

Melatonin supplementation for the prevention of hospital-associated delirium

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Abstract

Characterized by acute alterations in cognition or consciousness, delirium is a transient neuropsychiatric syndrome that develops in a large percentage of hospitalized patients. Delirium is a robust predictor of increased morbidity, mortality, and health care costs, especially when diagnosed in the critical care setting. Although the exact pathogenesis behind delirium has yet to be defined, disturbances in the sleep-wake cycle are a core feature. Currently, no pharmacologic interventions are recommended for delirium prophylaxis. Due to the role of melatonin in regulating the sleep-wake cycle, its use in delirium has been investigated in recent years. Objective data has shown altered serum levels of melatonin and its precursor, tryptophan, in patients with delirium, further suggesting a correlation between melatonin and delirium. This article examines the available evidence and discusses considerations surrounding melatonin supplementation for the prevention of hospital-associated delirium.

Keywords: melatonin, delirium, prevention, prophylaxis, complementary and alternative medicine

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Delirium

Delirium is an acute, transient neuropsychiatric syndrome that results in increased health care costs, morbidity, and mortality.^{1,2} Although the exact pathogenesis behind delirium has yet to be defined, disturbances in the sleep-wake cycle are a core feature. According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition,³ characteristics of delirium include a disturbance in attention and awareness and an acute change in cognition. These changes in cognition and awareness are accompanied by agitation or restlessness in the case of hyperactive delirium or by lethargy in hypoactive delirium, making the diagnosis of delirium a difficult one. In contrast with dementia, delirium waxes

and wanes and develops over a short period of time—within hours to days.³

Delirium is often precipitated by an acute medical illness and is more common in those over the age of 65. In elderly patients, rates of delirium postoperatively range from 15% to 53%, and in critical care settings, they range from 70% to 87%.^{4,5} Regardless of age or care level, hospitalization is the single most significant factor that places a patient at risk of delirium. With mortality rates ranging from 22% to 76%, delirium mortality mirrors rates associated with sepsis and acute myocardial infarction.⁵

The 2013 Critical Care Delirium Guidelines⁶ recommend nonpharmacologic measures for the prevention of delirium. Such measures include reorientation protocols, sleep regulation, and early mobilization. To date, no pharmacologic agents are recommended. These guidelines also advise against the use of both haloperidol and atypical antipsychotics for the prevention of delirium due to their extensive side effect profiles and their propensity to precipitate delirium.^{6,7}



Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous neurohormone, best known for its role in regulating the sleep-wake cycle. Tryptophan and serotonin are both precursors in the biosynthesis of melatonin, and melatonin is renally excreted as 6-sulfatoxymelatonin (6-SMT), its inactive metabolite. Melatonin production is stimulated by darkness and is secreted by the pineal gland in a diurnal pattern. In mammals, serum levels are lowest during the daylight and peak between 2:00 AM and 4:00 AM. Peak serum levels decline with age, and adults over the age of 60 have almost no peak in serum melatonin levels nocturnally.⁸

Safety

Overall, exogenous melatonin is well tolerated and safe; a median lethal dose (LD₅₀) has yet to be established.⁹ Although there have been reports of vivid dreams and nightmares, headache, nausea, confusion, worsening of depression, and seizures associated with melatonin, the majority of clinical studies have determined that there were no significant differences in adverse reactions between melatonin and placebo.

Roles in Therapy

Historically, melatonin has been used in the treatment of primary and secondary insomnia, jet lag, and shift work disorder. In the United States, melatonin has multiple orphan drug designations, including treatment of both non-24-hour sleep-wake disorder and circadian rhythm sleep disorders in blind individuals, treatment of neonatal hypoxic ischemic encephalopathy, and its most recent orphan designation: treatment of Smith-Magenis syndrome in combination with a beta-blocker. In recent years, the use of melatonin in disease states outside of sleep disturbances has been explored.

Is There a Link Between Melatonin and Delirium?

The most apparent link between delirium and melatonin involves the dysregulation of the sleep-wake cycle; melatonin supplementation may work to restore this synchronization. Objective data has shown that patients with delirium have altered urinary excretion of 6-SMT and reduced serum levels of melatonin and its precursor, tryptophan.⁷ Melatonin supplementation may initiate a negative feedback mechanism, reducing the breakdown of its precursors, tryptophan and serotonin.⁸ Although lacking causative data, these factors suggest a correlation between melatonin and delirium.

Review of the Literature

Recently, three clinical trials,¹²⁻¹⁴ summarized in the Table, drew inconsistent conclusions in their evaluations of melatonin versus placebo for delirium prophylaxis. Al-Aama et al¹³ and Sultan¹⁴ found a statistically significant benefit of melatonin over placebo in reducing the incidence of delirium, and De Jonghe et al¹² found no statistically significant benefit of melatonin in reducing the incidence of delirium in their postoperative patient population. The studies utilized various methods to diagnose delirium (see the Table), and although Sultan and De Jonghe et al excluded patients with the presence of delirium at baseline, this was not exclusion criteria for Al-Aama et al. A secondary analysis by Al-Aama et al determined that, even after excluding patients with delirium at baseline, melatonin had a statistically significant benefit over placebo in reducing the incidence of delirium. All three studies supported previous data in concluding that melatonin was well tolerated and associated with minimal adverse reactions.

In 2015, Chen et al⁷ conducted a meta-analysis of the abovementioned studies, which evaluated the incidence of delirium and a secondary outcome, improvement of the sleep-wake cycle. In their meta-analysis, melatonin showed a tendency to reduce the incidence of delirium; however, this tendency was not statistically significant. This suggests that the mechanism by which melatonin prevents delirium may be independent of its effects on the sleep wake cycle. In a subgroup analysis, Chen et al found that for elderly patients in medical wards, melatonin supplementation decreased the incidence of delirium by 75% (relative risk 0.25; 95% confidence interval 0.07, 0.88; $P=0.03$) but had no benefit over placebo in improving sleep-wake disturbances.⁷

Extrapolation of these studies to clinical practice is limited due to a number of variables, including the difficulty in diagnosing delirium, a lack of uniformity in diagnostic criteria, melatonin study dose, concomitant medications (including procedural sedation), and hospital-specific delirium prevention measures.

Conclusion

Based on the available data, melatonin appears to play a role in reducing the incidence of delirium, particularly in hospitalized elderly patients. Although there is an obvious need for more robust studies, this potential benefit of melatonin coupled with its affordability and safety, makes it a reasonable option for those at risk for delirium. Future research should further explore the relationship between delirium and melatonin and evaluate long term outcomes across various patient populations.

TABLE: Melatonin for the prevention of delirium—clinical trials

	De Jonghe et al ¹² (2014)	Al-Aama et al ¹³ (2011)	Sultan ¹⁴ (2010)
Design	R, DB, PG	R, DB, PG	R, DB
Length	14 d	14 d	1 Plus 3 follow up d
Setting	Netherlands; surgical, orthopedic, and trauma surgery wards	Canada; medical unit in a tertiary care hospital	Egypt; internal medicine unit
Subjects	N = 37, 8 aged ≥65 y (mean age: 84), excluded patients admitted to the ICU postoperatively	N = 14, 5 aged ≥65 y (mean age: 84)	N = 300, aged ≥65 y (mean age: 70) scheduled for hip arthroplasty, patients with delirium preoperatively were excluded
Intervention	Placebo versus melatonin 3 mg daily at 2100 h for 5 d	Placebo versus melatonin, 0.5 mg once daily between 1800 and 2400 h	Group 1: Placebo Group 2: Melatonin, 5 mg Group 3: Midazolam, 7.5 mg Group 4: Clonidine, 100 µg All medications were administered at bedtime the night before the operation and 90 min prior to operation
Outcome(s)	Incidence of delirium	Incidence of delirium	Incidence of postoperative delirium
Diagnostic tool	DSM-5	CAM	AMT
Results	No differences in the incidence of delirium between melatonin and placebo groups in noncritically ill patients	<ul style="list-style-type: none"> Delirium in all patients: ($P = .01$) Melatonin: 11.5% Placebo: 31.1% Incident delirium: ($P = .01$) Melatonin: 3.5% Placebo: 29.2% 	<ul style="list-style-type: none"> Percentage of patients with postoperative delirium: Group 1: Placebo 32.65% Group 2: Melatonin 9.43% Group 3: Midazolam 44.00% Group 4: Clonidine 37.25% Melatonin group had a statistically significant decrease in postoperative delirium ($P = .003$) Midazolam and clonidine increased the risk of delirium versus placebo, but this was not statistically significant ($P = .245$ and $.629$, respectively)

AMT = Abbreviated Mental Test; CAM = Confusion Assessment Method; DB = double blinded; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; ICU, intensive care unit; PG = parallel group; R = randomized.

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