Effect of melatonin on the daytime sleepiness side-effect of gabapentin in adults patients with neuropathic pain

Basak Altiparmak, Hemra Cil, Nalan Celebi

Mugla Sitki Kocman University, Department of Anesthesiology and Reanimation, Mugla, Turkey
University of California, Department of Orthopedics and Traumatology, San Francisco, United States
Hacettepe University, Department of Anesthesiology and Reanimation, Ankara, Turkey

Received 10 April 2018; accepted 21 August 2018
Available online 25 September 2018

Abstract

Background and objectives: Gabapentin is an antiepileptic drug. Widely used for the management of neuropathic pain. Although it is known to be well tolerated, somnolence and dizziness are the most frequent adverse effects. In this study, we aimed to evaluate the effect of melatonin on daytime sleepiness side effect of gabapentin, sleep quality and pain intensity of patients with neuropathic pain.

Methods: Patients suffering from "neuropathic pain" and planed to receive gabapentin therapy were randomly divided into two groups. Group 1 received melatonin 3 mg and gabapentin 900 mg orally, group 2 received matching placebo capsule and gabapentin 900 mg. The Epworth Sleepiness Scale, the Pittsburgh sleep quality index for assessment of sleep quality and Verbal Rating Scale were completed at the 0th, 10th and 30th days of treatment. Additive analgesic drug requirements were recorded.

Results: Eighty patients were enrolled to the study; age, gender, ratio of additive analgesic consumption, baseline Epworth Sleepiness Scale, Pittsburg Sleep Quality index and Verbal Rating Scale scores were similar between the groups. Epworth Sleepiness Scale scores, Pittsburgh sleep quality index scores and Verbal Rating Scale scores in Group 1 were significantly lower than group 2 at the 10th day of treatment \((p=0.002, p=0.003, p=0.002\) respectively). At the 30th day of treatment, Epworth Sleepiness Scale scores and Verbal Rating Scale scores were significantly lower in Group 1 \((p=0.002, p=0.008\) respectively). However, Pittsburgh sleep quality index scores did not significantly differ between the groups \((p=0.0566)\).

Conclusions: Melatonin supplementation rapidly and significantly improved daytime sleepiness side-effect of gabapentin, however sleep quality of the patients with neuropathic pain was similar between groups.

© 2018 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The study was carried out in Hacettepe University Hospital.

Corresponding author.

E-mail: basakugurlu@me.com (B. Altiparmak).

https://doi.org/10.1016/j.bjane.2018.08.002
0104-0014/© 2018 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Neuropathic pain (NP) has been defined as "the pain caused by a lesion or disease of the somatosensory system" by the International Association for the Study of Pain and comprises a wide variety of different central and peripheral disorders. It is prevalence is believed to be approximately 7% in general population. Patients who have NP may have a variety of sensory loss (numbness) and sensory gain (alldynia) clinical phenomena, the exact patterns of which vary between people and disease. Neuropathic pain can effect not only the patients’ quality of life for years, but also may be associated with symptoms like depression, anxiety, and sleep disturbance. Chronic pain and sleep disturbance often occur simultaneously and have multidirectional relations with each other.

Multimodal approaches including psycho- and physiotherapy, as well as pharmacological agents, are usually used for the management of NP. Gabapentin and pregabalin (gabapentinoids) are the current mainstream of pharmacological therapy. Gabapentin is an antiepileptic drug which have been shown to be effective in several previous clinical trials. Although it is known to be well tolerated, somnolence and dizziness are the most frequent adverse effects causing patients to discontinue the treatment.

Melatonin is a circadian hormone produced in the corpus pineal during night time. It is known to have analgesic and antidepressive effects. Melatonin is a relatively non-toxic drug and several times it has been used for sleep disturbances of both adults and children with no reported serious side effects. However, the effect of melatonin on the “day time sleepiness” side effect of gabapentin and consequently on “quality of sleep” in patients with NP has not previously been investigated.

In this study, our primary aims are to assess the effect of melatonin on daytime sleepiness side effect of gabapentin and the sleep quality of patients with neuropathic pain. Our secondary aim is to assess the effect of melatonin on attenuation of neuropathic pain.

Methods

After the institutional ethical committee approval, the study was conducted as a randomized, double-blind, placebo-controlled trial in an academic tertiary university hospital. A written informed consent was obtained from all individual participants included in the study. This trial is registered to Australia New Zealand Clinical Trials Registry with Trial Id: ACTRN12618000522213. The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANS) and The Douleur Neuropathique 4 Questionnaire (DN4) were used to screen for NP. The patients with LANS5 score >12 and DN4 score >4 were diagnosed with NP and included in the study.
Exclusion criteria were presence of sleep apnea syndrome, advanced liver disease, chronic kidney disease, abnormal thyroid hormone levels, anemia, preexisting gabapentin consumption or therapy for insomnia and NP diagnosis due to any type of malignancy were excluded from the study. Sequential randomization was done using dedicated software and the patients were allocated into two groups based this randomization: Group 1 (melatonin+/received melatonin) and Group 2 (melatonin−/not received melatonin).

All patients received oral gabapentin therapy: day 1, 300 mg; day 2, 600 mg (300 mg two times per day); day 3, 900 mg (300 mg, three times per day) and 900 mg (300 mg, three times per day) thereafter. The patients in Group 1 (melatonin+) received 3 mg melatonin orally 60 min before bedtime starting from the first day of gabapentin therapy, while patients in Group 2 (melatonin−) received matching placebo capsules for 30 days. The therapy drugs were prepared by university hospital pharmacy department in compliance with Food and Drug Administration (FDA) Good Compounding Practice regulations. A calendar with two boxes for each study drug under each day was given to all of the patients. The patients were asked to fill in the related boxes if they remembered to take their drugs on that day. The calendars were checked on 10th and 30th days to monitor adherence to the therapy. All the patients were evaluated at the 10th and 30th days of the treatment by the same anesthesiologist who was blinded to the study groups.

During the evaluation process, Epworth Sleepiness Scale (ESS)\(^{15}\) and The Pittsburgh Sleep Quality Index for assessment of sleep quality (PSQI)\(^{14}\) questionnaires were used for assessment of sleep health. In addition, Verbal Rating Scale (VRS) were used for assessment of pain. For ESS, the cut off score was determined as 10 and the score over 10 was accepted as “excessive day-time sleepiness”. For PSQI, the cut-off score was 5 and score over 5 was accepted as “patients with primary insomnia”.\(^{13}\)

All of the patients were directly asked for “headache, dizziness, nausea, vomiting, aggression, fatigue, drowsiness and paresthesia” complaints at the beginning, 10th day and 30th day of the treatment.

Statistics

Sample size of the study was calculated based on a pilot study with 5 patients in each group. The patients received melatonin/placebo capsules for 10 days and the differences in the ESS scores between 0th day and 10th day were recorded. Assuming a 2-sided significance level of 0.05, with a power of 0.80, 36 participants were needed per treatment group to provide a significant difference in ESS score changes between the groups. Considering drop-out ratio as 10%, 40 participants per group were included in the study.

Statistical analysis was performed by the SPSS System (version 15.0, SPSS Inc., Chicago, IL, USA). Values were expressed as mean ± standard deviation or as percentages. The groups were compared in parametric parameters using independent samples t-test and in non-parametric parameters using Mann–Whitney U test. The percentage was calculated in presence and absence group by Pearson’s Chi-square test. \( p < 0.05 \) was accepted statistically significant.

Results

Nightly patients were enrolled to the study. Six of them did not meet inclusion criteria and four of the patients did not want to participate. Consequently, eighty patients were included in the study; 40 patients were randomized to Group 1 (melatonin) and the other 40 in Group 2 (no melatonin) (Fig. 1). In the first group; 14 patients (35%) had NP due to lumbar spinal stenosis, 12 patients (30%) had failed back surgery, 10 patients (25%) had diabetes mellitus and 4 patients (10%) had developed NP after trauma. In the second group; 16 patients (40%) had NP due to lumbar spinal stenosis, 12 patients (30%) had diabetes mellitus, 10 patients (25%) had failed back surgery and 2 patients (5%) had nerve injury due to trauma. Age, gender, ratio of additional analgesic consumption, baseline pain scores (VRS), mean PSQI and ESS scores were similar between the groups (Table 1) (Fig. 1).

At the beginning of gabapentin treatment, number of patients with “excessive day-time sleepiness” complaint (ESS score > 10) was 36; 19 patients (47.5%) were in Group 1 and 17 patients (42.5%) were in Group 2. At the 10th day of treatment, number of patients with “excessive day-time sleepiness” was 2 (5%) and mean ESS score was 6.10 ± 2.01 in Group 1 and in Group 2, the number of patients was 12 (30%) and mean ESS score was 8.00 ± 2.66. The difference at mean ESS scores was statistically significant \( (p = 0.002) \). At the 30th day of treatment, none of the patients had ESS score over 10. Mean ESS score was 3.60 ± 0.96 and 4.28 ± 0.91 in Group 1 and Group 2 respectively. The difference was statistically significant between the groups.

| Table 1 | Baseline characteristics of the participants. |
|---------|---------------------------------------------|
|         | Group 1 (melatonin) (n = 40) | Group 2 (no melatonin) (n = 40) | p-value |
| Age (year) | 49.28 ± 13.73 | 47.15 ± 12.77 | 0.370 |
| Female/male | 18/22 | 21/19 | 0.655 |
| VRS pain score | 7.43 ± 1.06 | 7.53 ± 0.96 | 0.674 |
| PSQI (0th day) | 10.65 ± 2.46 | 10.70 ± 2.72 | 0.881 |
| ESS score (0th day) | 7.85 ± 1.33 | 7.75 ± 1.15 | 0.821 |
| Analgesic usage yes | 52.5% | 52.5% | 1.000 |
| No | 47.5% | 47.5% | |

VRS: Verbal Rating Scale; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale. Data are presented as mean ± standard deviation.
(p = 0.002) (Table 2). In both of the groups, mean ESS scores at the 10th and 30th day were significantly lower compared to the baseline ESS scores (p < 0.001).

Mean PSQI score at the 10th day of treatment was calculated as 4.63 ± 0.81 in Group 1 and 5.23 ± 0.95 in Group 2. Mean PSQI score difference between the groups was found to be statistically significant (p = 0.003). However, at the 30th day of treatment, mean PSQI scores of Group 1 (3.20 ± 0.52) and Group 2 (3.30 ± 0.76) were similar (p = 0.566) (Table 3). In both of the groups, mean PSQI scores at the 10th and 30th day improved significantly when compared to the baseline PSQI scores (p < 0.001).

At the 10th day of treatment, mean VRS score of patients decreased from 7.43 ± 1.06 to 4.85 ± 0.86 in Group 1 and 7.53 ± 0.96 to 5.55 ± 0.99 in Group 2. There was a significant difference between mean VRS scores of the groups (p = 0.002). At the 30th day of treatment, mean VRS score was 3.33 ± 0.73 in Group 1 and 3.88 ± 0.91 in Group 2. Similarly, the difference between the groups was statistically significant (p = 0.008) (Table 4).

The baseline side effects seen in the groups were similar at the beginning of gabapentin therapy. At the 10th and 30th days of the treatment, all side effects decreased compared to baseline and the ratios were similar between the groups (Table 5).

**Discussion**

In the current literature, this is the first study to assess effectiveness of external melatonin supplementation on
day-time sleepiness side effect of gabapentin. Our results show that melatonin supplementation rapidly and significantly improved day-time sleepiness side effect of gabapentin and QoS of the patients with NP. In addition, melatonin successfully attenuated pain scores of patients throughout the gabapentin treatment.

In several studies, patients with NP have been reported to define pain-related interference in health-related quality of life and consequently experience problems such as depression, fear, and sleep disturbances. Unfortunately, it is known that there is a complex relation between sleep disturbances and NP; Poor QoS may exacerbate pain perception, and in turn, pain may exacerbate the QoS. In an experimental mice model, Narita et al. reported an increase in wakefulness and a decrease in non-rapid eye movement sleep under a neuropathic pain-like state produced by sciatic nerve ligation. They determined an increase in membrane-bound GABA (γ-aminobutyric acid) transporters on activated glial fibrillary acidic protein-positive astrocytes in the cingulate cortex, while a rapid decrease in extracellular GABA levels in the same area after depolarization. With this experiment, they tried to explain the mechanism of insomnia in patients with NP. As a result of this phenomena, improvement of QoS gains a vital importance on management of patients with NP. Many authors have suggested to routinely evaluate the QoS in clinical practice, however sleep disturbances usually continue to be underdiagnosed and undertreated.

In the current study, 45% of the patients were found to have “excessive day-time sleepiness” according to ESS evaluation and mean PSQI scores were over 5 in both of the groups at the beginning of the gabapentin treatment. This results probably point out a very frequent and serious complication of NP. On the other hand, Melikoglu et al. have reported even higher ratios of sleep disturbances in their study. They have similarly evaluated the QoS by PSQI in patients with NP and 80% of patients were found to present poor QoS regardless of NP cause.

Melatonin (N-acetyl-5-methoxytryptamine) is the primary hormone produced by the pineal gland during nocturnal periods to properly time circadian sleep-wake rhythms, so previously it has been used to enhance nighttime sleepiness in the clinical studies of children and adult. In the study of Scheer et al., melatonin supplementation was used to improve sleep in hypertensive patients treated with beta-blockers. Melatonin was reported to increase total sleep time by 37 min and increase sleep efficiency by 7.6. Similarly, Gringras et al. have reported that children with autism spectrum disorder slept 57.5 min longer at night after 13 weeks of prolonged-release melatonin treatment. But all of these studies have evaluated the “night time” sleep quality of the patients. As melatonin plays a significant role in the regulation of the circadian rhythm and sleep-wake cycle, we hypothesized that melatonin may improve the “day-time sleepiness” that occurs as a complication of gabapentin treatment in the patients with NP. After 10 days of melatonin + gabapentin treatment, the percentage of sleepiness complaint decreased from 47.5% to 5% in Group 1. However, in Group 2 sleepiness complaint decreased only from 42.5% to 30% and this reduction was not statistically significant. These results met the primary endpoint of this study, demonstrating statistically significant effect of melatonin versus placebo on day-time sleepiness complaint of gabapentin treatment. At the 30th day of treatment, this effect became similar in both of the groups. Somnolence and dizziness are the most frequent side effects of gabapentin therapy and they are known to be transient. So, it is not surprising that day-time sleepiness complaint became similar between the groups at 30th day of treatment. However, early attenuation of these complaints have great importance; Somnolence and dizziness are also the most common side effects of gabapentin leading to cessation of therapy in many cases. Melatonin administration may improve consistency to gabapentin treatment by rapidly decreasing these complaints in the early period of treatment.

In our study, PSQI scores of the patients dramatically decreased at the 10th and 30th day in both of the groups, however the reduction at the 10th day was more significant in Group 1. In the study of Zhang et al., nine randomized clinical trials comparing melatonin with placebo for sleep disorders in neurodegenerative disorders were analyzed. In this meta-analysis, melatonin was reported to improve PSQI scores of patients with Alzheimer disease and Parkinson’s disease. So, the PSQI scores of our patients at the 10th day are similar to the current literature, however PSQI scores of groups were similar at 30th day of treatment. We think that the most possible reason is effective attenuation of pain with gabapentin treatment in both of the groups.

| Table 5 The side effects seen in the groups at different time points. |
|-----------------------|-----------------|-----------------|
|                       | 0th day  | 10th day | 30th day | 0th day  | 10th day | 30th day |
| Headache              | 12 (30%) | 5 (12.5%) | 0 (0%)   | 13 (32.5%) | 4 (10%) | 0 (0%)   |
| Dizziness             | 7 (17.5%) | 6 (15%)  | 2 (5%)   | 8 (20%)  | 6 (15%) | 1 (2.5%) |
| Nausea                | 4 (10%)  | 1 (2.5%)  | 0 (0%)   | 4 (10%)  | 2 (5%)  | 0 (0%)   |
| Vomiting              | 1 (2.5%) | 1 (2.5%)  | 0 (0%)   | 1 (2.5%) | 1 (2.5%) | 0 (0%)   |
| Aggression            | 12 (30%) | 6 (15%)  | 2 (5%)   | 11 (27.5%) | 5 (12.5%) | 3 (7.5%) |
| Fatigue               | 29 (72.5%) | 14 (35%) | 3 (7.5%) | 27 (67.5%) | 20 (50%) | 6 (15%)  |
| Drowsiness            | 18 (45%) | 8 (20%)  | 2 (5%)   | 20 (50%) | 16 (40%) | 7 (17.5%) |
| Paresthesia           | 19 (47.5%) | 10 (25%) | 3 (7.5%) | 21 (52.5%) | 12 (30%) | 4 (10%)  |

*p < 0.05 compared to Group 2 (no melatonin—).
In the latest Cochrane review, Wiffen et al.\textsuperscript{2} stated that the outcome of at least 50% pain intensity reduction was regarded as a useful outcome of treatment by patients, and the achievement of that degree of pain relief was associated with important beneficial effects on sleep interference, fatigue, depression and quality of life. In the current study, gabapentin treatment provided more than 50% pain intensity reduction in Group 1 and approximately 50% reduction in Group 2, which means that gabapentin successfully managed to attenuate neuropathic pain at 30th day in both groups. Effective pain relief may consequently improve the QoS during night time.

In previous experimental animal models and clinical studies, melatonin was found to represent a positive effect on pain management.\textsuperscript{11,25} In a recent study, Wang et al.\textsuperscript{16} investigated the role of systemic administration of melatonin on oxaliplatin-induced pain in an experimental rat model. Intraperitoneal melatonin was reported to significantly alleviate mechanical allodynia and thermal hyperalgesia in the oxaliplatin-vehicle group. Immunohistochemical evaluation showed that oxaliplatin induced a significant increase of Glial Fibrillar Acidic Protein (GFAP) immunodensities and melatonin significantly decreased oxaliplatin-induced upregulation of GFAP expressions.\textsuperscript{26} VRS scores of our patients were similar to the current literature. At the 10th day and 30th day of treatment, VRS scores of melatonin + group were found to be significantly lower. However, the difference between the groups has no clinical importance.

Although previous studies have reported no safety concerns when melatonin is used for sleep disorders in different patient groups,\textsuperscript{27,28} in a recent study Liu et al. reported that melatonin increased reactive aggression in healthy male volunteers.\textsuperscript{29} In the current study, aggression complaints of the patients decreased from 30% to 5% in Group 1 and 27% to 7.5% in Group 2 after 30 days of treatment. The most possible reason of this difference is the health status of the patients. Liu et al. has evaluated the healthy volunteers, whereas our patients have been suffering from NP and sleep disorders. Effective management of pain and sleep disorders probably provided an improvement on aggression of the patients.

Melatonin administration was not associated with any major side effects in the current study, confirming that it is well tolerated. Therefore, we believe that it is safe to use melatonin as an adjuvant to reduce day-time sleepiness complication of gabapentin treatment.\textsuperscript{11,20}

The major limitation of our study is the wide variety of diseases causing NP. Intervariable differences between diseases may interfere the results of this study. Future studies with specific diseases should be conducted to provide a clearer view of the role of melatonin in neuropathic pain and sleep disturbances.

In conclusion, melatonin may reduce the side effects of gabapentin on daily sleepiness; therefore, it may be helpful in patients with neuropathic pain treated with gabapentin for treatment compliance.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**

1. Jensen TS, Baron R, Haanpaa M, et al. A new definition of neuropathic pain. Pain. 2011;152:2204–5.
2. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6:CD007938.
3. Blackburn-Munro G, Blackburn-Munro RE. Chronic pain, chronic stress and depression: coincidence or consequence? J Neuroendocrinol. 2001;13:1009–23.
4. Castro CM, Lee KA, Bliwise DL, et al. Sleep patterns and sleep-related factors between caregiving and non-caregiving women. Behav Sleep Med. 2009;7:164–79.
5. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010;150:573–81.
6. Chadwick D. The evidence for pharmacological treatment of neuropathic pain. Lancet. 1994;343:89–91.
7. Claustre B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med. 2005;9:11–24.
8. Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment of delayed sleep phase syndrome. Sleep Med. 2010;11:131–6.
9. Srinivasan V, Pandi-Perumal SR, Spence DW, et al. Potential use of melatonergic drugs in anaglesia: mechanisms of action. Brain Res Bull. 2010;81:362–71.
10. Seabra ML, Bignotto M, Pinto LR, et al. Randomized, double-blind clinical trial, controlled with placebo, of the toxicity of chronic melatonin treatment. J Pineal Res. 2000;29:193–200.
11. Hussain SA, Al-Khalifa IL, Jasim NA, et al. Adjutant use of melatonin for treatment of fibromyalgia. J Pineal Res. 2011;50:267–71.
12. Gatto E, Romeo C, Reiter RJ, et al. Melatonin reduces oxidative stress in surgical neonates. J Pediatr Surg. 2004;39:184–9.
13. Izcı B, Ardic S, Firat H, et al. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008;12:161–8.
14. Aslan O, Sanisoglu Y, Akyol M, et al. Subjective sleep quality of cancer patients. J BUON. 2010;15:708–14.
15. O’Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics. 2009;27:95–112.
16. Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. Clin J Pain. 2007;23:15–22.
17. Bıyık Z, Solak Y, Atalay H, et al. Gabapentin versus pregabalin in improving sleep quality and depression in hemodialysis patients with peripheral neuropathy: a randomized prospective crossover trial. Int Urol Nephrol. 2013;45:831–7.
18. Narita M, Nilikura K, Nanjo-Nilkura K, et al. Sleep disturbances in a neuropathic pain-like condition in the mouse are associated with altered GABAergic transmission in the cingulate cortex. Pain. 2011;152:1358–72.
19. Roth T, van Severent R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. Curr Med Res Opin. 2010;26:2411–9.
20. Melikoglu MA, Celik A. Does neuropathic pain affect the quality of sleep? Eurasian J Med. 2017;49:40–3.
21. Gringras P, Nir T, Breddy J, et al. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2017;56:948–57.
22. Scheer FA, Morris CJ, Garcia JL, et al. Repeated melatonin supplementation improves sleep in hypertensive patients...
Effect of melatonin on daytime sleepiness of gabapentin treated with beta-blockers: a randomized controlled trial. Sleep. 2012;35:1395–402.

23. Beydoun A, Uthman BM, Sackellares JC. Gabapentin: pharmacokinetics, efficacy, and safety. Clin Neuropharmacol. 1995;18:469–81.

24. Zhang W, Chen XY, Su SW, et al. Exogenous melatonin for sleep disorders in neurodegenerative diseases: a meta-analysis of randomized clinical trials. Neurol Sci. 2016;37:57–65.

25. Borsani E, Buffoli B, Bonazze V, et al. Single administration of melatonin modulates the nitroxidergic system at the peripheral level and reduces thermal nociceptive hypersensitivity in neuropathic rats. Int J Mol Sci. 2017;18:2143–60.

26. Wang YS, Li YY, Cui W, et al. Melatonin Attenuates Pain Hypersensitivity and decreases astrocyte-mediated spinal neuroinflammation in a rat model of oxaliplatin-induced pain. Inflammation. 2017;40:2052–61.

27. Bourne RS, Mills GH, Minelli C. Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. Crit Care. 2008;12:R52.

28. Wade A, Downie S. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. Curr Med Res Opin. 2011;17:1567–72.

29. Liu J, Zhong R, Xiong W, et al. Melatonin increases reactive aggression in humans. Psychopharmacology (Berl). 2017;234:2971–8.

30. Ulugol A, Dokmeci D, Guray G, et al. Antihyperalgesic, but not antiallodynic, effect of melatonin in nerve-injured neuropathic mice: Possible involvements of the l-arginine-NO pathway and opioid system. Life Sci. 2006;78:1592–7.