially with Adderall (10mg), and later with Adderall XR (20mg). Patient still reported severe EDS (ESS was 18). He was prescribed armodafinil (200 mg), which improved wakefulness, but he experienced an acute drop in alertness in the evening. Patient A discontinued armodafinil before starting the pitolisant.

2.2.1.2 Pitolisant treatment

Patient A was titrated according to the recommended schedule (see Fig. 1) for the first two weeks. Sleep specialist did not titrate up at week 3 since 17.8mg demonstrated strong effectiveness in keeping the patient awake and alert. There was notable improvement in patient's EDS; alertness was sustained throughout the day. After four months he requested an increase in dose, reporting that pitolisant was not as effective at keeping him awake compared to the beginning of the program. Dose was adjusted to 35.6mg, however, after a few weeks his wife noted that he was more irritable at home, and "he was not doing activities that he used to enjoy." Both irritability and depression are adverse effects for pitolisant. In response, his dose was reduced to 17.8mg, following which symptoms resolved. In order to target sleepiness and avoid unwanted effects, his regimen was augmented with armodafinil (200 mg). His ESS was 15, and

he reported feeling more alert at work and better able to engage with his social circles. This combination treatment resulted in the most efficient pharmacotherapy for the patient.

Patient discontinued pitolisant given lack of insurance coverage and transitioned to armodafinil only. The patient did not report any acute physical reactions, though he noticed feeling "much more tired" after discontinuation.

2.2.2 Patient B

A 37-year-old Caucasian male diagnosed with Narcolepsy type 1 (see Table 1).

2.2.2.1 Treatment history

Patient B received his diagnosis in his early twenties. He was prescribed methylphenidate (dose unknown) and then modafinil (dose unknown) without improvement. He switched to Adderall (45mg) with mild improvement. A year later, still struggling with EDS, he requested an increased dose of Adderall (90mg) which he maintained for years. In 2013, he reported Adderall "[was] no longer effective" and needed additional assistance. Armodafinil (200mg) was added to his regimen without improvement. He was prescribed Adderall XR (30mg) with Adderall IR (15mg morning, 45mg afternoon) which better treated his EDS, but he reported getting a sudden drop in alertness in the afternoon. His ESS was 18 and his KQOL was 6 out of 7 (higher scores reflecting higher quality of life).

2.2.2.2 Pitolisant treatment

Titration followed the recommended schedule (see Fig. 1) for the first couple of weeks. The patient was asked to gradually cut down his Adderall XR and IR prescription. However, a few days into week 2, he reported difficulty falling and staying asleep at night. His dose was adjusted to three 4.45mg tablets (e.g. 13.35mg total) in order to increase the therapeutic effect from week 2 while attempting to minimize insomnia. 13.35mg was designated as his maintenance dose. He reported feeling more alert all day long. However, he continued experiencing severe fragmented sleep. After two months on pitolisant, Patient B withdrew from the program for two reasons. One was "[pitolisant] wasn't working as well as it was in the beginning", the other being the unresolved insomnia as patient stated "it wouldn't be worth the restless nights." There is no information about patient's cataplexy.

Fig. 1. Recommended titration schedule across three weeks

Table 1. Patient details

Patient	Narcolepsy Type	Age	Sex	Race	Mean Diagnostic MSLT (SOREMs)	Education	Previous medications for narcolepsy (dose)
A	2	44	M	Caucasian	2.9 min (2)	Some college	Modafinil (100 mg), methylphenidate (5mg), Adderall (5 mg), Adderall XR (20 mg), armodafinil (200 mg)
B	1	37	M	Caucasian	3.3 min (2)	Associate's Degree	Methylphenidate (unknown), modafinil (unconfirmed), Adderall (90mg), armodafinil (200 mg), Adderall XR (90 mg)

3. DISCUSSION

This case series allowed us to better understand the patient experience of symptom relief by pitolisant. The perception on daily wakefulness was subtle, as patients stated there was a less prominent and immediate "buzz" compared to other medications. However, our patients reported a diminished perception of the medication effectiveness over time. Research has not shown pitolisant to lead to tolerance build-up and these perceptions may reflect the histaminergic nature of the drug, in contrast to a dopaminergic mechanism of action.

Remarkably, under pitolisant patients reported a consistent sense of wakefulness lasting throughout the day. This contrasts with other medications (e.g., Adderall XR, armodafinil), in which patients reported a sudden drop in alertness. Interestingly, the half-life of pitolisant (10-12h) is similar to other wake-promoting agents (armodafinil:15h, Adderall XR: 10-13h). This sustained effect was reflected in patient-centered outcomes. Patient A reported no longer experiencing a sudden need to sleep after work, allowing him to be more engaged with his family. In a similar way, Patient B was able to maintain work productivity throughout the day, as he no longer needed to schedule naps during work hours.

We also saw the importance of close clinical monitoring during the titration period. Patients required dose adjustments deviating from titration protocol to accommodate tolerability and ensure safety. Patient A's dose adjustment spanned for a period of three months, suggesting a need for monitoring of tolerability during the first few months of dosing. In the case of Patient B, titration was influenced by insomnia. Sleep specialist opted for 13.35mg for maintenance dose, which falls between week 1 and week 2 doses. The flexibility for dose adjustment is due in part to the two tablet presentations: 4.45mg and 17.8mg. Together, this illustrates the importance of accounting for individual differences on medication effects and drug sensitivities.

Our case series also suggests some patients may benefit from supporting pitolisant with other wake-promoting agents to further optimize treatment gains. As seen in Patient A, the combination of pitolisant with armodafinil resulted in the most effective treatment for him. However, more clinical data is needed to determine recommendations for a combination approach.

Despite significant improvements in their EDS, some patients discontinued pitolisant beyond the program. A likely reason is lack of insurance coverage. Without insurance, pitolisant is $11k per month, and thus cost prohibitive for many patients. Though the rate of reimbursement is expected to increase with time, institutions may also explore ways to increase financial accessibility to pitolisant.

4. LIMITATIONS

First, none of our patients were drug-naive for narcolepsy treatments. Newly diagnosed patients could have different experiences to the ones above. Second, all patients enrolled were highly dissatisfied with their current treatment, which could reflect particularly drug sensitive individuals. Third, selecting only two subjects for this case report introduces selection bias.

5. CONCLUSION

Pitolisant is a promising new treatment for narcolepsy. Our case series present some valuable drug properties, the importance of individual evaluation of medication effects, and the relevance of tolerability assessments in pitolisant prescription.

CONSENT

As per international standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

This study was approved by the Henry Ford Health System Institutional Review Board (Edesel and Henry board; IRB no.12188).

ACKNOWLEDGEMENTS

The authors would like to thank the technical staff of Henry Ford Hospital Sleep Center for their invaluable assistance in the completion of the present study. We would also like to thank Scott Bitner from Harmony Biosciences and Ruth Ho from Parexel for their support throughout the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/64040