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ADMINISTRATIVE INFORMATION**Support** - None specified.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2024120052**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 December 2024 and was last updated on 13 December 2024.**INTRODUCTION**

Review question / Objective This article systematically analyzes the efficacy and safety of novel approved wake-promoting drugs.

Condition being studied Narcolepsy is a sleep disorder featuring excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and behavioral abnormalities during the rapid eye movement (REM) phase. The disorder can be categorized as type 1 narcolepsy (NT1) or type 2 narcolepsy (NT2). Patients with NT1 often exhibit decreased orexin levels with or without cataplexy. In contrast, patients with NT2, although they do not have cataplexy, exhibit typical EDS, manifesting as REM sleep in ≥ 2 naps and an average sleep latency of ≤ 8 minutes for 5 naps in the multiple sleep latency test (MSLT). The prevalence of narcolepsy, as a rare condition, ranges from around 1/5000 to 1/3300. Patients with narcolepsy often suffer from impaired daytime functioning, and their mental

health is also undermined to a certain extent, which is a great burden for patients themselves and society.

Five drugs have been approved for narcolepsy by the US FDA or the European EDA, including methylphenidate/amphetamines, modafinil/armodafinil, sodium oxybate (SXB), pitolisant, and lower-sodium oxybate (LXB). A recent report has evinced the efficacy of solriamfetol in daytime sleepiness in patients with narcolepsy.

Articles have compared the efficacy of several wake-promoting drugs in EDS in patients with narcolepsy from the perspectives of Epworth sleepiness scale (ESS) scores and the maintenance of wakefulness test (MWT) results. Other articles further estimate the clinical global impression of change (CGI-C) and patient global impression of change (PGI-C) and compare the safety of drugs in narcolepsy. This paper further compares the efficacy of different drugs in other symptoms (e.g., cataplexy) and daytime functioning (e.g., driving) in patients with

narcolepsy, as well as examines the efficacy of the same drug at different doses and combinations.

METHODS

Participant or population Patients with a definite diagnosis of narcolepsy, without restrictions on race, nationality, sex, age, or disease duration.

Intervention Novel wake-promoting drugs, including solriamfetol (75mg, 150mg, 300mg), SXB, and pitolisant.

Comparator Placebo and conventional wake-promoting drug modafinil.

Study designs to be included Randomized controlled trial (RCT).

Eligibility criteria The articles included met the following criteria:

Population: Patients with a definite diagnosis of narcolepsy, without restrictions on race, nationality, sex, age, or disease duration.

Intervention: Novel wake-promoting drugs, including solriamfetol (75mg, 150mg, 300mg), SXB, and pitolisant.

Comparison: Placebo and conventional wake-promoting drug modafinil

Outcome: Primary outcomes: a) ESS, a scale used to subjectively assess EDS, is now widely utilized in sleep centers. ESS scores evaluated sleepiness in patients in eight different states during daily activities. Each item was scored on a scale of 0 to 3 (0=never, 3=often), with a total score of 0 to 24. An ESS score of > 9 was deemed probable drowsiness. The patients were compared in terms of the reduction in ESS scores after drug application and the number of people with scores below 10. b) MWT: to compare sleep latency after drug application. 2. Secondary outcome: 1. Cataplexy frequency; 2. PGI-C score; 3. Daytime executive functioning (e.g., driving).

Study design: Randomized controlled trial (RCT).

Information sources Pubmed, Embase, and Cochrane Library.

Main outcome(s) The new wake-promoting drugs mentioned above have shown varying degrees of efficacy in improving EDS in patients, both at subjective scores and objective electro-neurophysiological indicators, with an acceptable safety profile. Among them, solriamfetol shows the best efficacy in drowsiness.

Quality assessment / Risk of bias analysis The risk of bias was appraised by 2 researchers using

the Cochrane risk of bias tool in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was rated as low bias, high bias, or unclear and manifested using Revman 5.4.

Strategy of data synthesis Bayesian random-effects model was leveraged to compare the efficacy of various interventions. The Markov chain Monte Carlo method was utilized for modeling, with four Markov chains running simultaneously, with 20,000 annealings and 50,000 iterations. Deviation information criterion was utilized for assessing model fitting and global consistency. If closed loops existed, local consistency was checked using the node splitting method. In addition, each intervention was ranked for SUCRA, and league tables were generated to compare differences among interventions.

Subgroup analysis Subgroup were mainly divided due to the types of wake-promoting drugs.

Sensitivity analysis In the included trials, the same drug was studied in a multi-arm study at different doses and durations of treatment. Therefore, compared with placebo, Bayesian NMA was leveraged to analyze differences in efficacy among novel drugs at different doses and treatment regimens. Funnel plots were mapped to visualize publication bias when the number of trials was ≥ 10 . The analysis was done in R4.3.0, with $P < 0.05$ indicating statistical significance.

Country(ies) involved China.

Keywords Narcolepsy; Solriamfetol; Pitolisant; Sodium oxybate; Epworth sleepiness scale.

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