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Letter to the Editor

Melatonin: A new game-changer in juvenile bipolar disorders?

Circadian rhythms disturbance is commonplace in Bipolar Disorders (BD) whilst decreased need for sleep without acknowledgement of fatigue is characteristic of mania. Of note, *sleep disruption* and *circadian rhythm disturbance* have both been implicated in BD, but they are not identical processes. Although there is an interaction between them, the amount and patterning of sleep depends on many factors, of which the circadian rhythm is only one. Sleep disturbance triggers an episode, and, is considered a relapse signature. Securing sleep is integral part of treatment, either pharmacologically, with benzodiazepines for instance especially early on, or by employing Interpersonal and Social Rhythm Therapy (IPSRT) after acute phase subsides. Circadian pathology in BD can, at least in part, account for higher rates of medical comorbidities seen in BD patients, and this is attributed to other biologic rhythms disturbance seen in BD governing body temperature, cortisol, melatonin, appetitive behaviours and metabolism. Seasonal patterns in BD also points to aetiopathologic link with circadian disturbances, and there thought to be bidirectional relationship between daytime affect regulation and night-time sleep pattern. Light therapy and melatonin, two interventions that manipulate circadian rhythm are being used widely for seasonal affective disorder. Although inconsistent, some studies demonstrated free-running clock, phase-advanced or unstable rhythms, and, hyper or insensitivity to zeitgebers, whilst abnormalities in clock genes have been reported too. This "clock" is lodged in the hypothalamic suprachiasmatic nucleus (SCN) regulating pineal body secretion of melatonin.

All this would converge to highlight a role of N-acetyl 5-methoxytryptamine (*melatonin*) in BD. And indeed, Bersani and Garavini (2000) reported 11 manic patients with treatment-resistant insomnia that responded favourably to add-on melatonin with resultant parallel improvement of manic symptomatology too (Bersani and Garavini, 2000). Melatonin might augment the efficacy of antipsychotics via anti-inflammatory and anti-oxidative actions, mitigates tardive dyskinesia (TD), and, by impacting tryptophan catabolic pathways (TRYCATS) via stress response and cortisol secretion, might impact cortex associated cognition, amygdala associated affect, and, striatal motivational processing (Anderson and Maes, 2012). Furthermore, burgeoning body of evidence in literature abound capitalizing on the interactive changes in oxidative/nitrosative pathways, immune-inflammatory activity, TRYCATs and the melatonergic pathways to form an emerging biological perspective on the etiology, course and management of BD (Anderson et al., 2016). But what is far more appealing is that melatonin may curtail the metabolic syndrome (MetS), through its presumed antihyperlipidemic action, as supported by recent RCTs (Goyal et al., 2014; Romo-Nava et al., 2014). A recent comprehensive review emphasized abnormal melatonin function in BD, the rationale of melatonin action in BD, the evidence supporting the exogenous administration of melatonin, and melatonin agonists (ramelteon and tasimelteon) as an adjunctive treatment of mood stabilizers in treating sleep disorders in BD to possibly prevent relapses when administered during remission phases with an additional interesting adjunctive therapeutic effect on preventing metabolic syndrome, particularly in patients treated with antipsychotics showing high tolerability with little dependence potential in contrast to most available sleep medications (Geoffroy et al., 2015).

Atypical antipsychotics (AAPs) have become the mainstay of treatment of bipolar and notably juvenile bipolar disorders (Goldstein et al., 2012). This practice is fraught with cardiometabolic syndromes, especially in children and adolescents who are more susceptible to adverse metabolic side-effects of AAP compared to adults (Cohen et al., 2012), and melatonin might open new venues to safeguard against these serious sequelae. *It is* noteworthy that melatonin has a widespread use in pediatric sleep disorders with reasonable safety and tolerability and devoid of abuse potential.

This simply translates into melatonin might be a new game-changer in BD, targeting core circadian rhythms disturbance that are central to BD aetiopathophysiology, mitigating TD, and, most importantly, alleviating MetS. Definitely, time would tell its real position in clinical practice with well-designed large clinical trials in paediatric and adolescent populations.

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