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Peer Reviewer of *World Journal of Psychiatry*, Délio M Conde, MD, PhD, Professor, Department of Gynecology and Obstetrics, Federal University of Goiás, Goiânia 74605-050, Brazil. delioconde@ufg.br

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yan; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

PUBLICATION DATE

March 19, 2022

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INSTRUCTIONS TO AUTHORS

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

Ahmed Naguy

Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

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

Received: September 16, 2021

Peer-review started: September 16, 2021

First decision: November 8, 2021

Revised: November 8, 2021

Accepted: February 12, 2022

Article in press: February 12, 2022

Published online: March 19, 2022



Ahmed Naguy, Al-Manara CAP Centre, Kuwait Centre for Mental Health (KCMH), Shuwaikh 22094, Kuwait

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

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

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Core Tip: Adjuvant 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.

Citation: Naguy A. Therapeutic use of melatonin in schizophrenia-more than meets the eye!. *World J Psychiatry* 2022; 12(3): 533-535

URL: <https://www.wjgnet.com/2220-3206/full/v12/i3/533.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v12.i3.533>

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 adjuvantia 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.

FOOTNOTES

Author contributions: Naguy A wrote the manuscript.

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

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Country/Territory of origin: Kuwait

ORCID number: Ahmed Naguy 0000-0002-6465-456X.

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Fan JR

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