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Dopamine agonists in restless leg syndrome treatment and their effects on sleep parameters: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 December 2023 and was last updated on 17 December 2023.

INTRODUCTION

Review question / Objective The effect of dopamine agonists (Pramipexole, Ropinirole, Rotigotine) on sleep architecture (PSG parameters) in patients with restless leg syndrome (RLS).

Rationale The impact of the aforementioned DAs (i.e., pramipexole, ropinirole, and rotigotine) on the sleep architecture has been a hot topic of research. However, the results from the different studies have been inconsistent. A recent meta-analysis demonstrated that patients with RLS exhibited lower sleep efficiency (SE), stage N2 sleep, and rapid eye movement (REM) sleep than healthy individuals [12]. Therefore, clarifying the effects of DAs on sleep architecture in patients with RLS is particularly important because they are prone to sleep disturbances. This meta-analysis elucidated the effects of DAs used in RLS treatment on the sleep structure of these patients.

Condition being studied Oral medications are primarily used to treat RLS and include dopamine agonists (DAs), alpha2-delta ligands, benzodiazepines, and opioids. Among them, DAs are recommended as the first-line therapy for RLS. The efficacy of pramipexole, ropinirole, and rotigotine in relieving RLS symptoms is well documented in the literature. Furthermore, the use of DAs in patients with RLS has been shown to improve their quality of life and sleep. However, the long-term use of DAs may be associated with RLS augmentation caused by decreased serum ferritin levels. Despite this, these pharmacological agents constitute the mainstay treatment for patients with RLS.

METHODS

Search strategy PubMed, ClinicalKey, Cochrane Library, Embase, ProQuest, ScienceDirect, and Web of Science databases using the following search keywords: dopamine agonist, pramipexole, ropinirole, rotigotine, apomorphine, bromocriptine, cabergoline, or lisuride; restless leg syndrome or

RLS; polysomnography or PSG or sleep; and randomized controlled trial or RCT. After excluding duplicate studies, the authors further filtered the eligible results of the search according to the title and abstract. A potential list of appropriate studies was then created for a full-text review.

Participant or population Patients with RLS.

Intervention Dopamine agonists (Pramipexole, Ropinirole, Rotigotine).

Comparator Placebo.

Study designs to be included Randomized controlled clinical trials.

Eligibility criteria The following inclusion criteria were applied: (a) randomized controlled clinical trials involving adult humans; (b) patients with a confirmed diagnosis of RLS; (c) studies evaluating the effects of DAs on sleep parameters detected using polysomnography (PSG); and (d) formally published articles. Only placebo-controlled trials were included in our review to eliminate a possible placebo effect.

Information sources PubMed, ClinicalKey, Cochrane Library, Embase, ProQuest, ScienceDirect, and Web of Science databases.

Main outcome(s) The primary result of the assessment was represented by the changes in sleep parameters in the study group that were identified using PSG. The analyzed sleep parameters of interest were sleep stage percentage (including slow-wave sleep [SWS] and REM sleep) and sleep efficiency.

Quality assessment / Risk of bias analysis We applied the Cochrane risk of bias tool for randomized trials (version 2, RoB 2, London, UK) to assess the risk of bias in interventional trials in five particular areas (i.e., randomization process, intervention adherence, missing outcome data, outcome measurement, and selective reporting).

Strategy of data synthesis Because of the expected heterogeneity of the sample, a random-effects model meta-analysis was performed because the former modeling could implement the assessment of a between-study variance in the calculations. The entire meta-analysis procedure was performed using Comprehensive Meta-Analysis (version 3; Biostat Inc., Englewood, NJ, USA). Hedges' g and 95% confidence intervals (CIs) were chosen to integrate the effect sizes (ESs), according to the manual of Comprehensive Meta-Analysis (version 3). ESs were outlined as small, medium, and large when Hedges' g was 0.8, respectively. For all analyses, two-tailed p-values <0.05 were used to denote statistical significance. Furthermore, we investigated the potential impact of DAs on sleep parameters in each DA subgroup.

Subgroup analysis Eventually, because of the considered wide range of treatment length among the included RCTs, we performed subgroup analysis regarding treatment length (i.e., 1 day and $\geq$ 4 weeks).

Sensitivity analysis A sensitivity test with the one-study-removal method for meta-analyses was applied to evaluate the potential confounding effect of any outlier within the assessed studies.

Language restriction No.

Country(ies) involved Taiwan.

Keywords dopamine agonist, restless leg syndrome, pramipexole, ropinirole, rotigotine, sleep architecture.

Contributions of each author

Author 1 - Wei-Chih Yeh - responsible for the literature search, statistical procedure, and manuscript drafting.
Email: weichihyeh@gmail.com
Author 2 - Ying-Sheng Li contributed to the literature search and data interpretation.
Author 3 - Yang-Pei Chang contributed to concept formation and manuscript revision.
Author 4 - Chung-Yao Hsu contributed as the corresponding author and was responsible for concept formation, manuscript revision, and manuscript submission.