TABLE 1.
Published Literature on Nightmares by Mirtazapine

Citation	Clinical Condition	Age/Sex	Country	Drug/Dose	Inference	Rescue Medication
Mathews et al.	Depressive symptoms	52/ M	Philadelphia	Mirtazapine 15 mg OD	Nightmares	Not Mentioned
Dang et al.	Depressive symptoms	21/ M	Goa, India	Mirtazapine 15 mg OD	Nightmares	Drug stopped. Treated with Fluoxetine
Menon et al.	Major depression	21/ F	Puducherry, India	Mirtazapine 7.5 mg OD	Nightmares	Sertraline 50 mg

References

1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 newgeneration antidepressants: A multipletreatments metaanalysis. Lancet 2009; 373: 746–758.
2. De Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatr 1996; 57: 19–25.
3. Dang A, Garg G, and Rataboli PV. Mirtazapine induced nightmares in an adult male. Br J Clin Pharmacol 2009; 67: 135–136.
4. Mathews M, Basil B, Evcimen H, Adetunji B, and Joseph S. Mirtazapineinduced nightmares. Prim Care Companion J Clin Psychiatry 2006; 8: 311.
5. Buschkamp JA, Frohn C, and Juckel G. Mirtazapine induces nightmares in depressed patients. Pharmacopsychiatry 2017; 50: 161.
6. Menon V and Madhavapuri P. Low-dose mirtazapine-induced nightmares necessitating its discontinuation in a young adult female. J Pharmacol Pharmacother 2017; 8: 182–184.
7. Schmid DA, Wichniak A, Uhr M, et al. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology 2006; 31: 832–844.
8. Doghramji K and Jangro WC. Adverse effects of psychotropic medications on sleep. Psychiatr Clin North Am 2016; 39: 487–502.
9. Farmer JA and Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. Drug Safety 2000; 23: 197–121.
10. van Zweiten PA and Timmermans PBMWM. Comparison between the acute hemodynamic effects and brain penetration of atenolol and metoprolol. J Cardiovasc Pharmacol 1979; 1: 85–96.

HOW TO CITE THIS ARTICLE: Sree Sudha TY, VenkataNaga S, and Pugazhenthan T. Nightmares and Mirtazapine—Time to be vigilant. *Indian J Psychol Med*. 2020;43(5):453–454.

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/0253717620926785

Management of Post-Liver-Transplant Delirium with Melatonin: A Case Report

Melatonin is known to play a key role in managing multiple bodily functions such as controlling the chronobiologic cycle of the body and resetting the circadian rhythm. It also acts as an antioxidant at the intracellular level, has strong anti-apoptotic activity, has anti-inflammatory and analgesic properties, helps in adaptation to the environmental and neuroendocrine system, and delays the progression of various hormone-dependent malignancies. It also plays a role in immune regulation, neuroprotection, and sleep regulation.[1]

Given its role in the chronobiological cycle, melatonin has been evaluated for the prevention and management of delirium.[2] The antioxidant properties of melatonin have been utilized for preventing and managing a range of liver injuries and diseases[3,4] and the prevention of medication-associated nephrotoxicity.[5] Given its potent antioxidant properties, it has also been used in organ transplant patients to prevent graft rejection. It has been evaluated in liver transplant patients as part of a multidrug pre-transplant pharmacological cocktail.[6]

Delirium is one of the acute complications of a liver transplant, with a reported incidence of 21%, and is associated with prolonged hospital stay, longer intensive care unit stay, and higher six months mortality.[7] Accordingly, effective management of delirium in patients undergoing liver transplantation is of paramount importance. Considering the antioxidant, anti-inflammatory, and beneficial effects of melatonin, with no associated cardiac complications, it can be considered as a promising agent for the management of delirium in patients undergoing a liver transplant. However, no studies have evaluated the role of melatonin in the management of

delirium in patients who have undergone liver transplantation. Here, we present a case who developed delirium during the immediate post-transplant period and was managed with melatonin.

Case Description

A 58-year-old female, diagnosed with type-2 diabetes mellitus, hypothyroidism, and non-alcoholic steatohepatitis, was considered for a liver transplant due to decompensated liver disease. Psychiatric evaluation before surgery did not reveal evidence of any psychiatric ailment.

On post-operative day 2, she was extubated and was maintaining saturation on oxygen supplementation with the mask. However, on the same day, she developed abnormal behavior in the form of agitation and persecutory delusion. On mental status examination, she was found to be conscious but uncooperative. She was easily distracted during conversation and did not cooperate with formal testing for attention. She was oriented to person but not to time or place. During the interview, she would drift off to sleep and had to be aroused by calling out her name repeatedly. These symptoms were seen to fluctuate during the day.

Given this, a diagnosis of delirium was made. Her Delirium Rating Scale Revised-98 (DRS-R-98)[8] total score was 29, and Mini-Mental State Examination (MMSE) score, 9. Review of all the investigations (including renal function test, fasting blood glucose levels, and serum electrolytes) did not reveal any abnormality except for hyponatremia (S. Na = 121 mEq/L), hypoalbuminemia (S. Albumin = 2.8 mg/dL) and deranged liver function tests (S. Bilirubin 3.9 mg/dL). Her liver function test showed an improvement trend, compared to her pre-transplant status. Ultrasound of the abdomen did not reveal any abnormality. A review of medications revealed that she was receiving intravenous methylprednisolone 300 mg/day and IV antibiotics in the form of imipenem and tazobactam for the prevention of post-transplant complications.

The delirium was considered to be of multifactorial etiology, with hyponatremia considered the primary cause, and post-operative pain, deranged liver functions, prolonged surgery, and use of methylprednisolone as other contributory factors.

Initially, the family members and other treating team members were educated about her condition and advised to provide re-orientation cues, avoid unnecessary stimulation, and avoid the frequent change of staff. Hyponatremia was corrected by an intravenous route along with the use of intravenous albumin for hypoalbuminemia.

At the initial evaluation, after discussing with the primary treating team, it was decided not to start any new medications. However, over the next day, she became more uncooperative and agitated, threatening to remove the tubing and not allowing anyone to go near her. Her DRS-R-98 score increased to 32, and the MMSE score reduced to 6. Given these symptoms, following a multidisciplinary team discussion and involvement of family members, she was started on tab. melatonin 1.5 mg at 9 pm. She slept well on the fourth post-operative night. The severity of her symptoms came down the next day, and she was slightly cooperative. Her DRS-R-98 score decreased to 26, and the MMSE score increased to 13. On the next night, she received melatonin 3 mg, with which her sleep remained better. From the fifth post-operative day, she was fully oriented and cooperative and did not have any persecutory delusions. Her DRS-R-98 score was 13, and the MMSE score was 19.

She was continued on melatonin 3 mg HS for the next week, and she maintained well. During this period, no side effects were noted that could be attributed to melatonin.

Discussion

We are not aware of any previous report of the use of melatonin in the management of delirium in a patient in the post-liver-transplant stage. The index case reveals that melatonin can be used safely in patients developing delirium in the context of a liver transplant. In the index case, melatonin led to an improvement in the symptoms within 24 hours, and the continued use of melatonin was not associated with any untoward side effects. Available data suggest that melatonin may have a beneficial effect in other organ transplantations, too, due to its antioxidative properties. Because the incidence of delirium is reported to be as high as 21% in patients undergoing liver transplant,[7] melatonin needs to be evaluated further for its efficacy in the prevention and management of delirium in this group of patients. Data also suggest the association of lower melatonin levels with the use of mechanical ventilation[9] and of abnormal melatonin release with sepsis,[9] which are established risk factors for delirium.

We did not consider an antipsychotic for the management of delirium because of the risk of cardiac side effects, which the hepatic team was not comfortable about. The second reason was that melatonin has been found to have antioxidant properties and has been used previously in people with liver injury.[1,3] Keeping these points in mind, melatonin was considered.

In the index case, the improvement in delirium could be due to the correction of underlying metabolic parameters (i.e., hyponatremia), the use of re-orientation cues, and the use of melatonin. Since, in general, the incidence of delirium is high in all the post-operative patients, melatonin may be an ideal agent that needs to be evaluated further for its efficacy in the management and prevention of delirium.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Sandeep Grover[1], Devakshi Dua[1], Madhumita Premkumar[2], Arunanshu Behera[3], Radhakrishan Dhiman[2]

[1]Dept. of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India. [2]Dept. of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. [3]Dept. of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Address for correspondence:

Sandeep Grover, Dept. of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. E-mail: drsandeepg2002@yahoo.com

Submitted: 25 Apr. 2020
Accepted: 30 May 2020
Published Online: 14 Jul. 2020

References

1. Bellapart J and Boots R. Potential use of melatonin in sleep and delirium in the critically ill. Br J Anaesth 2012; 108: 572–580.
2. Choy SW, Yeoh AC, Lee ZZ, et al. Melatonin and the prevention and management of delirium: a scoping study. Front Med 2018; 4: 242–247.
3. Zhang J-J, Meng X, Li Y, et al. Effects of melatonin on liver injuries and diseases. Int J Mol Sci 2017; 18: 673.
4. Mortezaee K and Khanlarkhani N. Melatonin application in targeting oxidative-induced liver injuries: A review. J Cell Physiol 2018; 233: 4015–4032.
5. Tavakoli M. Kidney protective effects of melatonin. J Nephropharmacol 2014; 3: 7–8.
6. Esteban-Zubero E, García-Gil FA, López-Pingarrón L, et al. Potential benefits of melatonin in organ transplantation: A review. J Endocrinol 2016; 229: R129–46.
7. Oliver N, Bohorquez H, Anders S, et al. Post-liver-transplant delirium increases mortality and length of stay. Ochsner J 2017; 17: 25–30.
8. Frisk U, Olsson J, Nylén P, et al. Low melatonin excretion during mechanical ventilation in the intensive care unit. Clin Sci (Lond Engl 1979) 2004; 107: 47–53.
9. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. Crit Care Med 2002; 30: 536–540.

HOW TO CITE THIS ARTICLE: Grover S, Dua D, Premkumar M, Behera A, Dhiman R. Management of post-liver-transplant delirium with melatonin: A case report. *Indian J Psychol Med*. 2020;43(5):454–456.

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/0253717620935577

Very Low Dose Aripiprazole (2 mg/d) for Venlafaxine-Induced Bruxism: A Case Report

The association of bruxism with selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors (SSRI/SNRI) has been noted for a long time.[1,2] Here we report a case of venlafaxine-induced sleep bruxism and its successful management with very low dose aripiprazole.

Case Report

Mr U, a 21 years old male, presented with four months' history of a severe depressive episode without psychotic symptoms. An adequate trial of escitalopram failed, and he was initiated on venlafaxine. The dose was gradually increased to 225 mg/d over a period of three weeks. His depressive symptoms improved partially over four weeks (40% reduction in the Hamilton Depression Rating Scale, i.e., from 42 to 25). After four weeks, the dose of venlafaxine was increased to 300 mg/d. In the following 4–5 days, the patient's caregivers, who had stayed throughout this period with him, noticed the sound of teeth grinding and clinching when the patient was asleep in the night. The frequency of night bruxism increased in the next few days, occurring for 3–4 minutes every hour. Mr U reported discomfort in his jaws after waking up in the morning, but there was no history of awake bruxism, and the patient neither remembered sleep bruxism nor complained of sleep disturbance. Because of an increase in the frequency of suicidal ideas, the patient was offered inpatient care. By this time, he had received Cap venlafaxine 300 mg/d for about ten days. Diagnostic possibility of venlafaxine-induced bruxism was considered, and aripiprazole 2 mg/d was added to venlafaxine 300 mg/d on the second day of inpatient care. The frequency of sleep bruxism decreased from the first day of adding aripiprazole and it completely stopped. As depressive symptoms were persisting, the clinical history was reclarified, and an episode suggestive of hypomania in the past was noted. The primary psychiatry diagnosis was revised to bipolar affective disorder (BPAD) current episode severe depressive episode without psychotic symptoms. Lithium carbonate (1050 mg/d) was added to venlafaxine (300 mg/d) and aripiprazole (2 mg/d) after about a week of IP care. On this treatment, his depressive symptoms improved completely in three weeks, and he was discharged. Mr U was continued on the same medications for two months after discharge, and he did not have any recurrence of sleep bruxism during this period. Later, venlafaxine dose was decreased to 225 mg/d, and aripiprazole was stopped after a week of decreasing the venlafaxine dose. It has been two months since stopping aripiprazole. Mr. U did not have a relapse of sleep bruxism, and he has been maintaining well on venlafaxine 225 mg/d and lithium 1050 mg/d. We intend to taper off venlafaxine in the follow-up. Score on Naranjo Adverse Drug Reaction Probability Scale was 4, which suggest probable role of venlafaxine in the occurrence of bruxism.

Discussion

Our report highlights the utility of very low dose aripiprazole (2 mg/d) in the