



## Philippine COVID-19 Living Clinical Practice Guidelines

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### **Melatonin**

#### **RECOMMENDATION**

We recommend against the use of melatonin as prevention for COVID-19 infection. (*Very low quality of evidence; Strong recommendation*)

#### **Consensus Issues**

It was discussed that among the limitations of the efficacy study was the lack of information on the dose administered and duration of intake, hence the panel cannot compare it against the usual dose used for sleep disorder, which is one (1) 3-mg capsule a day for at least a month. The cost per capsule ranges from Php 16.00 to 20.00. With regard to melatonin's adverse effects, it was noted that indirect studies were evaluated (i.e., use of 2 mg to 10 mg melatonin for different indications), hence, the observation on excessive sleepiness may be dose-related. The panel raised a concern on the potential for its misuse or overuse considering that it may be marketed as prophylaxis for COVID-19, which is an off-label indication. Likewise, its potential adverse effects over long-term use are unknown.

Considering that the quality of evidence to support the use of melatonin is very low, and in the context of potential adverse events as well as cost considerations, the panel decided to strongly recommend against its use for COVID-19 infection.

### **EVIDENCE SUMMARY**

#### **Should melatonin supplements be used as prevention of COVID-19?**

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#### **Key Findings**

One observational study reported lower odds of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not. The study was found to be with serious risk of bias because of absence of randomization and allocation concealment and the lack of details which precluded assessment of blinding and follow-up. For safety, one systematic review reported that overall, melatonin supplements have a good safety profile. However, there are some adverse effects that are dose- and timing-related, and one study stated that caution should be exercised in the use of melatonin in patients with hypertension.

#### **Introduction**

Melatonin (5 methoxy-N-acetyltryptamine) is a hormone produced by the pineal gland at night, which controls circadian rhythms such as the sleep-wake rhythm [1]. Melatonin supplements have been used to treat sleep disorders and are reported to have a potential anti-viral action through its



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inflammatory and antioxidant properties [2]. It was also reported that it indirectly targets human coronavirus (HCoV) cellular targets, including ACE2, BCL2L1, JUN, and IKBKB [3].

## Review Methods

We conducted a literature search using PubMed and the Cochrane Library using terms “COVID-19,” “melatonin,” and “systematic review” or “randomized controlled trials” and their synonyms or MESH terms. The date of last search was on 26 December 2020. We also searched the following databases: [clintrials.gov](http://clintrials.gov), [ChinaXiv.org](http://ChinaXiv.org), [MedRxiv.org](http://MedRxiv.org), [BioRxiv.org](http://BioRxiv.org), [chictr.org](http://chictr.org) and WHO International Clinical Trials Registry Platform (ICTRP).

Randomized controlled trials, systematic review, meta-analysis that assessed the effect of melatonin supplement as prevention for COVID-19 infection were included. Observational studies or quasi-experimental studies were included in case of lack of data. We excluded in vitro and animal studies and those that did not meet our PICO criteria (Please see below).

The following PICO criteria were used:

**Population:** people at risk for COVID-19

**Intervention:** Melatonin supplements as a prophylaxis, as a single agent, any dose, any duration;

**Comparator:** placebo, any active control, no intervention plus minimum health standards

**Outcomes:** incidence of COVID-19; Adverse events;

**Study design:** observational studies, quasi-experimental studies, randomized controlled trials (RCTs)

## Results

### Efficacy

Zhou and colleagues conducted retrospective case control studies using a COVID-19 registry (N=26,779) of patients tested for COVID-19 in the Cleveland Clinic Health System in Ohio and Florida [4]. It was stated that patients were actively taking melatonin or other drugs at the time of testing. Investigators used combination network-based prediction and propensity score (PS) matching and found that the odds ratio of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not was 0.72 (95% CI 0.56–0.91), after adjusting for age, sex, race, smoking history, and comorbidities such as diabetes, hypertension, coronary artery disease, and COPD [4]. The characteristics of this study are shown in Appendix 1 and 2.

Five (5) subgroup analyses were done to further observe the effect of melatonin [4]. Results showed that melatonin significantly reduced the likelihood of a positive laboratory test result for SARS-CoV-2 in black Americans (aOR = 0.48, 95% CI 0.31–0.75) after adjusting for age, sex, race, smoking, and various disease comorbidities; the same was true for patients with diabetes (aOR = 0.52, 95% CI 0.36–0.75) [4]. However, no significant difference was observed for asthma (aOR = 0.61, 95% CI 0.36–1.06), hypertension (aOR = 0.80, 95% CI 0.61–1.05) and white



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Americans (aOR = 0.77, 95% CI 0.57–1.04), [4]. The authors concluded that melatonin could have a potential benefit in preventing and treating COVID-19 [4].

Level of evidence was graded as very low as it was an observational study and had serious risk of bias because of absence of randomization and allocation concealment, and the lack of details which precluded assessment of blinding and follow-up. The study did not specify clinical details such as timing or duration of melatonin intake, but only stated the analysis of drug-outcome relationships from a large dataset from a COVID-19 registry. Moreover, the investigators did not clearly describe if they identified the outcome first before the exposure. In the results part, they mentioned that they used retrospective cohort analysis (Appendix 2).

### Safety

We did not find any article that assessed the safety of melatonin use as prophylaxis for COVID-19. Instead, we report here the findings from one systematic review regarding the adverse events of oral supplementation of melatonin [5]. Foley and Steel reported that oral melatonin supplementation in humans has a generally good safety profile, but there are some exceptions. Out of 50 studies included in their systematic review, 24 reported at least one statistically significant adverse event. Generally minor and transient were fatigue, mood disturbance, or psychomotor and neurocognitive performance. Those pertaining to the endocrine and cardiovascular systems were often related to dose, timing, and potential interactions with antihypertensives. The systematic review found two studies which reported that melatonin could elevate blood pressure and heart rate. This is contradicted in other literature which reported that melatonin could lower blood pressure and heart rate [6].

In-vitro and animal studies suggest that melatonin may have possible drug interactions with calcium channel blockers [5]. Thus, caution in the use of melatonin would be needed in patients with hypertension [5]. The review also reported adverse events relating to endocrine function, such as reproductive parameters and glucose metabolism [5].

The most common adverse events reported were related to reduction in psychomotor and neurocognitive function or fatigue and excessive sleepiness, which may be due to melatonin's sedative and hypnotic activity [5]. Other adverse events reported are dizziness, headache, nausea and sleepiness [6].

### Recommendations from Other Groups

There are no guidelines that mentioned the use of melatonin in preventing COVID-19 [7, 8, 9]. Moreover, the (National Institutes of Health (NIH) COVID-19 guidelines “recommends against the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial” [7].

### Research gaps

There is one ongoing randomized placebo-controlled trial. The MeCOVID trial aims to evaluate the efficacy of daily melatonin as a pre-exposure prophylaxis against SARS-CoV-2 infection



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among healthcare workers at high risk of SARS-CoV-2 exposure [10]. The eligible participants will be randomized to receive either 2 mg of melatonin or placebo orally before bedtime for 12 weeks [10]. The primary outcome to be measured is the number of confirmed COVID-19 symptomatic infections confirmed by SARS-CoV 2 infection rate (12 weeks) [10]. The completion date is supposed to be in December 2020; however, as of 16 Feb 2021 the results have not yet been published [10].

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## Appendix 1: Characteristics of Included Studies

Author	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
Zhou et al [4]	Patients registered in COVID-19 registry from the Cleveland Clinic Health systems in Ohio and Florida	Melatonin use before testing for COVID-19	Non-melatonin use before testing for COVID-19	Positive laboratory test result for COVID-19

## Appendix 2: GRADE Evidence Profile

### Melatonin compared to Non-melatonin Use for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Non-melatonin Use	With Melatonin		Risk with Non-melatonin Use	Risk difference with Melatonin

### COVID-19 positive

8274 cases 18505 controls (1 observational study)	serious <sup>a</sup>	not serious	not serious	not serious	none	⊕○○ ○ VERY LOW	8274 cases 18505 controls	<b>OR 0.72</b> (0.56 to 0.91)	<b>Low</b>	
									0 per 1,000	<b>0 fewer per 1,000</b> (from 0 fewer to 0 fewer)

CI: Confidence interval; OR: Odds ratio

### Explanations

a. Unclear study design/methodology: clinical details such as timing and duration of melatonin intake not given

## Appendix 3: Study Characteristics of Ongoing Trials

Title/ Clinical Trial ID Number	Study design	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
Efficacy of Melatonin in the Prophylaxis of Coronavirus Disease 2019 (COVID-19) Among Healthcare Workers. (MeCOVID) NCT04353128 [6]	RCT	Healthcare workers from the public and private Spanish hospital network at risk of SARS-CoV 2 infection with no previous COVID-19 infection	2 mg of melatonin orally before bedtime for 12 weeks	Identically looking placebo orally before bedtime for 12 weeks	Primary SARS-CoV 2 infection rate (12 weeks)