**The association between melatonin and episodic migraine: a pilot network meta-analysis of randomized controlled trials to compare the prophylactic effects with exogenous melatonin supplementation and pharmacotherapy**

*Running title: NMA of melatonin and migraine*

Ping-Tao Tsenga,b,c,1, Chun-Pai Yangd,e, Kuan-Pin Suf,g, Tien-Yu Chenh,i, Yi-Cheng Wu j, Yu-Kang Tuk,l, Pao-Yen Linm,n, Brendon Stubbs o,p,q, Andre F. Carvalho r,s, Yutaka J. Matsuoka f,t, Dian-Jeng Li u, Chih-Sung Liang v,w, Chih-Wei Hsum, Yen-Wen Chenb, Yow-Ling Shiuec,\*

a WinShine Clinics in Specialty of Psychiatry, Kaohsiung, Taiwan

b Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung, Taiwan

c Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

d Department of Neurology, Kuang Tien General Hospital, Taichung, Taiwan

e Department of Nutrition, Huang-Kuang University, Taichung, Taiwan

f Department of Psychiatry & Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

g College of Medicine, China Medical University, Taichung, Taiwan

h Department of Psychiatry, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan

i Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

j Department of Sports Medicine, Landseed International Hospital, Taoyuan, Taiwan

k Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

l Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan

m Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

n Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital

o Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK

p Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK

q Positive Ageing Research Institute (PARI), Faculty of Health, Social Care Medicine and Education, Anglia Ruskin University, Chelmsford, UK

r Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

s Centre for Addiction & Mental Health (CAMH), Toronto, Ontario, Canada

t Division of Health Care Research, Center for Public Health Sciences, National Cancer Center Japan, Tokyo, Japan

u Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung City, Taiwan

v Department of Psychiatry, Beitou branch, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei, Taiwan

w Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan

1: contributed as first author

\*: contributed as corresponding author

**\* Please corresponding to:**

Shiue, Yow-Ling, PhD

Professor, Institute of Biomedical Sciences

National Sun Yat-sen University

Address: 70 Lienhai Rd. 80424 Kaohsiung, Taiwan

Tel: +886-7-525-2000 ext. 5818; +886-915-515-971

Fax: +886-7-525-0197

Email: shirley@imst.nsysu.edu.tw

**Abstract**

Although exogenous melatonin supplementation has been suggested to be effective for episodic migraine prophylaxis, there is no conclusive evidence comparing the efficacy of exogenous melatonin supplementation to the other FDA-approval pharmacotherapy for episodic migraine prophylaxis. The aim of the current network meta-analysis (NMA) was to compare the efficacy of exogenous melatonin supplementation in patients with episodic migraine.The randomized controlled trials (RCTs) of placebo-controlled or trials incorporating a placebo in the study designs were eligible for our analyses. All of the NMA procedures were conducted under the frequentist model. The primary outcome was changes in frequency of migraine days and response rate after migraine prophylaxis with melatonin supplementation or pharmacologic interventions. We included 25 RCTs in total with 4499 patients (mean age = 36.0 years, mean female proportion = 78.9%). The NMA demonstrated that migraine prophylaxis with oral melatonin 3 mg/day (immediate release) at bedtime was associated with the greatest improvement in migraine frequency [mean difference = -1.71 days, 95% confidence interval (CI): -3.27 to -0.14 days compared to placebo] and the second highest response rate (odds ratio = 4.19, 95% CI = 1.46 to 12.00 compared to placebo). Furthermore, oral melatonin 3 mg (immediate-release) at bedtime was the most preferred pharmacologic intervention among all of the investigated interventions when improvements in migraine frequency, response rate, drop-out rate, and rates of any adverse events were taken into account. This pilot NMA suggests the potential prophylactic role of exogenous melatonin supplementation in patients with episodic migraine.

*Keywords: network meta-analysis; melatonin; sleep; migraine; circadian rhythm.*

**1. INTRODUCTION**

Episodic migraine affects 12-20% of the global population,1 contributing to a substantially impaired quality of life in both adult and pediatric patients. Although the mechanism of migraine remains unclear, many different prophylactic agents have been proposed for patients with episodic migraine, including medications dealing with neurogenic pain,2 anticonvulsants,3 and antidepressants.4 However, most of these prophylactic agents do not provide satisfactory responses and cause unwanted adverse events.4

Melatonin is endogenously secreted from the pineal gland and plays an important role in modulating the circadian rhythm.5 Melatonin could theoretically be beneficial for migraine prophylaxis through its biological characteristics, including antioxidation effects, modulating dopamine and glutamine activity, and suppressing calcitonin gene-related peptide release.6,7 However, evidence from randomized controlled trials (RCTs) has not conclusively supported the benefits of melatonin in migraine prophylaxis.8-10 Specifically, although exogenous melatonin supplementation has been proven to provide beneficial treatment effects on migraine frequency and intensity compared to placebo in patients with episodic migraine,9,10 the results from other RCTs have not supported this beneficial effect.8 Bedtime melatonin supplementation has been shown to significantly reduce the frequency of migraine attacks in patients with episodic migraine compared to placebo,9 but to be inferior to the traditional anti-migraine medication, amitriptyline.11 The most recent pair-wise meta-analysis, via pooling all different dosages of exogenous melatonin supplementation into one group, yielded controversial results, which limits its clinical application. Specifically, exogenous melatonin supplementation as migraine prophylaxis has only been associated with significant improvements in migraine frequency and intensity but not response rate compared to placebo.6

Previous studies have shown that exogenous melatonin supplementation exerts different physiological effects depending on the dosage. For example, a low dose is generally thought to have a “high physiological” and “low pharmacological” effect, whereas a high dose is considered to have a “high pharmacological” effect with a sleep-promoting effect.12-15 Therefore, it would be more appropriate to consider different dosages of exogenous melatonin as different groups in clinical practice. Network meta-analysis (NMA) can improve the power of multiple comparisons of the efficacy and superiority of individual pharmacologic interventions of different dosages, thereby providing incremental detailed evidence-based information to guide clinical practice.16 The primary aim of this study was to compare the efficacy of changes of migraine frequency and response rate associated with pharmacologic interventions in patients with episodic migraine.

**2. METHODS**

**2.1 General guidelines applied in the current study**

The current NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension guidelines (eTable 1).17

**2.2 Search strategy and selection criteria**

In the current NMA, our search strategy consisted of two stages. In the first stage, we conducted a systematic review of publications retrieved from PubMed, Embase, ProQuest, ScienceDirect, Cochrane CENTRAL, ClinicalKey, Web of Science, and ClinicalTrials.gov from inception to November 7th, 2019 to search for RCTs of melatonin and melatonergic agents in the management of episodic migraine. In the second stage, to include evidence about the efficacy/safety of the FDA-approved oral forms of agents used for episodic migraine management, we performed an extra search to find RCTs of topiramate, valproate, propranolol, and timolol in the management of migraine. No language restrictions were applied. We also conducted manual searches for potentially eligible articles from the reference lists of review articles or pairwise meta-analysis.6,9,18,19

**2.3 Inclusion and exclusion criteria**

To improve the quality of the included articles and to reduce the unwanted impact of a potential placebo effect (in clinical trials for headache and pain treatment, a placebo effect has been found to be high as high as 40-55%),4,20,21 we only included peer-reviewed formal published articles on RCTs of either placebo-controlled or active-controlled but applied placebo in the study design. The targets of comparison were pharmacologic interventions applied for prophylaxis in patients with episodic migraine (i.e. patients with fewer than 15 migraine attacks per month).

The exclusion criteria were: (1) studies that were not clinical trials in humans, (2) those in which target outcomes were not reported, (3) those not specific to episodic migraine patients, (4) those that were not RCTs, and (5) those not using placebo. In cases of duplicated data (i.e., different articles based on the same sample sources), we only included the reports with more information and larger sample sources.

**2.4 Data extraction**

Two authors (PT Tseng and CP Yang) independently screened the studies, extracted relevant data from the articles, and assessed the risk of bias among the included studies. In cases of discrepancy, the corresponding author (YL Shiue) was involved. Because exogenous melatonin supplementation exerts a different physiology effect according to the dosage (i.e. a low melatonin dosage is generally thought to have a “high physiological” and “low pharmacological” effect, whereas a high dose is considered to have a “high pharmacological” effect with a sleep-promoting effect),12-15 we did not merge all of the melatonin supplementations into one group. If there was a lack of available data in the manuscript, we contacted the corresponding author or co-authors to obtain the original data. We followed the flowchart reported in previous network meta-analyses.15,22-25

**2.5 Outcome definition**

The primary outcome was (1) changes of migraine frequency associated with pharmacologic interventions and (2) the response rate, which was defined as a 50% reduction in baseline frequency of migraine days after pharmacologic interventions. The safety profile was assessed according to drop-outs and any adverse events, where drop-out was defined as leaving the study before its end due to any reason.

**2.6 Cochrane risk-of-bias tool**

Two independent authors (PT Tseng and CP Yang) evaluated the risk of bias (interrater reliability, 0.85) for each domain described in the Cochrane risk-of-bias tool.26 Studies were then further classified in the overall risk of bias category.

**2.7 Statistical analysis**

The NMA was performed using STATA version 14.0 (StataCorp, 4905 Lakeway Drive College Station, Texas 77845, USA). For continuous data, we calculated summary standardized mean differences (SMDs) with 95% confidence intervals (CIs). However, in cases where the same units were used (i.e. the outcomes of migraine frequency or monthly days of acute rescue medication usage), we calculated the summary mean difference (MD) with 95% CIs. For categorical data, we estimated summary odds ratios (ORs) with 95% CIs. For categorical data, we used a 0.5 zero-cell correction during the meta-analysis procedure. However, if in one study both intervention and control arms were zero, we did not apply this correction procedure because of the risk of increasing bias.27,28 We used the frequentist NMA model to compare the effect sizes (ES) among studies with the same interventions. All comparisons were two-tailed, and a *p-*value cut-off point of 0.05 denoted statistical significance. Heterogeneity among the included studies was evaluated using the tau value, which is the estimated standard deviation of the effect across the included studies.

Regarding the meta-analysis procedure applied in the current study, we used mixed comparisons with generalized linear mixed models to analyze the direct and indirect comparisons for NMA.29 Specifically, indirect comparisons could be calculated by transitivity, through which the differences between treatment A and B could be calculated from their comparisons with the third treatment, C. For comparisons among multiple treatment arms, we combined direct and indirect evidence from the included studies.30 The direct evidence between two treatment arms (i.e., treatment A and treatment B) indicated that there was a direct comparison between treatment A and treatment B in at least one of the included studies. On the other hand, the indirect evidence between two treatment arms (i.e., treatment A and treatment C) meant that we obtained the ESs between comparing pairs of treatment A and treatment C through combining the ESs between comparing pairs of treatment A and treatment B and the ESs between comparing pairs of treatment B and treatment C. In the current NMA, we used a suite of STATA programs using mvmeta for data manipulation.31 We used the restricted maximum likelihood method to evaluate between-study variance.32

To increase the clinical application, we calculated relative ranking probabilities between the preventive effects of all treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) is the percentage of the mean rank of each pharmacologic intervention relative to an imaginary intervention that is the best without uncertainty.33 The larger the area under the curve, the lower the rank of the treatment in migraine prophylaxis. We further calculated the joint SUCRA for both co-primary outcomes using an approach previously validated.22 We calculated the “Value preference of SUCRA” = “(SUCRA frequency migraine attack x SUCRA response rate)/(SUCRA drop-out rate x SUCRA any adverse event rate)”. The lower “Value preference of SUCRA” is associated with a better value of the overall preference for the indicated treatment.

We conducted meta-regression to assess the relationships between the migraine response rate and the characteristics of the participants (e.g., mean age, and gender distribution). Finally, we evaluated potential inconsistencies between the direct and indirect evidence within the network using the loop-specific approach, and local inconsistencies using the node-splitting method. Further, we used the design-by-treatment model to evaluate global inconsistencies among the whole NMA.34 We used comparison-adjusted funnel plots35 and Egger regression to evaluate potentially small study effects and publication bias. Finally, we arranged sensitivity analysis focusing RCTs with adult participants.

**3. RESULTS**

**3.1 Eligibility of the retrieved studies and treatment arms**

The Figure 1 depicted the whole flowchart of the current NMA. After the initial screening procedure, a total of 74 articles were considered for full-text review, of which 49 were excluded for various reasons (eTable 2).3,4,6,9,11,18,19,36-77 Finally, 25 articles were included in the current study (eTable 3).8,10,78-100 The overall geometric distribution of the treatment arms is provided in Figures 2A-2B and eFigures 1A-1B.

**3.2 Characteristics of the included studies**

A total of 4499 participants (mean age = 36.0 years, 25**–**75% interquartile = 37.1-40.9 years; mean female proportion = 78.9%, 25-75% interquartile = 73.9-86.1%) were included. The mean follow-up duration was 19.5 weeks (25**–**75% interquartile = 12.0-26.0 weeks). Fourteen of the RCTs recruited adults,8,10,78-89 five recruited children,90-94 and the other six recruited both adults and children.95-100

**3.3 Primary outcome:** **changes of frequency of migraine days**

Seventeen articles with 10 individual pharmacological intervention arms were investigated in the current NMA. Only oral melatonin 3 mg/day (immediate-release) at bedtime (MD = -1.71 days, 95% CI: -3.27 to -0.14 days), valproate (MD = -1.44 days, 95% CI = -2.33 to -0.56 days), and topiramate (MD = -0.80, 95% CI = -1.38 to -0.21) were associated with significantly better improvements in frequency of migraine days than placebo (Table 1 and Figure 3A). According to the SUCRA, oral melatonin 3 mg/day (immediate-release) at bedtime was associated with the greatest improvement in frequency of migraine days among all of the pharmacologic interventions, followed by Botox-A (MD = -1.74 days, 95% CI = -3.62 to 0.14 days compared to placebo group) and valproate (eTable 6). A meta-regression using restricted maximum likelihood estimators was performed to examine the potential effects of age and gender distribution (i.e. female proportion) on changes in migraine frequency. The results of this meta-regression did not reveal a significant effect on changes in migraine frequency when using a moderating variable including age and female proportion. When focusing on RCTs with adult participants in the sensitivity test, the Botox-A, valproate, and oral melatonin 3 mg/day (immediate-release) at bedtime remained to be the three regimens with the greatest improvement in frequency of migraine days among all of the pharmacologic interventions (MD = -2.23 days, 95% CI = -3.60 to -0.85 days; MD = -1.93 days, 95% CI = -2.66 to -1.19 days; MD = -1.60 days, 95% CI = -3.62 to -0.14 days compared to placebo group, respectively).

**3.4 Primary outcome:** **response rate**

The detailed NMA results are shown in Table 2 and Figure 3B. In brief, topiramate *plus* nortriptyline (OR = 9.57, 95% CI =2.17 to 42.21), oral melatonin 3 mg/day (immediate-release) at bedtime (OR = 4.19, 95% CI = 1.46 to 12.00), topiramate (OR = 2.50, 95% CI = 1.77 to 3.54), propranolol (OR = 2.30, 95% CI = 1.26 to 4.21), and valproate (OR = 2.11, 95% CI = 1.28 to 3.46) were associated with significantly higher response rates than placebo. According to the SUCRA, topiramate *plus* nortriptyline was associated with the highest response rate among all of the pharmacologic interventions, followed by oral melatonin 3 mg/day (immediate-release) at bedtime and Botox-A (eTable 7). A meta-regression using restricted maximum likelihood estimators was performed to examine the potential effects of age and gender distribution (i.e. female proportion) on the response rate. The results of this meta-regression did not reveal a significant effect on the response rate when using a moderating variable including age and female proportion. When focusing on RCTs with adult participants in the sensitivity test, the topiramate *plus* nortriptyline, Botox-A, and oral melatonin 3 mg/day (immediate-release) at bedtime remained to be the three regimens with the greatest improvement in frequency of migraine days among all of the pharmacologic interventions (OR = 10.36, 95% CI = 2.54 to 42.24s; OR = 5.15, 95% CI = 1.19 to 22.32; OR = 4.27, 95% CI = 1.65 to 11.08 compared to placebo group, respectively).

**3.5 Safety profile:** **drop-out rate and rate of any adverse event**

We then evaluated the safety profiles of the investigated pharmacologic interventions using the NMA. In brief, none of the investigated pharmacologic interventions were associated with significantly different drop-out rates compared to placebo (eTable 4 and eFigure 2A). In addition, topiramate *plus* nortriptyline (OR = 8.41, 95% CI = 1.78 to 39.70), amitriptyline (OR = 6.98, 95% CI = 2.91 to 16.72), and topiramate (OR = 3.05, 95% CI = 1.91 to 4.86) were associated with significantly higher rates of any adverse event during the pharmacologic intervention than placebo (eTable 5 and eFigure 2B). According to SUCRA, oral melatonin 2 mg (prolonged release) at bedtime was associated with the lowest drop-out rate (OR = 0.18, 95% CI = 0.01 to 4.09 compared to placebo) (eTable 8) and the lowest rate of any adverse event (OR = 0.54, 95% CI = 0.09 to 3.34 compared to placebo) among all of the investigated pharmacologic interventions (eTable 9).

**3.6 Overall preferred pharmacologic interventions considering improvements in frequency of migraine days, response rate, drop-out rate, and rate of any adverse events (count with “Value preference of SUCRA”)**

According to the calculated “Value preference of SUCRA”, oral melatonin 3 mg/day (immediate-release) at bedtime was the most preferred pharmacologic intervention among all of the investigated interventions (“Value preference of SUCRA” = 0.102323) (eTable 10).

**3.7 Risk of bias and publication bias**

We found that 57.2% (100/175 items), 27.4% (48/175 items), and 15.4% (27/175 items) of the included studies had an overall low, unclear, and high risk of bias, respectively. The funding sources and concealing procedure after randomization mainly contributed to the high and unclear risk of bias, respectively (eFigures 3A-3B).

Funnel plots of publication bias across the included studies (eFigures 4-7) revealed general symmetry, and the results of Egger’s test indicated no significant asymmetry that might suggest publication bias among the articles included in the present NMA. In general, inconsistencies, concerning either local inconsistency as assessed using the loop-specific approach and the node-splitting method, or global inconsistency as determined using the design-by-treatment method, were not demonstrated in the present NMA (eTables 11-13). The results of GRADE evaluation had been listed in the eTable 14.

**4. DISCUSSION**

To the best of our knowledge, the current pilot NMA is the first to investigate associations between the effects of episodic migraine prophylactics with melatonergic agents compared to other FDA-approved agents. The results of this study demonstrated that oral melatonin 3 mg (immediate-release) at bedtime was associated with the greatest improvements in migraine frequency for episodic migraine prophylaxis, and that it had the second highest response rate. Furthermore, with regards to the safety profile, oral melatonin 2 mg (prolonged-release) at bedtime was associated with the lowest drop-out rate and the lowest rate of any adverse events among all of the investigated pharmacologic interventions. Finally, when considering improvements in migraine frequency, response rate, drop-out rate, and rate of any adverse events (count with “Value preference of SUCRA”) as a whole, oral melatonin 3 mg/day (immediate-release) at bedtime was the most preferred pharmacologic intervention among all of the investigated interventions.

The main result of the current NMA is that a high dosage (up to 3 mg/day immediate-release) of melatonin at bedtime was associated with the greatest improvements in migraine frequency for episodic migraine prophylaxis, but that this was not found with a lower dosage (2 mg/day prolonged-release). Many studies have reported an association between migraine features and sleep disturbance,101 and the timing of migraine attacks has also been associated with circadian periodicity.102 In addition, physiological plasma melatonin levels in patients with migraine have been reported to display a diurnal phase delay in melatonin peak compared to controls, suggesting chronobiological dysfunction in patients with chronic migraine.103 Similar findings have been reported of significantly lower concentrations of urinary melatonin or its metabolites in patients with migraine104 and those with menstrual migraine throughout the whole menstrual cycle than controls.105 The rationale for using exogenous melatonin supplementation for migraine prophylaxis could be supported by evidence of several of its biological effects.19 In addition to anti-inflammatory properties (through reducing toxic free radicals), neurotransmitter modulation (i.e. dopamine, serotonin, and glutamine), antinociceptive effects (through modulation of brainstem descending antinociceptive pathways via the mediating effect of MT2 receptors),106,107 and cerebrovascular regulation,10,108 another important rationale for using melatonin supplementation as migraine prophylaxis is modulation of the circadian rhythm. Exogenous melatonin supplementation could modulate activity of the suprachiasmatic nucleus (SCN) by acting on the hypothalamic-pineal axis, thereby correcting abnormal circadian rhythm.109 With regards to migraine following insomnia, melatonin may contribute to a sleep-promoting effect through melatonin 1a receptors in the SCN.14 Higher dosages of melatonin and immediate-release preparations have been shown to be more suitable for promoting sleep14 and phase shifting modulation,8 respectively. This would support the phenomenon observed in the current NMA that immediate-release high dosage (up to 3 mg/day) melatonin provided superior benefits with regards to improvements in migraine frequency for episodic migraine prophylaxis compared to the other investigated interventions.

Considering improvements in frequency of migraine days, response rate, drop-out rate, and rate of any adverse events overall, oral melatonin 3 mg/day (immediate-release) at bedtime was the most preferred pharmacologic intervention among all of the investigated interventions. This is consistent with previous studies7 which have demonstrated a favorable safety profile compatible with placebo8 or superior to other traditional medications.3,10 This finding also reflects another clinically relevant fact that the high rates of adverse events with traditional pharmacologic regimens such as topiramate, valproate, and propranolol in episodic migraine prophylaxis may limit the options of a clinician when managing episodic migraine.110 Therefore, the evidence from the current pilot NMA may provide a rationale for future large-scale RCTs to investigate the potential role of exogenous melatonin supplementation in episodic migraine prophylaxis.

The current pilot NMA has several strengths. First, due to the large numbers of included RCTs and participants (25 RCTs and 4499 participants), the current pilot NMA could provide more information and higher evidence than RCTs and traditional meta-analyses. Second, we only included RCTs and trials using placebo to increase the reliability of the current study. As addressed before, in pain and headache research, the placebo effect has been reported to account for 40-55% of the treatment effect.4,20,21 Third, to be more clinically applicable, we performed extra searches to include RCTs of FDA-approved regimens in the current study, which could help clinicians to make relevant comparisons with traditional pharmacologic interventions.

There are also several limitations to the current NMA. First, some analyses in this study were limited by underpowered statistics, including heterogeneity in the characteristics of the participants (e.g., underlying diseases, different concomitant medications, wide variety of ages, lack of uniform diagnostic criteria for migraine, and trial duration) and the small number of trials for some treatment arms. Second, because of the weak network structure, the results of the current NMA should be interpreted with caution. Third, although we tried to investigate the efficacy of different dosages of exogenous melatonin supplementation in episodic migraine prophylaxis, we could only investigate two dosages because of the limited number of RCTs available. Future studies focusing on different dosages of exogenous melatonin supplementation are warranted to assess their efficacy. Finally, although our study is strengthened by comparing different treatments with NMA, the generalization of our results are still highly limited depending on the studies included and the possible comparisons within them. Future studies are warranted to assess the efficacy of melatonergic agents, focusing on the optimal dosage and treatment duration, for the prevention of episodic migraine in different medical settings. Clinicians should consider specific preventive strategies in specific clinical conditions.

The current pilot NMA suggests that prophylactic melatonergic agents was associated with reduction of the frequency of migraine, improvement of the response rate of migraine, and good safety profiles. Oral melatonin 3 mg (immediate-release) at bedtime was the most preferred pharmacologic intervention among all of the investigated interventions when taking improvements in frequency of migraine days, response rate, drop-out rate, and rate of any adverse events into account. Our findings provide a rationale for designing future large-scale RCTs to investigate associations between circadian rhythm regulation, sleep-promoting effects, antioxidation effects, and preventive effects conferred by melatonergic agents in subjects with episodic migraine.

**Declaration of Interest**

The authors report no financial interests or potential conflicts of interest.

**Acknowledgements**

The authors of this work were supported by the following grants: Brendon Stubbs is supported by a Clinical Lectureship (ICA-CL-2017-03-001) jointly funded by Health Education England (HEE) and the National Institute for Health Research (NIHR). Brendon Stubbs is part funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust. Brendon Stubbs is also supported by the Maudsley Charity, King’s College London. This paper presents independent research. The views expressed in this publication are those of the authors and not necessarily those of the acknowledged institutions.

**Author contribution:**

Ping-Tao Tseng, the first author, took the responsibility of literature search, data extraction, risk of bias evaluation, and manuscript draft and had full access to the data.

Chun-Pai Yang, the second author, took the responsibility of literature search, data extraction, and risk of bias evaluation.

Kuan-Pin Su, Tien-Yu Chen, Pao-Yen Lin, Brendon Stubbs, Andre F. Carvalho, Yutaka J. Matsuoka, Dian-Jeng Li, Chih-Sung Liang, Chih-Wei Hsu, and Yen-Wen Chen, all contributed in concept formation, study design, and literature revision.

Yi-Cheng Wu and Yu-Kang Tu, the specialist of statistics, took responsibility of supervision data analysis.

Yow-Ling Shiue, the corresponding author, took the full responsibility of data collection, manuscript revision, and submitting manuscript.

**Figure 1: Flowchart of the current network meta-analysis**

**Figure 2: Network structure of the primary outcome: (2A) changes in migraine frequency; (2B) response rate**

The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.

**Figure 3: Forest plot of the primary outcome in reference to placebo: (3A) changes in migraine frequency; (3B) response rate**

Specific medications were associated with (3A) better improvements in migraine frequency than the placebo if the mean difference was less than 0 (unit: day) or (3B) better response rate than the placebo if the odds ratio was higher than 1.

*Abbreviation: Abbreviation: Ami: amitriptyline; Bot: botox-A; CI: confidence interval; Cyc: cyclandelate; ES: effect size; Lam: lamotrigine; MD: mean difference; Me3mg: oral melatonin 3mg (immediate-release) at bedtime; Mel2mg: oral melatonin 2mg (prolong-release) at bedtime; NMA: network meta-analysis; Nor: nortriptyline; Pla: placebo; Pro: propranolol; RCT: randomized controlled trial; Top: topiramate; Val: valproate*

**REFERENCES**

1. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry.* 2010;81(4):428-432.

2. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain.* 2013;154 Suppl 1.

3. Ebrahimi-Monfared M, Sharafkhah M, Abdolrazaghnejad A, Mohammadbeigi A, Faraji F. Use of melatonin versus valproic acid in prophylaxis of migraine patients: A double-blind randomized clinical trial. *Restor Neurol Neurosci.* 2017;35(4):385-393.

4. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. *N Engl J Med.* 2017;376(2):115-124.

5. Valdes-Tovar M, Estrada-Reyes R, Solis-Chagoyan H, et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. *Br J Pharmacol.* 2018;175(16):3200-3208.

6. Long R, Zhu Y, Zhou S. Therapeutic role of melatonin in migraine prophylaxis: A systematic review. *Medicine (Baltimore).* 2019;98(3):e14099.

7. Fallah R, Shoroki FF, Ferdosian F. Safety and efficacy of melatonin in pediatric migraine prophylaxis. *Curr Drug Saf.* 2015;10(2):132-135.

8. Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI. Prophylaxis of migraine with melatonin: a randomized controlled trial. *Neurology.* 2010;75(17):1527-1532.

9. Gelfand AA, Goadsby PJ. The Role of Melatonin in the Treatment of Primary Headache Disorders. *Headache.* 2016;56(8):1257-1266.

10. Goncalves AL, Martini Ferreira A, Ribeiro RT, Zukerman E, Cipolla-Neto J, Peres MF. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry.* 2016;87(10):1127-1132.

11. Fallah R, Fazelishoroki F, Sekhavat L. A Randomized Clinical Trial Comparing the Efficacy of Melatonin and Amitriptyline in Migraine Prophylaxis of Children. *Iran J Child Neurol.* 2018;12(1):47-54.

12. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ.* 2006;332(7538):385-393.

13. Brzezinski A, Vangel MG, Wurtman RJ, et al. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev.* 2005;9(1):41-50.

14. Sack RL, Hughes RJ, Edgar DM, Lewy AJ. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep.* 1997;20(10):908-915.

15. Yang CP, Tseng PT, Pei-Chen Chang J, Su H, Satyanarayanan SK, Su KP. Melatonergic agents in the prevention of delirium: A network meta-analysis of randomized controlled trials. *Sleep Med Rev.* 2019;50:101235.

16. Higgins JP, Welton NJ. Network meta-analysis: a norm for comparative effectiveness? *Lancet.* 2015;386(9994):628-630.

17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.

18. Rosenberg K. Melatonin: Safe And Effective for the Prevention of Migraine Headache. *Am J Nurs.* 2016;116(9):69.

19. Peres MF, Masruha MR, Zukerman E, Moreira-Filho CA, Cavalheiro EA. Potential therapeutic use of melatonin in migraine and other headache disorders. *Expert Opin Investig Drugs.* 2006;15(4):367-375.

20. Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. *Cephalalgia.* 2009;29(4):436-444.

21. Faria V, Linnman C, Lebel A, Borsook D. Harnessing the placebo effect in pediatric migraine clinic. *J Pediatr.* 2014;165(4):659-665.

22. Hsieh MT, Tseng PT, Wu YC, et al. Effects of different pharmacologic smoking cessation treatments on body weight changes and success rates in patients with nicotine dependence: A network meta-analysis. *Obes Rev.* 2019.

23. Tu YK, Faggion CM, Jr. A primer on network meta-analysis for dental research. *ISRN Dent.* 2012;2012:276520.

24. Wu YC, Tseng PT, Tu YK, et al. Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium: A Network Meta-analysis. *JAMA Psychiatry.* 2019.

25. Zeng BS, Lin SY, Tu YK, et al. Prevention of Postdental Procedure Bacteremia: A Network Meta-analysis. *J Dent Res.* 2019;98(11):1204-1210.

26. Higgins J. GS. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2.* The Cochrane Collaboration; 2009.

27. Cheng J, Pullenayegum E, Marshall JK, Iorio A, Thabane L. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. *BMJ Open.* 2016;6(8):e010983.

28. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. *Stat Med.* 2014;33(28):4861-4874.

29. Tu YK. Use of generalized linear mixed models for network meta-analysis. *Med Decis Making.* 2014;34(7):911-918.

30. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23(20):3105-3124.

31. White IR. Network meta-analysis. *The Stata Journal.* 2015;15:951-985.

32. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. *PLoS One.* 2013;8(7):e69930.

33. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;64(2):163-171.

34. Higgins JP, Del Giovane C, Chaimani A, Caldwell DM, Salanti G. Evaluating the Quality of Evidence from a Network Meta-Analysis. *Value Health.* 2014;17(7):A324.

35. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One.* 2013;8(10):e76654.

36. Nagtegaal JE, Smits MG, Swart AC, Kerkhof GA, van der Meer YG. Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. *Headache.* 1998;38(4):303-307.

37. Plasencia-Garcia BO, Romero-Guillena SL, Quiros-Lopez A, Ruiz-Doblado S. Agomelatine and migraine management: a successfully treated case series. *Ther Adv Psychopharmacol.* 2015;5(4):243-245.

38. Mei D, Ferraro D, Zelano G, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol.* 2006;29(5):269-275.

39. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia.* 2014;34(7):523-532.

40. Apostol G, Pakalnis A, Laforet GA, et al. Safety and tolerability of divalproex sodium extended-release in the prophylaxis of migraine headaches: results of an open-label extension trial in adolescents. *Headache.* 2009;49(1):36-44.

41. Brandes JL, Kudrow DB, Rothrock JF, Rupnow MF, Fairclough DL, Greenberg SJ. Assessing the ability of topiramate to improve the daily activities of patients with migraine. *Mayo Clin Proc.* 2006;81(10):1311-1319.

42. Dahlof C, Loder E, Diamond M, Rupnow M, Papadopoulos G, Mao L. The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. *Health Qual Life Outcomes.* 2007;5:56.

43. Diamond M, Dahlof C, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache.* 2005;45(8):1023-1030.

44. Freitag FG, Forde G, Neto W, et al. Analysis of pooled data from two pivotal controlled trials on the efficacy of topiramate in the prevention of migraine. *J Am Osteopath Assoc.* 2007;107(7):251-258.

45. Green MW, Giordano S, Jiang P, Jafari M, Smith TB. Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. *Headache.* 2005;45(8):1031-1037.

46. Limmroth V, Biondi D, Pfeil J, Schwalen S. Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache. *Headache.* 2007;47(1):13-21.

47. Lofland JH, Gagne JJ, Pizzi LT, Rupnow M, Silberstein SD. Impact of topiramate migraine prophylaxis on workplace productivity: results from two US randomized, double-blind, placebo-controlled, multicenter trials. *J Occup Environ Med.* 2007;49(3):252-257.

48. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. *Headache.* 2006;46(7):1151-1160.

49. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. *Curr Med Res Opin.* 2006;22(6):1021-1029.

50. Drummond PD. Effect of tryptophan depletion on symptoms of motion sickness in migraineurs. *Neurology.* 2005;65(4):620-622.

51. Citera G, Arias MA, Maldonado-Cocco JA, et al. The effect of melatonin in patients with fibromyalgia: a pilot study. *Clin Rheumatol.* 2000;19(1):9-13.

52. Genazzani AR, Sandrini G, Facchinetti F, et al. Effects of L-5HTP with and without carbidopa on plasma beta-endorphin and pain perception. Possible implications in migraine prophylaxis. *Cephalalgia.* 1986;6(4):241-245.

53. Genazzani AR, Sandrini G, Facchinetti F, et al. Effects of L-5HTP with and without carbidopa on plasma beta-endorphin and pain perception: possible implications in migraine prophylaxis. *Cephalalgia.* 1986;6(3):175-179.

54. Bougea A, Spantideas N, Lyras V, Avramidis T, Thomaidis T. Melatonin 4 mg as prophylactic therapy for primary headaches: a pilot study. *Funct Neurol.* 2016;31(1):33-37.

55. Miano S, Parisi P, Pelliccia A, Luchetti A, Paolino MC, Villa MP. Melatonin to prevent migraine or tension-type headache in children. *Neurol Sci.* 2008;29(4):285-287.

56. Peres MF, Zukerman E, da Cunha Tanuri F, Moreira FR, Cipolla-Neto J. Melatonin, 3 mg, is effective for migraine prevention. *Neurology.* 2004;63(4):757.

57. Sicuteri F. The ingestion of serotonin precursors (L-5-hydroxytryptophan and L-tryptophan) improves migraine headache. *Headache.* 1973;13(1):19-22.

58. Whewell J. Methysergide in prophylaxis of migraine: a clinical trial in general practice. *Br Med J.* 1966;2(5510):394-395.

59. al-Qassab HK, Findley LJ. Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo controlled study. *Cephalalgia.* 1993;13(2):128-131.

60. Ashrafi MR, Shabanian R, Zamani GR, Mahfelati F. Sodium Valproate versus Propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol.* 2005;9(5):333-338.

61. Boiardi A, Picotti GB, Di Giulio AM, et al. Platelet met-enkephalin immunoreactivity and 5-hydroxytryptamine concentrations in migraine patients: effects of 5-hydroxytryptophan, amitriptyline and chlorimipramine treatment. *Cephalalgia.* 1984;4(2):81-84.

62. Couch JR, Amitriptyline Versus Placebo Study G. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache.* 2011;51(1):33-51.

63. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol.* 1979;36(11):695-699.

64. de Tommaso M, Guido M, Sardaro M, et al. Effects of topiramate and levetiracetam vs placebo on habituation of contingent negative variation in migraine patients. *Neurosci Lett.* 2008;442(2):81-85.

65. de Tommaso M, Marinazzo D, Nitti L, et al. Effects of levetiracetam vs topiramate and placebo on visually evoked phase synchronization changes of alpha rhythm in migraine. *Clin Neurophysiol.* 2007;118(10):2297-2304.

66. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia.* 1992;12(2):81-84.

67. Lakshmi CV, Singhi P, Malhi P, Ray M. Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. *J Child Neurol.* 2007;22(7):829-835.

68. Santucci M, Cortelli P, Rossi PG, Baruzzi A, Sacquegna T. L-5-hydroxytryptophan versus placebo in childhood migraine prophylaxis: a double-blind crossover study. *Cephalalgia.* 1986;6(3):155-157.

69. Shahnawaz K, Mughal BB, Madni B, Malhi KA, Siddiqui MA. Comparison of efficacy and tolerability of melatonin and amitriptyline in children suffering with migraine. *Medical Forum Monthly.* 2019;30(5):12-15.

70. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology.* 2004;63(2):261-269.

71. Titus F, Davalos A, Alom J, Codina A. 5-Hydroxytryptophan versus methysergide in the prophylaxis of migraine. Randomized clinical trial. *Eur Neurol.* 1986;25(5):327-329.

72. Bono G, Criscuoli M, Martignoni E, Salmon S, Nappi G. Serotonin precursors in migraine prophylaxis. *Adv Neurol.* 1982;33:357-363.

73. De Benedittis G, Massei R. Serotonin precursors in chronic primary headache. A double-blind cross-over study with L-5-hydroxytryptophan vs. placebo. *J Neurosurg Sci.* 1985;29(3):239-248.

74. Nicolodi M, Sicuteri F. L-5-hydroxytryptophan can prevent nociceptive disorders in man. *Adv Exp Med Biol.* 1999;467:177-182.

75. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded crossover study. *Headache.* 2006;46(4):642-648.

76. Hershey AD, Powers SW, Coffey CS, et al. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. *Headache.* 2013;53(5):799-816.

77. Ghaderibarmi F, Tavakkoli N, Togha M. Intravenous Valproate versus Subcutaneous Sumatriptan in Acute Migraine Attack. *Acta Med Iran.* 2015;53(10):633-636.

78. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. *Headache.* 2008;48(2):210-220.

79. Diener HC, Tfelt-Hansen P, Dahlof C, et al. Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. *J Neurol.* 2004;251(8):943-950.

80. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther.* 2009;31(3):542-559.

81. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol.* 1997;54(9):1141-1145.

82. Krymchantowski AV, da Cunha Jevoux C, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. *J Headache Pain.* 2012;13(1):53-59.

83. Lipton RB, Silberstein S, Dodick D, et al. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. *Cephalalgia.* 2011;31(1):18-30.

84. Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. *Clin Ther.* 2006;28(7):1002-1011.

85. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. *Headache.* 2001;41(10):968-975.

86. Diener HC, Foh M, Iaccarino C, et al. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. *Cephalalgia.* 1996;16(6):441-447.

87. Edwards KR, Potter DL, Wu SC, Kamin M, Hulihan J. Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. *CNS Spectr.* 2003;8(6):428-432.

88. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology.* 1994;44(4):647-651.

89. Mei D, Capuano A, Vollono C, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurol Sci.* 2004;25(5):245-250.

90. Apostol G, Cady RK, Laforet GA, et al. Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. *Headache.* 2008;48(7):1012-1025.

91. Gelfand AA, Qubty W, Patniyot I, et al. Home-Based Trials in Adolescent Migraine: A Randomized Clinical Trial. *JAMA Neurol.* 2017;74(6):744-745.

92. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. *Pediatrics.* 2009;123(3):924-934.

93. Winner P, Gendolla A, Stayer C, et al. Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. *Headache.* 2006;46(10):1503-1510.

94. Winner P, Pearlman EM, Linder SL, et al. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache.* 2005;45(10):1304-1312.

95. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA.* 2004;291(8):965-973.

96. Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology.* 2002;58(11):1652-1659.

97. Gupta P, Singh S, Goyal V, Shukla G, Behari M. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). *Headache.* 2007;47(3):402-412.

98. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia.* 1997;17(2):103-108.

99. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis with divalproex. *Arch Neurol.* 1995;52(3):281-286.

100. Silberstein SD, Neto W, Schmitt J, Jacobs D, Group M-S. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol.* 2004;61(4):490-495.

101. Alstadhaug K, Salvesen R, Bekkelund S. Insomnia and circadian variation of attacks in episodic migraine. *Headache.* 2007;47(8):1184-1188.

102. Alstadhaug K, Salvesen R, Bekkelund S. 24-hour distribution of migraine attacks. *Headache.* 2008;48(1):95-100.

103. Peres MF, Sanchez del Rio M, Seabra ML, et al. Hypothalamic involvement in chronic migraine. *J Neurol Neurosurg Psychiatry.* 2001;71(6):747-751.

104. Masruha MR, Lin J, de Souza Vieira DS, et al. Urinary 6-sulphatoxymelatonin levels are depressed in chronic migraine and several comorbidities. *Headache.* 2010;50(3):413-419.

105. Brun J, Claustrat B, Saddier P, Chazot G. Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses. *Cephalalgia.* 1995;15(2):136-139; discussion 179.

106. Posa L, De Gregorio D, Gobbi G, Comai S. Targeting Melatonin MT2 Receptors: A Novel Pharmacological Avenue for Inflammatory and Neuropathic Pain. *Curr Med Chem.* 2018;25(32):3866-3882.

107. Lopez-Canul M, Palazzo E, Dominguez-Lopez S, et al. Selective melatonin MT2 receptor ligands relieve neuropathic pain through modulation of brainstem descending antinociceptive pathways. *Pain.* 2015;156(2):305-317.

108. Li SR, Wang T, Wang R, Dai X, Chen Q, Li RD. Melatonin enhances antinociceptive effects of delta-, but not mu-opioid agonist in mice. *Brain Res.* 2005;1043(1-2):132-138.

109. Kalsbeek A, Palm IF, La Fleur SE, et al. SCN outputs and the hypothalamic balance of life. *J Biol Rhythms.* 2006;21(6):458-469.

110. Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn).* 2015;21(4 Headache):973-989.