

**SOLRIAMFETOL - BREAKING NEW GROUND IN THE TREATMENT OF
NARCOLEPSY****¹M. Mark Praveen Kumar, ²Dr. Pearlsy Grace Rajan, ³Dr. D. K. Sriram, ⁴*Dr. Melvin George**¹Academic Degree: M.Tech²Academic Degree: MBBS, MD³Academic Degree: MBBS, M.Sc, MRCP, FRCP⁴Academic Degree: MBBS, MD, DM***Corresponding Author: Dr. Melvin George**

Academic Degree: MBBS, MD, DM.

Article Received on 02/02/2020

Article Revised on 23/02/2020

Article Accepted on 14/03/2020

ABSTRACT

Narcolepsy is a chronic, disabling neurologic disorder characterized by excessive daytime sleepiness (EDS) and, in up to 60% of patients, cataplexy. Despite major advances in our understanding of the neurobiological basis of NT1, management remains nowadays only symptomatic. The main and most disabling symptom, EDS, is managed with psychostimulants, such as modafinil/ armodafinil, methylphenidate, or amphetamines as a third-line therapy. Narcolepsy is an active area for drug development, and new wake-promoting agents have been developed over the past years. Solriamfetol, is a phenylalanine derivative used activity for treating EDS. Solriamfetol is an orally active, selective dopamine and norepinephrine reuptake inhibitor that was recently approved in the USA as a treatment for excessive daytime sleepiness (hypersomnia) associated with narcolepsy. Clinical trials showed that solriamfetol could significantly improve the ability to stay awake and subjective symptoms of excessive sleepiness in adults with narcolepsy. Solriamfetol was well tolerated. Very common adverse reactions were headache, nausea, decreased appetite, insomnia, and anxiety. This review summarizes the mechanism of action, pharmacokinetics, efficacy, and safety/tolerability of solriamfetol in the treatment of narcolepsy.

KEYWORDS: Excessive daytime sleepiness; narcolepsy; solriamfetol.**INTRODUCTION**

Narcolepsy is a central disorder of hypersomnolence that clinically presents as cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations.^[1,2] Narcolepsy may be classified as two types; 1) NT1 that are caused by extensive loss of hypothalamic neurons (hypocretin/orexin deficiency) and 2) NT2 includes most of the same symptoms, but its cause is unknown^[3] NT1 include EDS, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations and disrupted nighttime sleep. NT2 is defined as narcolepsy without cataplexy and may include all other symptoms.^[4] Although narcolepsy has a low prevalence, it is associated with a substantial socioeconomic burden resulting from high direct and indirect costs to the general population.^[5] Employees with narcolepsy have higher degree of absence; inflicting financial burden on their employers.^[6,7] Getting fired due to these symptoms could indeed be exasperating and affect their social lives. Additionally, it also causes major socio-economic burden on their partners.^[8]

Current treatments for narcolepsy include the central nervous system depressant sodium oxybate^[9], stimulants such as methylphenidate and amphetamines^[10], and the

wakepromotingagents modafinil and armodafinil.^[11] However, each of these medications is associated with limitations. Solriamfetol is a next-generation wake-promoting agent. It is distinct from otherwake-promoting agents by its dual reuptake inhibition at dopamine and norepinephrine transporters.^[12] Solriamfetol has high solubility and high permeability. It is rapidly absorbed after oral administration. Clinical trials indicated that solriamfetol has robust effects for improving wakefulness. The aim of the review is to explore the evidence from the published literature on the utility of solriamfetol in the management of narcolepsy.

MECHANISM OF ACTION (MOA)

Solriamfetol inhibits dopamine and norepinephrine reuptake through dopamine and norepinephrine transporters respectively, without significant effects on other targets, including 5-HT, histamine H1, histamine H3, α 2-adrenergic and orexin 2 receptors. In vivo, solriamfetol increases extracellular concentrations of dopamine and norepinephrine in the prefrontal cortex and striatum; it does not have substantial monoamine-releasing effects. However wake-promoting effects of solriamfetol are thought to be attributable to its actions at dopamine transporter and norepinephrine transporter,

and not to other neurotransmitter receptors involved in regulating sleep (e.g. histamine, orexin).^[13]

EFFICACY

Solriamfetol was evaluated in 465 patients with narcolepsy who were randomized to receive the drug at doses of 75, 150, 300 mg or placebo for a period of 12 weeks. At the completion of the study, the least square mean change in the maintenance of wakefulness test was 12.3 and 9.8 minutes for the doses of 300 and 150 mg in comparison to 2.1 minutes with placebo. Similar improvements were also seen with Epworth sleep score. 78% of patients on solriamfetol 150 mg and 85% of patients on the highest dose of 300 mg reported improvement in PGI-C score in comparison to placebo (40%).^[14]

Solriamfetol was evaluated in a study by Malhotra *et al.*,^[15] in which participants with narcolepsy and obstructive sleep apnea were provided solriamfetol for a duration of 52 weeks. At the end of 26 weeks, patients were subjected to a randomized withdrawal design for a period of 2 weeks, in which patients were randomized to either continue solriamfetol or given placebo for two weeks. At the end of this period, the percentage of patients who worsened was measured as per Epworth sleep score. It was observed that patients in the placebo group had greater worsening.

In a study by Emsellem *et al.*,^[16] 239 patients were randomized to receive solriamfetol in doses of 75, 150 or 300 mg or placebo. The drug showed improvement in functional outcomes with all doses as compared with placebo when using the FOSQ-10 questionnaire. Vitality, general health and physical component summary scores in SF-36 were found to be better with solriamfetol than placebo irrespective of the dose used. Solriamfetol was also found to reduce the work-related impairment, presenteeism and activity impairment as assessed by WPAI:SHP score.

SAFETY

The most common safety concerns for solriamfetol as seen in clinical trials were headache, nausea, nasopharyngitis, decreased appetite, anxiety, dry mouth and insomnia. Solriamfetol is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor, because of the risk of hypertensive reaction. Solriamfetol increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. In the phase III study, based on 24-h ambulatory BP monitoring, mean changes from baseline to week 8 in systolic BP (SBP) were -0.5 – 2.4 mmHg with solriamfetol (across doses 75–300 mg) and -0.4 mmHg with placebo; in diastolic BP (DBP) were 0.8 – 3.0 mmHg with solriamfetol and -0.2 mmHg with placebo.^[15] As epidemiological data have shown that chronic elevations in blood pressure increase the risk of major adverse

cardiovascular events (MACE), including stroke, myocardial infarction and cardiovascular death, one should exercise caution when using these drugs in patients with pre-existing hypertension. The blood pressure requires thorough assessment before initiating treatment with solriamfetol. Solriamfetol is also known to have a certain degree of abuse potential. This has been identified in human abuse potential studies which revealed that subjects experienced a feeling of relaxation and elevated mood on consuming the drug which was not unlike that seen with phentermine.^[17]

PHARMACOKINETICS

The approved dose range of solriamfetol in the United States is 75–150 mg once daily for patients with narcolepsy. The oral bioavailability of solriamfetol is approximately 95%. Peak plasma concentration of solriamfetol occurs at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) post-dose under fasting conditions. However post-meal, the ingestion of solriamfetol has a delay of approximately 1 hour in T_{max} . Solriamfetol exhibits first-order elimination after oral administration. The apparent mean elimination half-life is about 7.1 hours. Patients with moderate or severe renal impairment may be at a higher risk of increase in psychiatric symptoms such as anxiety and irritability, rise in blood pressure and heart rate because of the prolonged half-life of solriamfetol. Solriamfetol is minimally metabolized in humans. Approximately 95% of the dose was recovered in urine as unchanged solriamfetol, and 1% or less of the dose was recovered as the minor inactive metabolite N-acetyl solriamfetol.

CURRENT STATUS

Solriamfetol received its first global approval on March 20, 2019 in the USA as a treatment to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or OSA.^[18] Solriamfetol is a selective dopamine and noradrenaline reuptake inhibitor and through favorable outcomes that had been reported in phase IIb and phase III trials; during March 2019, this agent was approved by the FDA for the treatment of EDS in patients with narcolepsy.^[14, 19] A Marketing Authorization Application for these indications is under review with the European Medicines Agency.

CONCLUSION

Although narcolepsy is an uncommon disease, it causes untold suffering to the affected as they are at a great risk of losing their occupation and are a major liability at the workplace. Excessive day time sleepiness is undoubtedly the most distressing symptom in these patients. The approval of solriamfetol for EDS in narcolepsy is a welcome step taken by the regulators in alleviating the burden of the disease. The drug has been found to be reasonably effective in short term studies and it is reassuring to note that this beneficial effect was sustained even when the drug was consumed for a longer duration. It remains to be seen if the drug could overhaul

the current battery of drugs available for the treatment of EDS in narcolepsy.

REFERENCE

1. Fund N, Green A, Chodick G, Orin M, Koren G, Shalev V, Dagan Y. The epidemiology of sleep disorders in Israel: results from a population-wide study. *Sleep Medicine*. 2020 Mar 1; 67: 120-7.
2. Feketeova E, Tormasiova M, Klobučníková K, Durdik P, Jarcuskova D, Benca M, Vitkova M. Narcolepsy in Slovakia—Epidemiology, clinical and polysomnographic features, comorbid diagnoses: a case-control study. *Sleep Medicine*. 2020 Mar 1; 67: 15-22.
3. Champion EW, Scammell TE. Narcolepsy. *N Engl J Med*. 2015; 373: 2654-3262.
4. American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual. 2005: 51-5.
5. Black J, Reaven NL, Funk SE, McGaughey K, Ohayon M, Guilleminault C, Ruoff C, Mignot E. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. *Sleep medicine*. 2014 May 1; 15(5): 522-9.
6. Flores NM, Villa KF, Black J, Chervin RD, Witt EA. The humanistic and economic burden of narcolepsy. *Journal of Clinical Sleep Medicine*. 2016 Mar 15; 12(03): 401-7.
7. Dodel R, Peter H, Walbert T, Spottke A, Noelker C, Berger K, Siebert U, Oertel WH, Kesper K, Becker HF, Mayer G. The socioeconomic impact of narcolepsy. *Sleep*. 2004 Sep 1; 27(6): 1123-8.
8. Jennum P, Ibsen R, Petersen ER, Knudsen S, Kjellberg J. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. *Sleep medicine*. 2012 Sep 1; 13(8): 1086-93.
9. Zeman A, Zaiwalla Z. Prescribing sodium oxybate for narcolepsy.
10. Scammell TE. Treatment of narcolepsy in adults. UpToDate, Waltham, MA. Accessed October. 2016; 23.
11. Barateau L, Lopez R, Dauvilliers Y. Treatment options for narcolepsy. *CNS drugs*. 2016 May 1; 30(5): 369-79.
12. Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001 Jan 1; 39(1): 32-41.
13. Baladi MG, Forster MJ, Gatch MB, Mailman RB, Hyman DL, Carter LP, Janowsky A. Characterization of the neurochemical and behavioral effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. *Journal of Pharmacology and Experimental Therapeutics*. 2018 Aug 1; 366(2): 367-76.
14. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y, Black J. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Annals of neurology*. 2019 Mar; 85(3): 359-70.
15. Malhotra A, Shapiro C, Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, Strollo Jr PJ, Mayer G, Sarmiento K, Baladi M, Chandler P. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep*. 2020 Feb; 43(2): zsz220.
16. Emsellem HA, Thorpy MJ, Lammers GJ, Shapiro CM, Mayer G, Plazzi G, Chen D, Carter LP, Villa KF, Lee L, Menno D. Measures of functional outcomes, work productivity, and quality of life from a randomized, phase 3 study of solriamfetol in participants with narcolepsy. *Sleep Medicine*. 2020 Mar 1; 67: 128-36.
17. Highlights of prescribing information, 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/lab el/2019/211230s0001bl.pdf. Accessed on 03/2019.
18. Jazz Pharmaceuticals. Jazz Pharmaceuticals announces U.S. FDA approval of Sunosi™ (solriamfetol) for excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea [media release]. 20 Mar 2019. <http://www.jazzpharmaceuticals.com>.
19. Ruoff C, Swick TJ, Doekel R, Emsellem HA, Feldman NT, Rosenberg R, Bream G, Khayrallah MA, Lu Y, Black J. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016 Jul 1; 39(7): 1379-87.