

Rapid Effect of Suvorexant on COVID-19 Associated Delirium: A Retrospective Study

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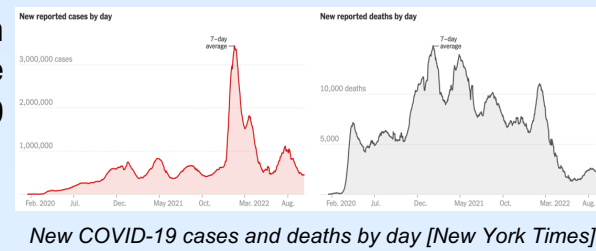
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INTRODUCTION

In the context of more than 12 billion administered vaccines, there are emerging **new cases** of coronavirus 2019 (COVID-19) daily across the world. There are also continued resulting deaths.



COVID-19 typically presents with respiratory symptoms, and presentations range from asymptomatic to fatal. The variety in expression of the infection may be attributed to the widespread presence of the angiotensin-conversion enzyme 2 receptor – including bronchial epithelial cells and **neurons**.

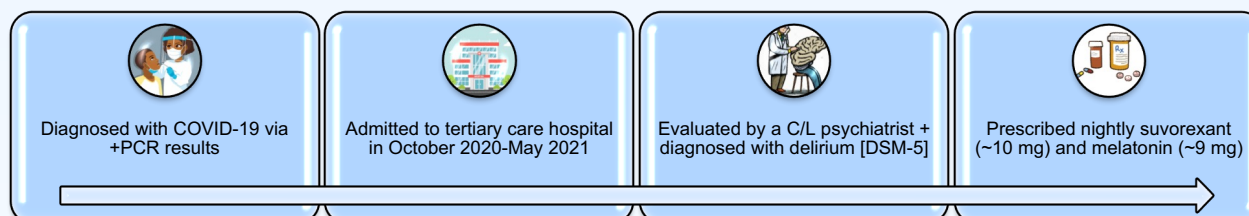
Delirium in patients with COVID-19 is associated with a **threefold increase in mortality risk**. But there are limited reports of COVID-19 induced delirium.

One case report [Sher 2020] proposed **combined nightly use of suvorexant**, an orexin dual-receptor antagonist (DORA), and **high-dose melatonin**.

We add to their findings by **examining twenty patients with COVID-19 induced delirium** who were treated with nightly suvorexant and melatonin.

METHODS

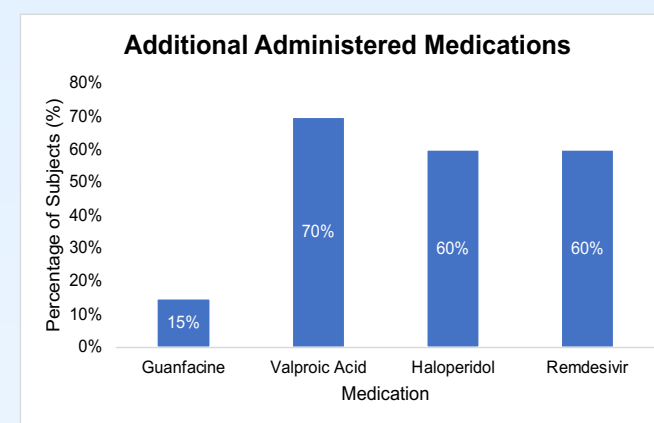
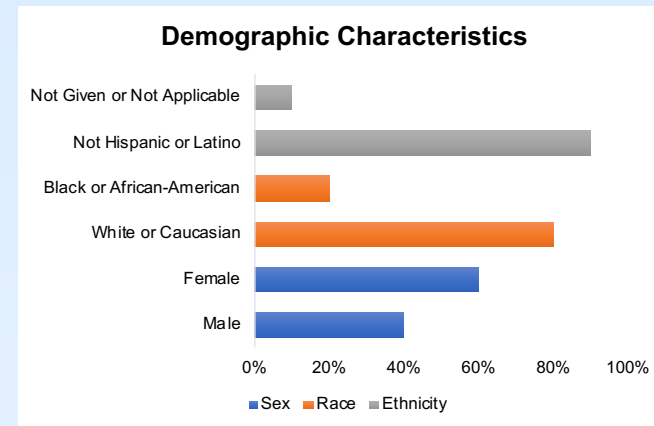
Subjects (n = 20)



Data Collection

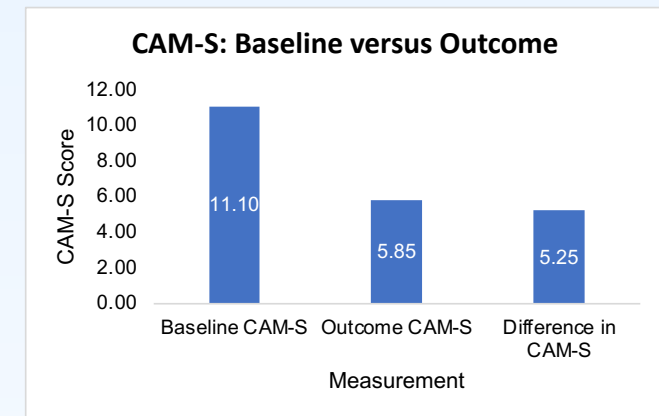
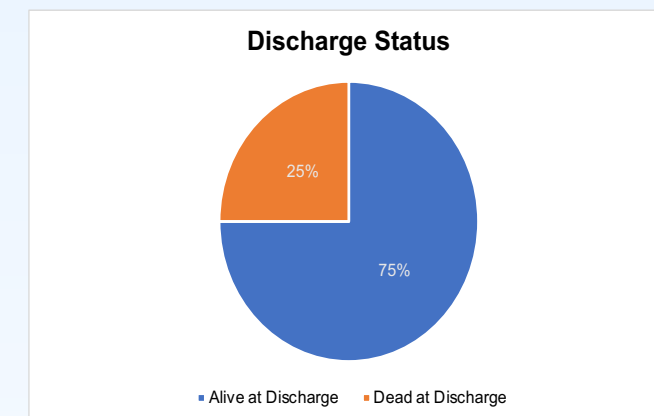
Demographics	Hospital Course	Medications	Confusion Assessment Method-Severity (CAM-S)
<ul style="list-style-type: none"> Age Sex Gender Race Ethnicity 	<ul style="list-style-type: none"> COVID-19 status Length of stay in hospital Day(s) prior to C/L evaluation Past medical history Psychosis, catatonia, dementia, and delirium Living or dead at discharge 	<ul style="list-style-type: none"> Suvorexant* Melatonin* Guanfacine* Valproic acid* Haloperidol* Remdesivir* History of suvorexant use prior to admission <p><small>*Doses were recorded.</small></p>	<ul style="list-style-type: none"> Baseline score Outcome score** <p><small>CAM-S is a validated scale measuring delirium severity for each DSM-5 symptom. This study used the long form.</small></p> <p><small>**Obtained on assessment after suvorexant initiation.</small></p>

RESULTS



	Mean	Standard Deviation
Age (years)	68.70	10.87
Length of Hospital Admission (days)	28.70	20.39
Time to C/L Evaluation (days)	9.55	9.99

Outcome Measurements



Paired sample t-test (baseline versus outcome CAM-S scores) was performed, resulting in $t(19) = 8.31$, $p < 0.001$ with a Cohen's $d = 1.51$ effect size (large).

	Mean	Standard Deviation
Time to Resolution of Delirium	3.2	2.07

A linear regression analysis with **predictor variables** (days to suvorexant administration and prior psychiatry history) and **control variables** (age, gender, baseline CAM-S score, average dose of suvorexant, average dose of melatonin, and inclusion of valproic acid, haloperidol, guanfacine, or remdesivir) found **none of the variables were significantly associated with the change in CAM-S score**.

CONCLUSIONS

Main Findings

The combination of suvorexant and high-dose melatonin is associated with a **statistically significant decrease in COVID-19 induced delirium severity**.

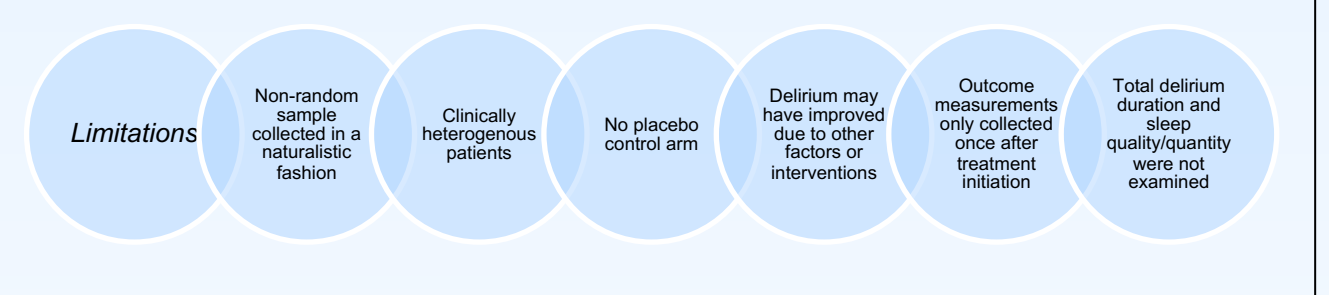
The course of delirium typically improves over time especially as its underlying etiology is addressed. **Our study finds the average time to resolution was 3.2 days – shorter than previously reported times to resolution (3-7 days)**.

Discussion

There is **no widely accepted protocol to safely and effectively treat COVID-19 induced delirium**, which is heterogenous in its pathogenesis. Interventions for delirium often address circadian rhythm desynchrony and impaired sleep. This includes melatonin, which **decreases inflammation**.

Suvorexant acts on the hypothalamus. It induces sleep by **regulating transitions** from wake to rapid eye movement (REM) sleep and non-REM to REM sleep. As a DORA, it promotes sleep **by dampening wakefulness**.

Neither suvorexant nor melatonin impact respiratory drive, which is often compromised in COVID-19 infections. They may also synergistically provide **anti-inflammatory effects**.



FUTURE DIRECTIONS

The **exact pathophysiology of COVID-19's neuropsychiatric complications is yet to be defined** although there are many currently proposed theories.

Our study provides **support for the inclusion of suvorexant** as part of a much-needed systematic approach to treating COVID-19 induced delirium.

Further studies are needed to **elucidate the mechanism** of suvorexant and the **extent of its efficacy** in treating COVID-19 induced delirium.