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

Ahmed Naguy

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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: Adjunctive 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.

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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!

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