Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Reply to 'Delirium, sleep, COVID-19 and melatonin'

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Dear Editor,

In his comment to our letter, Viroj Wiwanitkit states that melatonin “is effective for reducing anxiety and useful for controlling insomnia” [1]. Indeed, some evidence exists in support of the equivalent effectiveness of Exogenous Melatonin (EM) and Midazolam premedication in reducing preoperative anxiety in adults [2]. However, meta-analytic findings suggest the most convincing evidence for EM to be in primary insomnia (sleep onset latency reduction), delayed sleep phase syndrome, and sleep-wake pattern regulation in blind individuals [3].

Based on sufficiently robust findings on delirium in intensive care units, we argued in our letter that the stabilization of sleep-wake rhythms might also improve delirium in hospitalized 2019 novel coronavirus (COVID-19) patients. Pooled results of six randomized controlled trials (RCTs), two cohort studies and one case-control study further suggest that preventive EM but also Melatonin Receptor Agonists (MRA) reduce the incidence of postoperative delirium in the adults [4].

Dr. Wiwanitkit also recommends that "melatonin should be used in any COVID-19 cases regardless of delirium or sleep disturbance” [1]. Based on its well–established anti-oxidant and anti–inflammatory properties, we did speculatively suggest that high–dose melatonin could interfere with immunopathological pathways that are thought to intensify severity in some COVID-19 patients. Of note, melatonin was validated by enrichment analyses of drug-gene signatures and SARS-CoV-2-induced transcriptomics data in human cell lines [5]. Given the low incidence and mildness of reported adverse events at daily doses ranging from 0.15 mg to 12 mg, some authors also encourage clinicians to consider it an adjunctive therapy in patients with severe sepsis and septic shock [6].

However, currently there is no evidence to support its use as prevention or treatment for the infection itself. At the time of writing, only one low–dose study has been registered to evaluate its efficacy as prophylaxis in healthcare workers exposed to the virus, rather than patients (MeCOVID, EudraCT number 2020-001530-35). Therefore, well–designed studies are needed (i) to evaluate efficacy and safety at high doses, and (ii) to discriminate between a putative antiviral effect and the indirect influence of improved sleep and consciousness on patients’ global outcomes.

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