

# Melatonin

## A Review of Pertinent Drug Information for SARS-CoV-2

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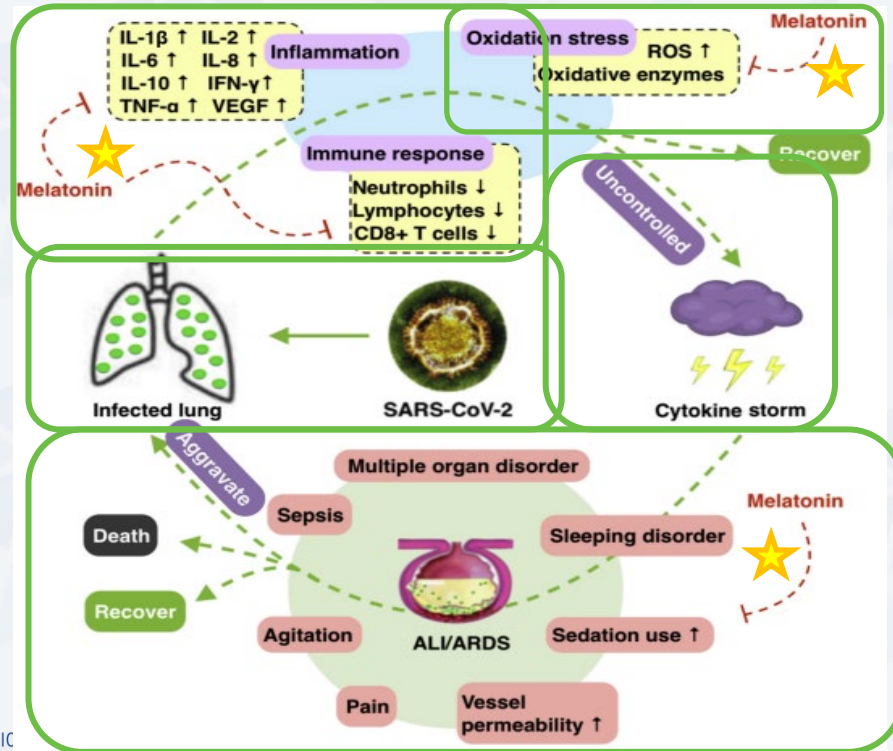
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*Data as of August 15, 2020*



# Mechanism of Action



# Dosing

- Current clinical practice (variable): 0.5-10 mg nightly for prevention of circadian rhythm derangement and delirium in hospitalized patients
- “High dose” for SARS-CoV-2: 36-72 mg/day PO in 4 divided doses<sup>1</sup>
- Various reports of higher doses: 50 mg/kg once pre-operatively in liver resections with no serious adverse effects noted<sup>2</sup>

# Available Animal Data

Virus	Animal	Total Daily Melatonin Dose	Inflammatory Cytokines	Mortality
RSV	Mouse	15 mg/kg	↓ TNF-α	
VEEV	Mouse	0.5-1 mg/kg	--	↓
RHDV	Rabbit	10-20 mg/kg	↓ TNF-α, IL-6	--
SFV	Mouse	0.5 mg/kg	--	↓
WNV	Mouse	0.17 mg/kg	--	↓
Influenza A	Mouse	10-100 mg/kg	--	↓

RSV: respiratory syncytial virus, VEEV: Venezuelan equine encephalomyelitis virus, RHDV: rabbit hemorrhagic disease virus, SFV: Semliki Forest virus, WNV: West Nile virus

# Available Human Data

Disease State - Patients	Sample Size (Treatment/Control)	Total Daily Melatonin Dose	Effect on Inflammatory Cytokines	Outcomes
Respiratory Distress Syndrome - Pediatric	120 (60/60)	33 mg/kg	↓ TNF- $\alpha$ , IL-6, IL-8	No mortality in melatonin group
Sepsis - Neonatal	20 (10/10) 50 (25/25) 40 (20/20)	5.7 mg/kg 8.2 mg/kg 8.1 mg/kg	--	Melatonin groups: no mortality, improvements in clinical outcomes compared to control
Surgical - Neonatal	20 (10/10)	33 mg/kg	↓ TNF- $\alpha$ , IL-6, IL-8	Improved clinical outcomes
Endotoxemia - Adult	24 (12/12) 24 (12/12)	1.4 mg/kg 1.4 mg/kg	↓ IL-1 $\beta$ ↔	--
Sepsis - Adult	20	1.3 mg/kg	--	Dose escalation & ex-vivo study-only reported adverse effect = drowsiness in all patients



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# Case Series: Melatonin for SARS-CoV-2

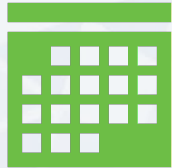
Baseline Characteristics	N=10
Confirmed SARS-CoV-2 + by PCR	70%
No ARDS ( $paO_2/FiO_2 \geq 300$ mmHg)	60%
Mild ARDS ( $paO_2/FiO_2 = 200-300$ mmHg)	10%
Moderate ARDS ( $paO_2/FiO_2 = 100-200$ mmHg)	30%
Severe ARDS ( $paO_2/FiO_2 \leq 100$ mmHg)	0
Presence of high risk features*	100%
Receipt of antibiotics	100%
Receipt of antivirals	90%
Receipt of IL-6 inhibitor	30%

- Retrospective descriptive case series of 10 patients hospitalized for confirmed or suspected SARS-CoV-2
- No patients were mechanically ventilated at baseline

*\*High risk features included >60 years of age, established cardiovascular disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, bronchial asthma, obesity*

# Case Series: Melatonin for SARS-CoV-2

## Stabilization



4-5  
days

## Time to Discharge



8.6  
days

- No patients required mechanical ventilation
- All patients survived hospital stay

## Author Conclusions:

*“High-dose melatonin may have a beneficial role as adjuvant therapy in patients being treated for COVID-19 pneumonia, in terms of shorter time to clinical improvement, less need for intubation and mechanical ventilation, shorter hospital stay, and possibly lower mortality.”*

# Safety & Adverse Drug Reactions

- Favorable safety profile, even in high doses<sup>1</sup>
- Most frequently reported adverse effects are mild
  - Dizziness, headache, nausea, sleepiness
- No reported respiratory or hemodynamic effects



# Drug Interactions

- Potential added drowsiness when used with other sedatives
- Anecdotal: melatonin may have added anticoagulant effect and caution is warranted with other anticoagulants and antiplatelets, however no clinical data to support this claim

# Clinical Pearls

- If a sleep aid is needed, consider melatonin
- Align highest doses with sleep schedule to avoid circadian rhythm disruption
- Not enough data to determine optimal dose for treatment of infections due to SARS-CoV-2
  - “High doses” are difficult to administer: highest available dosage form in U.S. is 10mg/tablet

# Relevant Clinical Trials

1	<input type="checkbox"/> Not yet recruiting <b>NEW</b>	<a href="#">Safety and Efficacy of Melatonin in Outpatients Infected With COVID-19</a>	<ul style="list-style-type: none"> <li>• COVID-19</li> </ul>	<ul style="list-style-type: none"> <li>• Drug: <b>Melatonin</b></li> <li>• Other: Placebo (Methylcellulose) capsule</li> </ul>	<ul style="list-style-type: none"> <li>• University at Buffalo Buffalo, New York, United States</li> </ul>
2	<input type="checkbox"/> Recruiting	<a href="#">Evaluation of Therapeutic Effects of Melatonin by Inhibition of NLRP3 Inflammasome in COVID19 Patients</a>	<ul style="list-style-type: none"> <li>• COVID-19</li> </ul>	<ul style="list-style-type: none"> <li>• Drug: <b>Melatonin</b></li> <li>• Drug: The usual treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Mohammad Sadegh Bagheri Baghdasht Tehran, Iran, Islamic Republic of</li> </ul>
3	<input type="checkbox"/> Not yet recruiting <b>NEW</b>	<a href="#">Melatonin Agonist on Hospitalized Patients With Confirmed or Suspected COVID-19</a>	<ul style="list-style-type: none"> <li>• Covid19</li> <li>• Lung Injury</li> </ul>	<ul style="list-style-type: none"> <li>• Drug: Ramelteon 8mg</li> </ul>	
4	<input type="checkbox"/> Recruiting	<a href="#">Efficacy of Melatonin in the Prophylaxis of Coronavirus Disease 2019 (COVID-19) Among Healthcare Workers.</a>	<ul style="list-style-type: none"> <li>• Covid19</li> <li>• SARS-CoV 2</li> <li>• Coronavirus Infection</li> </ul>	<ul style="list-style-type: none"> <li>• Drug: <b>Melatonin</b> 2mg</li> <li>• Drug: Placebo oral tablet</li> </ul>	<ul style="list-style-type: none"> <li>• Hospital Universitario La Paz Madrid, Spain</li> </ul>



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# Summary

- Melatonin is a potential option for adjuvant therapy given safety and accessibility
- Randomized controlled trials are needed to fully elucidate clinical benefit of melatonin in COVID-19

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