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Letter to the editor

Rapid effect of suvorexant and high-dose melatonin on COVID-19 associated delirium

Delirium, an acute confusional state with fluctuating consciousness and cognition, arises in nearly one of two COVID-19 patients in the intensive care unit and it is associated with a threefold increase in mortality [1,2]. There are limited reports on COVID-19-induced delirium treatment. We add to Sher et al., a case report suggesting the combination of nightly suvorexant, an orexin dual-receptor antagonist (DORA), and melatonin for COVID-19-induced delirium [3].

We included twenty subjects diagnosed with COVID-19, admitted to a tertiary care hospital between October 2020 and May 2021, and diagnosed with delirium, as per Diagnostic Statistic Manual-V (DSM-5) criteria [4], by consultation-liaison (C/L) psychiatrists. All patients were prescribed nightly suvorexant and high-dose melatonin.

Subjects' demographics (Supplemental Table A; Supplemental Fig. 2), clinical history (Supplemental Table B; Supplemental Fig. 3), hospital course (Supplemental Fig. 4), and Confusion Assessment Method-Severity (CAM—S) long form scores (Supplemental Table C) were collected (Supplemental Fig. 1). The validated CAM-S long form provides objective measurements of delirium severity [5] at baseline (prior to suvorexant and high-dose melatonin administration) and outcome (assessment following administration). Each symptom of delirium in the CAM-S is rated on a whole number scale of 0–1 or 0–2; delirium severity positively correlates with cumulative score [5]. Dual-boarded C/L internist-psychiatrists scored the CAM—S. The Institutional Review Board approved this retrospective chart review.

The average age of patients, of which 60% were female, was 68.70 (± 10.87) years. Patients served as their own controls. A paired sample *t*-test with a large effect size of Cohen's d = 1.51 [6], revealed a significant average decrease of 5.25 points (*SD = 2.38)* in CAM-S scores from baseline to outcome ($t(19) = 8.31$, $p < 0.001$) (Fig. 1).

A linear regression evaluating the change in CAM-S scores (outcome variable), time to suvorexant administration and psychiatry history (predictor variables), and age, gender, baseline CAM-S [7], suvorexant dose, melatonin dose, and administration of valproic acid, haloperidol, guanfacine, or remdesivir (control variables) demonstrated that none of the explored variables were significantly associated with the change in CAM-S score (Supplemental Table D).

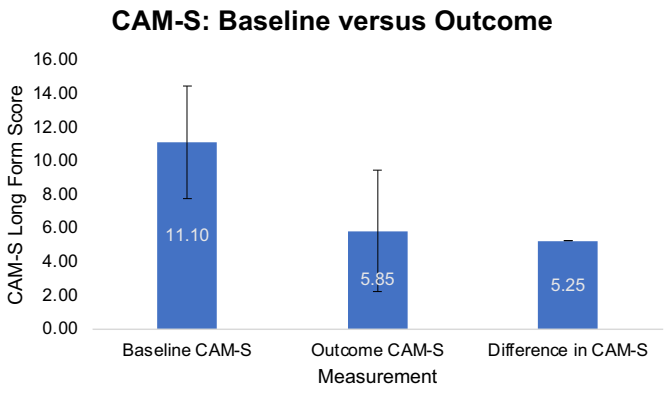

Fig. 1. Average baseline and outcome measurement CAM-S long form scores.

Though the course of delirium is expected to naturally improve over time, there is paucity of data regarding COVID-19-induced delirium severity or duration. Sher et al. noted delirium resolution in the patient after 10 days of combination treatment [3]. Okino et al. describe a "significant therapeutic impact on Day 3 and Day 7" by suvorexant in cases of delirium due to infectious disease; the authors did not denote specific resolution time [8]. We found the average time to resolution was 3.20 (± 2.07) days. Eight patients no longer met DSM-5 criteria for delirium at the time of outcome assessment. Fifteen were alive at the time of discharge whereas 4 of the 5 who had died during their hospitalization still met criteria for delirium at their outcome assessment.

Suvorexant induces sleep, rather than acting on circadian rhythm, via the OX_1R and OX_2R receptors regulating transitions from (1) wake to rapid eye movement (REM) sleep, (2) non-REM sleep to REM sleep, and (3) wake to non-REM to REM sleep [8]. DORA hypnotics promote sleep by dampening wakefulness - decreasing the risk of wake disrupting the process of sleep, including consequential REM deprivation leading to REM rebound, an implication in delirium pathophysiology [8].

The unique challenge posed by COVID-19-induced delirium is its infectious etiology and significant impact on respiratory drive. Melatonin, which inhibits tumor necrosis factor alpha [9], and suvorexant may also have synergistic anti-inflammatory effects in addition to promoting sleep. The overall effect might include dampening of neuroinflammation, thus decreasing the severity of COVID-19 delirium. Moreover, neither suvorexant nor melatonin impact respiratory drive, which is often compromised in COVID-19.

There are several limitations in this analysis that prevent definitive attribution of improvement to the combination of suvorexant and high-dose melatonin. Although we systematically provided the treatment to all patients demonstrating delirium, we included a non-random and small sample of 20 patients without a control group. A majority of the patients received other treatments for delirium such as valproic acid (70%) and haloperidol (60%), for which the results of the linear regression may have been impacted by the small sample size or bias in that patients with more severe or refractory systems required additional medication agents. We also expect that delirium severity would improve as the underlying medical conditions improved.

Given the neuropsychiatric complications associated with COVID-19, this retrospective chart review supports further research in evaluating the combination of suvorexant and high-dose melatonin as a potential treatment option for COVID-19-induced delirium.

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Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2023.01.006.

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