**Name of Journal:** *World Journal of Psychiatry*

**Manuscript NO:** 71664

**Manuscript Type:** LETTER TO THE EDITOR

**Therapeutic use of melatonin in schizophrenia-more than meets the eye!**

Naguy A. Melatonin in schizophrenia

Ahmed Naguy

**Ahmed Naguy,** Al-Manara CAP Centre, Kuwait Centre for Mental Health, Shuwaikh 22094, Kuwait

**Author contributions:** Naguy A wrote the manuscript.

**Corresponding author: Ahmed Naguy, MBChB, MSc, Staff Physician,** Al-Manara CAP Centre, Kuwait Centre for Mental Health, Jamal Abdul-Nassir Street, Shuwaikh 22094, Kuwait. ahmednagy@hotmail.co.uk

**Received:** September 16, 2021

**Revised:** November 8, 2021

**Accepted: February 12, 2022**

**Published online:**

**Abstract**

Adjunctive melatonin use in schizophrenia, as supported by a modicum of evidence, has multiple transcending chronobiotic actions, including fixing concurrent sleep problems to bona fide augmentative antipsychotic actions, mitigating the risk of tardive dyskinesias, curbing the drastic metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

**Key Words:** Melatonin; Schizophrenia; Chronobiotic; Neuroprotectant; Antipsychotic; Tardive dyskinesia; Metabolic syndrome

Naguy A. Therapeutic use of melatonin in schizophrenia-more than meets the eye!. *World J Psychiatry* 2022; In press

**Core Tip:** Adjuventia melatonin use in schizophrenia is strongly recommended, although it is supported by a modicum of evidence. Its use has multiple transcending chronobiotic actions, rectifying sleep disturbance in schizophrenia to bona fide augmentative antipsychotic actions, mitigating the risk of relentless tardive dyskinesias, curbing the drastic cardio-metabolic syndrome and ultimately providing neuroprotective actions in the face of the neuroprogressive course of schizophrenia.

**TO THE EDITOR**

In a recent issue of the *World J Psychiatry*, Duan *et al*[1] conducted an interesting systematic review of melatonin use for schizophrenia. They concluded that add-on melatonin can help with sleep, might curtail metabolic risk and possibly mitigate tardive dyskinesia in patients with schizophrenia. We completely agree with authors, and we[2] have previously published on melatonin adjuventia in patients with bipolar mood disorders as well. Herein, we will try to expand a bit more on the therapeutic potential of melatonin in schizophrenia.

Sleep and circadian rhythm disturbances, as high as 80%, lie at the core of the etiopathogenesis of schizophrenia, as supported by both human studies and preclinical evidence in animal (mice) models with genetic mutations pertinent to schizophrenia[3]. Wide heterogeneity in phenotypes has been demonstrated. This includes, among other things, severe circadian misalignment, phase advances and delays, non-24 h rhythms that were not entrained by the light/dark cycle and disturbed sleep/wake cycle, perhaps reflecting the heterogeneity of the disease itself.

Melatonin secretion is reduced in schizophrenia. Therefore, it follows that melatonin (N-acetyl 5-methoxytryptamine) use addresses a core pathophysiology central to schizophrenia, beyond being a mere sleeping aid.

Moreover,it has been shown that melatonin might augment anti-psychotic efficacy by virtue of anti-inflammatory and anti-oxidant actions. Melatonin impacts tryptophan catabolic pathways *via* its effect on stress response and cortisol secretion, and this might impact cortex associated cognition, amygdala associated affect and striatal motivational processing. Melatonin in schizophrenia has been demonstrated to serve both as a biologic marker and as a treatment adjunct[4].

Melatonin mitigates risk of tardive dyskinesia, akin to similar use of vitamin E, given that melatonin is 6-10 times more potent than vitamin E. Moreover, it curbs metabolic syndrome. Mechanistically, melatonin regulates the photo-neuroendocrine axis. It has complex interactions with leptin, improves insulin resistance, and possesses cardio-protective actions.

Schizophrenia relapses are typified with neuroprogression leading to subcortical atrophy, ventriculomegaly and further white matter loss. This is chiefly mediated through microglial activation, neuroinflammation and oxidative/nitrosative stress. Mitochondrial dysfunction due to deficiency of the antioxidant glutathione also contributes[5]. Taken together, these findings make case for a role for melatonin in neuroprotection, owing to its anti-apoptotic actions and its regulation of adult hippocampal neurogenesis.

Quo Vadis? melatonin use in schizophrenia, as supported by a modicum of evidence base, has multiple transcending chronobiotic actions, including bona fide antipsychotic actions, mitigation of tardive dyskinesia, curbing metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

**ACKNOWLEDGEMENTS**

Author extends his deepest gratitude to Dr. Bibi Alamiri, MD, ScD, ABPN for her invaluable scientific input to the manuscript.

**REFERENCES**

1 **Duan C**, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. *World J Psychiatry* 2021; **11**: 463-476 [PMID: 34513608 DOI: 10.5498/wjp.v11.i8.463]

2 **Naguy A**, Francis K. Melatonin: A new game-changer in juvenile bipolar disorders? *Psychiatry Res* 2019; **279**: 364-365 [PMID: 30812069 DOI: 10.1016/j.psychres.2016.04.052]

3 **Delorme TC**, Srivastava LK, Cermakian N. Are Circadian Disturbances a Core Pathophysiological Component of Schizophrenia? *J Biol Rhythms* 2020; **35**: 325-339 [PMID: 32498652 DOI: 10.1177/0748730420929448]

4 **Naguy A**, Al-Amiri B, Shoukry T. Melatonin Use in Psychiatry-Quo Vadis? *Am J Ther* 2020; **27**: e495-e499 [PMID: 30277908 DOI: 10.1097/MJT.0000000000000833]

5 **Naguy A**, Moodliar-Rensburg S, Alamiri B. The long-acting injectable atypical antipsychotics-merits and demerits!. *CNS Spectr* 2021; **26**: 442-443 [PMID: 32641186 DOI: 10.1017/S1092852920001558]

**Footnotes**

**Conflict-of-interest statement:** Author declares no conflicts of interest or financial affiliations.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 16, 2021

**First decision:** November 8, 2021

**Article in press:**

**Specialty type:** Psychiatry

**Country/Territory of origin:** Kuwait

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** de Oliveira I, Mogulkoc R, Stoyanov D **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:** Fan JR