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Treatment of Sleep, Motor and Sensory Symptoms with the Orexin Antagonist Suvorexant in Adults with Idiopathic Restless Legs Syndrome: A Randomized Double-Blind Crossover Proof-of-Concept Study

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Abstract

Background and objectives: Current treatment guidelines for restless legs syndrome (RLS) recommend treatment be initiated with non-dopaminergic drugs. Given the potential role of orexins in the pathophysiology of RLS, we performed a pilot, proof-of-concept study to investigate the therapeutic effects of suvorexant, a dual orexin receptor antagonist (DORA), on sleep and sensory/motor symptoms in individuals with idiopathic RLS.

Methods: This was a randomized, double-blind, crossover and placebo-controlled study. Inclusion criteria were diagnosis with idiopathic RLS, an International RLS Study Group Severity Rating Scale (IRLS) score > 15, and the absence of significant RLS symptoms before 9 pm. Following washout from any previous central nervous system (CNS)-active drugs, patients were randomized to receive either suvorexant or placebo for two consecutive 2-week treatment periods. Treatment was administered at 9 pm at a fixed dose of 10 mg/day during the first week, and 20 mg during the second week. Primary and coprimary endpoints were wake after sleep onset (WASO) and total sleep time (TST), respectively, while IRLS rating scale score, multiple suggested immobilization tests (m-SIT), and periodic limb movements (PLMs) were secondary endpoints. RLS severity was measured weekly using the IRLS and Clinical Global Improvement (CGI) scales. m-SIT were also performed between 8 pm and midnight at the end of each treatment phase and were followed by a sleep study.

Results: A total of 41 participants were randomized, 40 of whom completed the study. Compared with placebo, treatment with suvorexant significantly improved RLS symptoms (according to IRLS total score, CGI, and the m-SIT), PLM during sleep, and PLM with arousal. Improvement of RLS symptoms was greater in those who had not been exposed to dopaminergic agents in the past. Sleep architecture also improved with significant changes in TST, WASO, sleep onset latency, sleep efficiency, non rapid-eye movement stage 1 (N1) %, non rapid-eye movement stage 2 (N2) %, and rapid eye movement (REM) %. Suvorexant was well tolerated in RLS, with few and mild adverse events.

Conclusions: Our results provide the first proof of evidence of the therapeutic efficacy of DORAs in improving sleep and sensory and motor symptoms in RLS. Given orexin's role in pain and sensory processing, potential mechanisms of action are discussed.

Classification of evidence: The study provides class II evidence supporting the therapeutic efficacy of suvorexant in patients with RLS with sleep disturbance.

Trial registration: EudraCT#: 2017-004580-12.

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