Systematic Review and Meta-Analysis

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Therapeutic role of melatonin in migraine prophylaxis

A systematic review

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Abstract

Background Melatonin is the "clock factor" generated from pineal gland dominating regular circadian rhythm in humans. Migraine is one of the most severe and debilitating primary headache disorders. Thus far, many diseases have been found to associate with melatonin, including the migraine. Therefore, melatonin's therapeutic potential for migraine is drawing attention.

Objectives The aim of this study is to offer a systematic review of extant data of melatonin in migraine prophylaxis and to provide clinical implications and specific recommendations for future studies.

Data sources and study methods A systematic research was conducted in September 2018 by using PubMed and Google Scholar databases to search for science literature published after 1988.

Results In all, 7 eligible articles were identified, including 4 randomized controlled studies and 3 observational studies. Due to high heterogeneities and limited number of studies, meta-analysis was not feasible, and only systematic review was performed. The results show that present evidence cannot claim melatonin's effectiveness according to the conflicting outcomes; however, the two negative outcomes of melatonin not different from placebo and melatonin inferior to amitriptyline are possible under-powering because of methodological, pharmacological, and therapeutic shortcomings. Observational studies also support melatonin's efficacy in migraine. As a result, melatonin is very likely to benefit migraine in prophylaxis and may have a similar effectiveness to other main preventive medications. Immediate-release melatonin 3 mg was established as effective, melatonin receptor agonist (Agomelatine) 25 mg and prolonged-release melatonin 4 mg were observed efficacious in observational studies. Melatonin displayed ineffective in the 2-month trial; thus, 3 months or more may be an enough duration for migraine therapy. Despite melatonin being generally safe, emerging literature is illustrating that a few severe adverse effects can be caused by melatonin, for example, liver injuries, reproductive system dysfunctions, and detrimental immunostimulation.

Conclusions Melatonin is very likely to be a promising alternative for migraine prophylaxis. Current literature examining melatonin's efficacy in migraine prevention is growing, but still limited. Future studies of perfect design in methodology, pharmacology, and therapeutics are needed to achieve a deeper awareness of melatonin's role in migraine as well as more studies to explore the safety issues of melatonin medicine.

Abbreviations: 5-HT = 5-hydroxytryptamine, AF = attack frequency, aMT6s = 6-sulphatoxymelatonin, CGRP = calcitonin gene-related peptide, CNS = central nervous system, EMA = European Medicines Agency, GABA = γ-aminobutyric acid, HIT-6 = Headache Impact Test-6, ICHD = International Classification of Headache Disorders, MADRS = Montgomery-Asberg Depression Rating Scale, MD = mean difference, MIDAS = Migraine Disability Assessment Score, PSQI = Pittsburgh Sleep Quality Index, RR = rate ratio, Std MD = standard mean difference, VAS = Visual Analogue Scale.

Keywords: melatonin, migraine, systematic review, therapy

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1. Introduction

Melatonin is the "clock factor" generated from pineal gland dominating regular circadian rhythm in humans. In 1958, Turkish scientist Aron B. Lerner first discovered melatonin and successfully extracted it from pineal gland.[1] Synthesis and secretion of melatonin are mainly controlled by suprachiasmatic nucleus in hypothalamus, which is further regulated by light signals transmitting through retinal ganglion cells.[2,3] In night, the secretion dramatically increases in darkness, while pineal gland hardly secretes melatonin in daytime.

The receptors of melatonin, MT1, and MT2 were found to widely exist in cells and tissues. By far, melatonin has been proved related to a number of diseases such as epilepsy, insomnia, depression, Alzheimer's disease, Parkinson's disease, Huntington's disease, cancer, alopecia, obesity, diabetes, ocular pathologies, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's disease, ischemic heart diseases, hypertension, and Stein-Leventhal syndrome.[4–7] Thus, melatonin's therapeutic potentials for primary headache disorders are drawing attention.

As one of the most severe and debilitating primary headache disorders, migraine affects at least 12–20% population in the world.[8] Although the mechanism of migraine remains unclear, most scientists agree that abnormal activation and sensitization of trigeminovascular system play an important role in migraine pathology.[9] Many published articles have demonstrated that melatonin can exert antimigraine effect via a variety of ways. Through free radicals cleaning and inflammatory factors release inhibition, melatonin can protect brain from direct toxic molecule damages and help to maintain brain structural and functional integrity by working as a membrane-stabilizing factor.[10–13] Melatonin can benefit migraine by its regulation on neurotransmitters and neural pathways, for example, restraining nitric oxide synthesis, inhibiting dopamine release, and antagonizing glutamate-induced excitotoxicity, and so on.[14–17] Calcitonin gene-related peptide (CGRP), a powerful vasodilatation factor, its release from trigeminovascular system dramatically increases during migraine attacks resulting in pathological vasodilatation in brain blood vessels. Melatonin can suppress CGRP release, hence regulate blood flow in brain.[18] In addition, melatonin is perceived as a strong analgesic performing powerful pain killing effect in pain syndromes. The analgesic mechanism is considered to be relevant to β-endorphin release increase, melatonin receptors activation, and brain γ-aminobutyric acid energic (GABAergic) system enhancement.[5,12] Moreover, in the presence of similar structure to indomethacin, melatonin may have an indomethacin-like analgesic effect through inhibitions on prostaglandin and pain-producing substances.[5] Melatonin's anxiolytic and antidepressant properties can also help with migrainers' pain feelings, which is achieved via its influence on GABA, 5-hydroxytryptamine (5-HT), N-methyl-D-aspartate receptors, and L-arginine/nitric oxide pathway.[12,19–22]

Low level of 6-sulphatoxymelatonin (aMT6s), the metabolite of melatonin excreting in the urine, has been found in migraine patients.[23,24]

Melatonin's excellent tolerability makes it a possible favorable candidate for migraine therapy. The adverse events are generally few and mild. It has been reported even at very high doses, melatonin was outstandingly safe causing no serious adverse effects.[25–27]

The purpose of this study is to provide a systematic review of extant literature of melatonin in migraine prophylaxis. Additionally, clinical implications and specific recommendations for future studies are provided.

2. Methods

2.1. Search strategy

A systematic search consistent with the guidelines in Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement was conducted in September 2018 using PubMed and Google Scholar databases. The search strategy focused on science literature published after 1988 when the first edition of International Classification of Headache Disorders (ICHD) was published which first provided a formal and comprehensive definition for migraine. We used the following combination of terms: "melatonin" AND "migraine" OR "migraineur" OR "hemicrania" to search for original clinical experiments of melatonin for migraine prevention. Reference of included articles was assessed, and relevant articles fulfilling inclusion criteria were included. Inclusion criteria were (1) original clinical experiments, (2) fulfilling migraine diagnostic criteria in ICHDs, (3) present in English, and (4) full text available. Data extraction was conducted independently by R.L. and Y.Z.

2.2. Statistical analysis

Risk of bias on randomized controlled trials was assessed by the authors independently using the Risk of Bias table recommended in Cochrane Handbook for Systematic Reviews of Interventions. We used STATA 10.0 software to conduct statistical analysis. The Cochran Q chi-square test and the I^2 statistic were utilized to examine heterogeneity among studies. An I^2 value of $>50\%$ for the Q-statistic was considered as significant heterogeneity. Random-effects model was used when heterogeneity exist as its assumption account for the variability in studies; otherwise, fixed-effects model was used. About the effect estimates, we used mean difference (MD) or standard mean difference (Std MD) for continuous outcome measures and rate ratio (RR) for dichotomous outcome measures. Std MD was utilized in the outcome measure of frequency because there were two types of frequency measures (attack frequency and number of headache days). RR was utilized in the outcome measure of number of responders. Melatonin's effectiveness was estimated by odds and corresponding 95% confidence intervals produced from comparisons between experimental and control groups.

3. Results

In the end, the search strategy identified 7 articles that were considered eligible, including 4 randomized controlled studies and 3 observational studies (Fig. 1). The results of risk of bias are listed in Figure 2. However, meta-analysis on 4 randomized controlled studies presents high heterogeneities, which were listed in Figures 3 and 4. Given the high heterogeneities and limited number of studies, meta-analysis was not feasible. Accordingly, only systematic review was performed. Specific information of 7 articles was given in Table 1, and follow-up stages in the studies were not evaluated in this article.

3.1. Clinical trials

In an early controlled study, prolonged-release melatonin 2 mg was reported not different from placebo.[28] The study was a crossover design, and 48 subjects were enrolled, among whom 26 patients had comorbidity tension-type headaches and 16 patients had comorbidity insomnia. Subjects were assigned randomly to melatonin and placebo groups for an 8-week treatment (phase I).

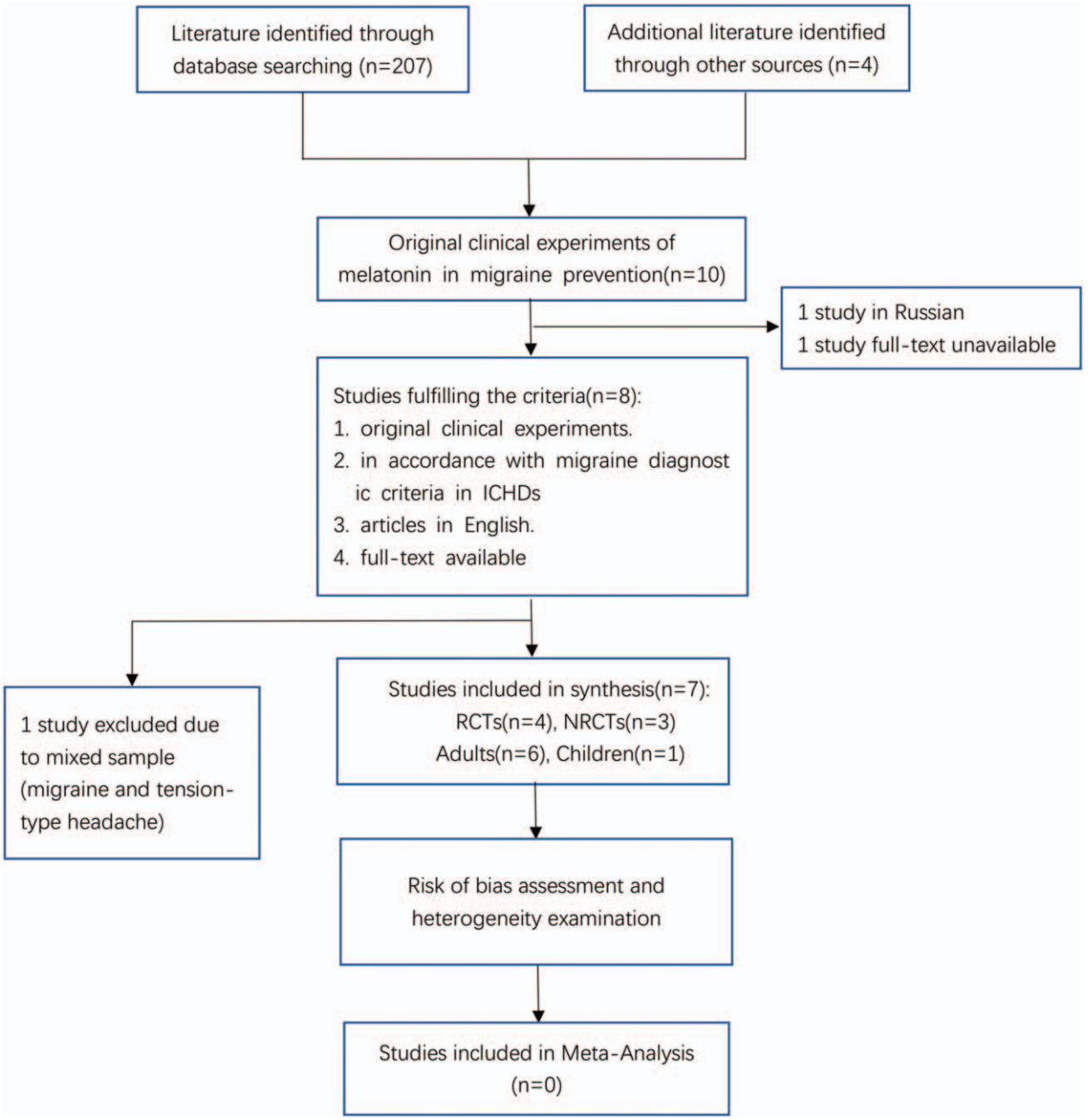

Figure 1. Criteria of selection of studies included in meta-analysis in the literature.

Then, subjects underwent 6-week washout period, later switched to the other group following another 8-week treatment (phase II). Attack frequency (AF) declined to 2.8 ± 1.6 and 2.9 ± 1.6, respectively, in melatonin and placebo groups, from baseline 4.2 ± 1.2. There was no difference between two groups ($P = .75$). In addition, there was no clear benefit of melatonin in Pittsburgh Sleep Quality Index (PSQI) score compared to placebo (4.7 ± 3.2 vs. 5.6 ± 4.1, $P = .09$). However, when evaluating PSQI in insomnia subjects (patients with PSQI > 6 at baseline), melatonin was better than placebo (6.8 ± 4.0 vs. 9.4 ± 4.0, $P < .05$).

A more recent controlled trial reported that melatonin was superior to placebo and as effective as amitriptyline, based on melatonin 3 mg and amitriptyline 25 mg.[29] Though specific pharmaceutical information of melatonin was not provided in the article, it is more likely to be immediate-release melatonin. A total of 196 subjects were enrolled. After 3-month treatment, the number of headache days declined to 4.6 ± 2.3, 5.0 ± 2.5, 6.2 ± 2.5 in melatonin, amitriptyline, and placebo groups, from baseline 7.3 ± 2.8. Headache intensity (on the scale from 0 to 10) declined to 3.6 ± 3.5, 3.5 ± 3.5, and 4.8 ± 3.3, respectively, from baseline 6.9 ± 1.8. Attack duration (hours) declined to 10.9 ± 9.5, 9.8 ± 10.5, and 16.2 ± 15.3, from baseline 17.8 ± 14.5. Number of analgesics taken declined to 2.9 ± 1.7, 3.2 ± 2.0, and 3.6 ± 1.2, from baseline 4.4 ± 1.6. Compared to placebo, both melatonin and amitriptyline were more effective. Melatonin and amitriptyline were equally effective in reducing number of headache days, and comparisons in the other three measures were not mentioned in the study. For the number of responders (patients with a higher

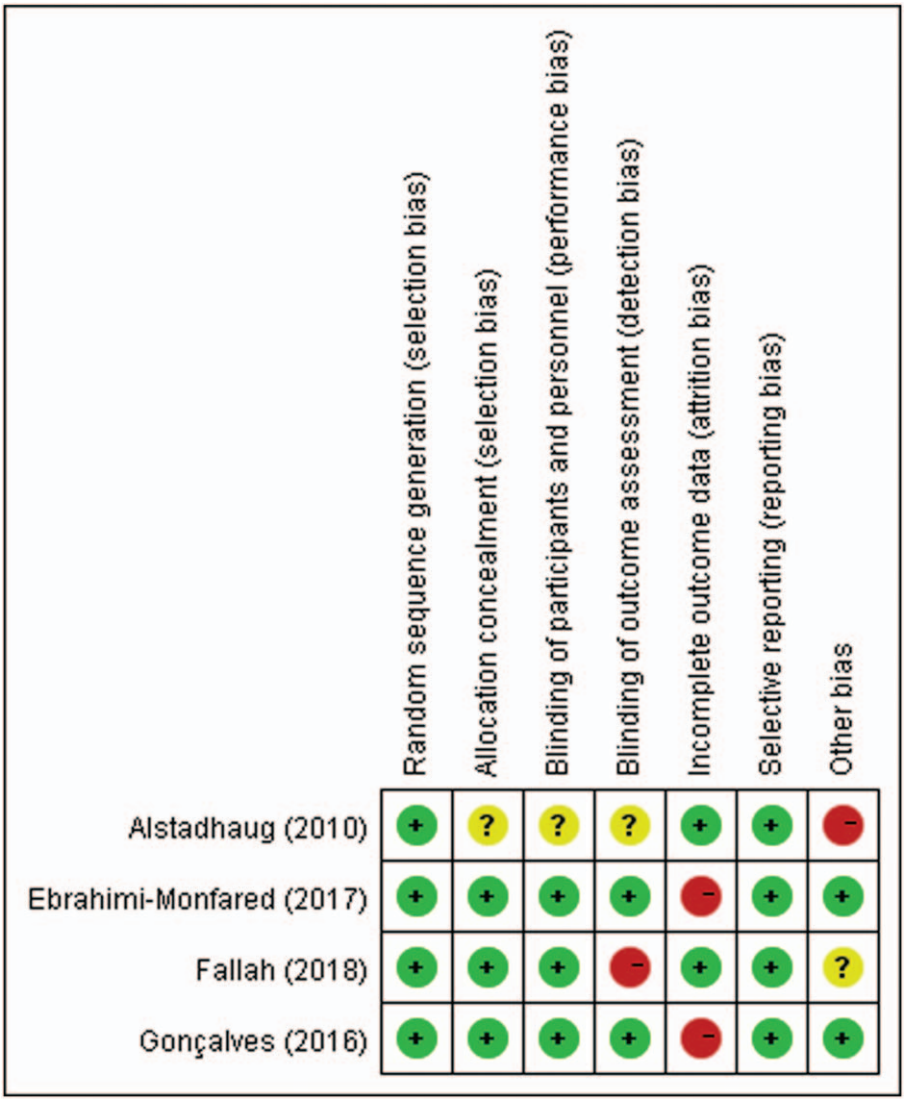

Figure 2. Risk of bias.

than 50% reduction in number of headache days), melatonin was demonstrated superior to amitriptyline and placebo (54.4% vs. 39.1% and 20.4%, $P < .05$).

A controlled study assessing immediate-release melatonin 3 mg against placebo and sodium valproate 200 mg reported that melatonin was superior to placebo and as effective as sodium valproate.[30] A total of 105 subjects underwent treatment for 2 months. Finally, AF declined to 2.5 ± 1.3, 2.3 ± 1.5, and 3.8 ± 1.1 in melatonin, sodium valproate, and placebo groups, respectively, from baseline 4.2 ± 1.2. Attack duration declined to 8.7 ± 12.4, 8.8 ± 9.4, and 14.1 ± 8.1, from baseline 19.7 ± 18.5. Attack severity declined to 3.5 ± 2.6, 3.4 ± 1.7, and 6.0 ± 3.2, from baseline 7.4 ± 1.4. Numbers of analgesic declined to 2.1 ± 2.0, 2.0 ± 0.5, and 4.1 ± 1.1, from baseline 7.3 ± 3.2. Migraine Disability Assessment Score (MIDAS) score declined to 8.9 ± 2.2, 8.3 ± 1.2, and 12.1 ± 4.2, from baseline 15.8 ± 5.1. Compared to baseline, both melatonin and sodium valproate significantly improved migraine, while placebo present no significant therapeutic effect. Melatonin was found had same efficacy as sodium valproate (though some specific *P* values of the comparisons were not provided).

Another controlled study tested melatonin and amitriptyline in a single-blinded trial of 80 children migrainers, without a placebo group.[31] The children were assigned to two groups to receive immediate-release melatonin 0.3 mg/kg or amitriptyline 1 mg/kg/day for 3 months. In the end, AF declined to 9.03 ± 4.47 and 4.28 ± 2.68 in melatonin and amitriptyline groups, respectively, from baseline 16.25 ± 7.6. Headache intensity declined to 4.03 ± 1.54 and 2.25 ± 1.21, from baseline 6.23 ± 1.65. Headache duration declined to 1.41 ± 0.41 and 0.56 ± 0.51, from baseline 2.16 ± 1.54. MIDAS score declined to 23.38 ± 9.51 and 8.28 ± 3.75, from baseline 32.27 ± 9.23. Number of analgesic usage declined to 7.22 ± 2.81 and 6.11 ± 2.7, from baseline 12.78 ± 3.33. In total, 25 (62.5%) and 33 (82.5%) responders were seen in melatonin and amitriptyline groups. The results indicated that amitriptyline was more effective than melatonin in improving attack frequency, intensity, duration, disability of headache, and number of responders. And the number of analgesic usage was not statistically different between two groups.

Three observational studies reported melatonin was effective in migraine prevention, headache was significantly improved compared to baseline.[32–34] One of the studies, conducting

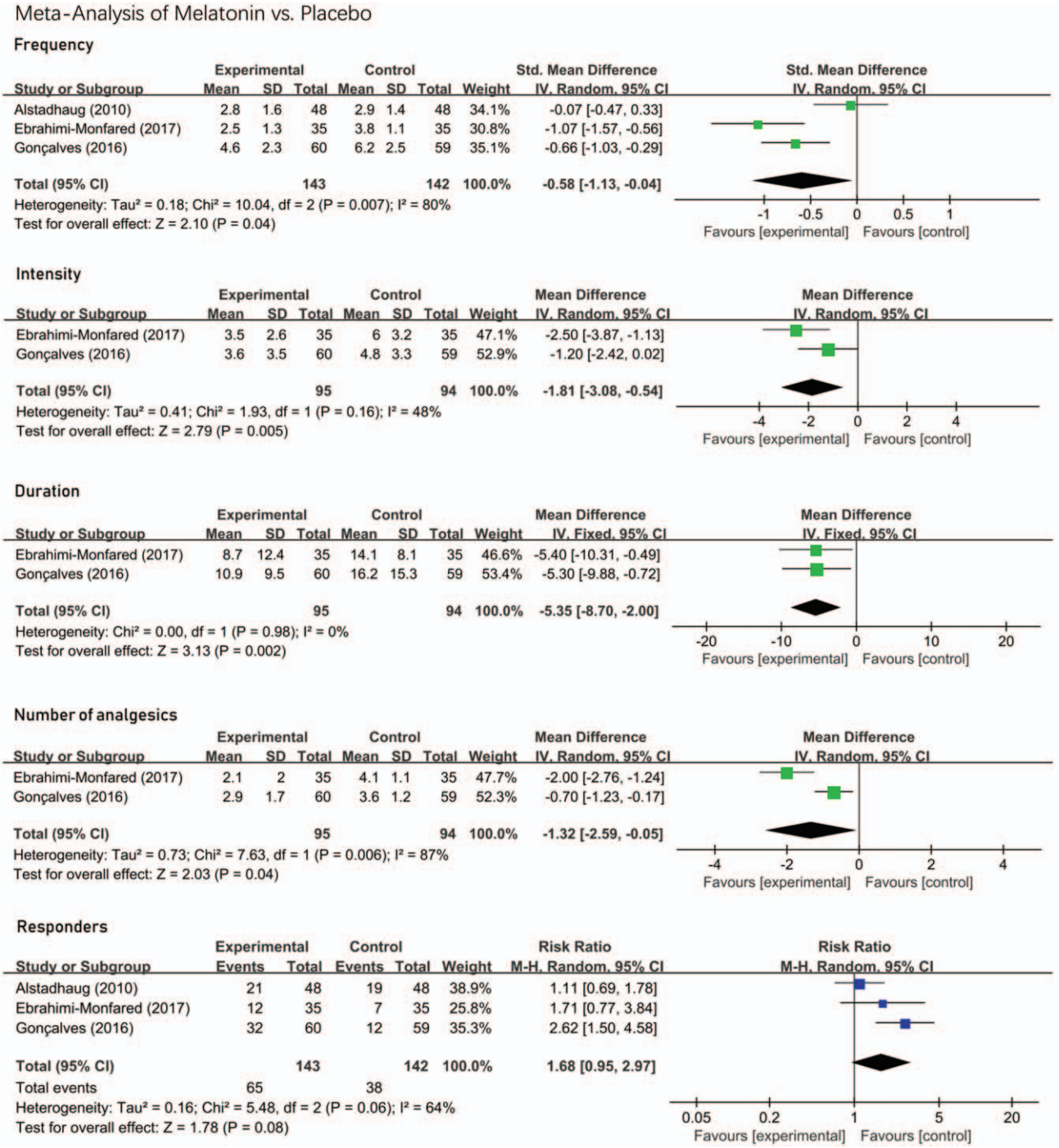

Figure 3. Meta-analysis of melatonin vs. placebo.

immediate-release melatonin 3 mg on 34 subjects for 3 months, found AF declined to 3.0 ± 3.1 from 7.6 ± 3.2 and headache intensity declined to 3.6 ± 2.7 from 7.4 ± 1.3. Twenty five (73.5%) of responders were observed. Consumption of analgesics and triptan pharmaceuticals also significantly reduced. Another study of prolonged-release melatonin 4 mg was taken on migraine and tension-type headache patients. Thirty seven migraine patients received a 6-month treatment. AF declined to 2.18 ± 0.84 from 4.72 ± 0.73, and Headache Impact Test-6 (HIT-6) score declined to 44.37 ± 23.94 from 63.51 ± 5.43. Also, significant reductions in AF and HIT-6 score occurred in 12 tension-type headache patients. Finally, the study of melatonin receptor agonist (Agomelatine) 25 mg recruited 6 migraine patients who had comorbidity depression to receive therapy for 4 months. Four of the 6 subjects received Agomelatine 25 mg during the first 2 months then received 50 mg during the latter 2 months. The outcomes showed that AF declined to 0.7 ± 1.0 from 3.8 ± 1.8, Visual Analogue Scale (VAS) score declined to 2.0 ± 1.4 from 9.0 ± 0.9, and Montgomery-Asberg Depression Rating Scale (MADRS) score declined to 1.2 ± 1.2 from 26.7 ± 3.7. In addition, significant improvement was observed in a few outcome measures by the end of the first month.

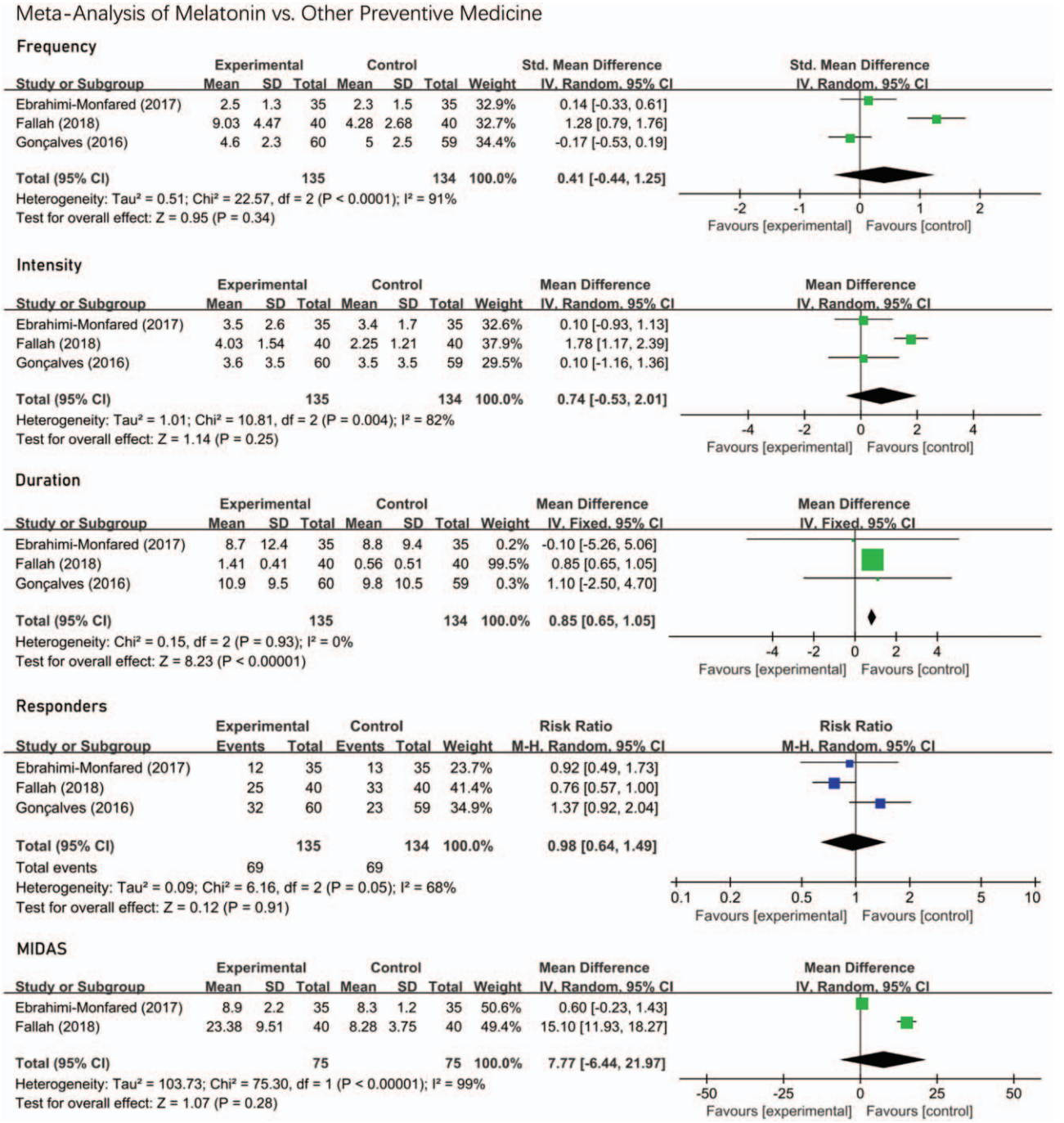

Figure 4. Meta-analysis of melatonin vs. other preventive medications.

3.2. Outcomes

To sum up, in both controlled and uncontrolled studies, compared to baseline, melatonin reduced headache frequency (attack frequency or number of headache days), duration and intensity in general, all the *P* values were significant. Headache frequency decreased by 33%–83%, average 51%. The reduction of headache duration was 32%–56% (average 46%), and headache intensity was 33%–78% (average 53%). Similar reductions in other outcome measures were observed as well. In conclusion, migraine was improved from patients receiving melatonin treatment.

However, melatonin could not demonstrate its prophylactic effects compared to parallel placebo groups due to the contradictory results in three randomized controlled trials. Melatonin showed superior therapeutic efficacy to placebo in Goncalves study (number of headache days 4.6 ± 2.3 vs. 6.2 ± 2.5, duration 10.9 ± 9.5 vs. 16.2 ± 15.3, intensity 3.6 ± 3.5 vs. 4.8 ± 3.3, number of analgesics taken 2.9 ± 1.7 vs. 3.6 ± 1.2, number of responders 54.4% vs. 20.4%, *P* values <.05), and in Mohsen Ebrahimi-Monfared study (AF 2.5 ± 1.3 vs. 3.8 ± 1.1, duration 8.7 ± 12.4 vs. 14.1 ± 8.1, severity 3.5 ± 2.6 vs. 6.0 ± 3.2, number of analgesics taken 2.1 ± 2.0 vs. 4.1 ± 1.1, MIDAS score 8.9 ± 2.2 vs. 12.1 ± 4.2, specific *P* values were not provided). In the trial of Alstadhaug and his colleagues, melatonin was not better than placebo (AF 2.8 ± 1.6 vs. 2.9 ± 1.4, $P = .75$).

Table 1

Characteristics and results of included studies.

Study	Year	Design	Sample size	Drug and dose		Period (months)	Outcomes						
							Measure	Baseline[§]	P[*]	P[†]	Placebo	Melatonin	Other drugs	P[‡]
Alstadhaug KB	2010	Double-blind, placebo-controlled, crossover design	48	Circadin placebo	2 mg	2	Attack frequency	4.2±1.2	<.05	.75	2.9±1.4	2.8±1.6		
							PSQI	6.3±3.8	<.05	.09	5.6±4.1	4.7±3.2		
							PSQI at baseline>6	10.5±2.8	<.05	<.05	9.4±4.0	6.8±4.0		
							Responders[‖]			NS	19 (40%)	21 (44%)		
Conclusion: melatonin was not superior to placebo. (amitriptyline)														
Gonçalves AL	2016	Double-blind, placebo-controlled, parallel design	178	Melatonin amitriptyline placebo	3 mg 25 mg	3	Number of headache days	7.3±2.8	<.05	<.05	6.2±2.5	4.6±2.3	5.0±2.5	NS
							Intensity	6.9±1.8	<.05	<.05	4.8±3.3	3.6±3.5	3.5±3.5	/[¶]
							Duration	17.8±14.5	<.05	<.05	16.2±15.3	10.9±9.5	9.8±10.5	/
							Number of analgesics	4.4±1.6	<.05	<.05	3.6±1.2	2.9±1.7	3.2±2.0	/
							Responders			<.05	12 (20.4%)	32 (54.4%)	23 (39.1%)	<.05
Conclusion: melatonin was superior to placebo and as effective as amitriptyline. (valproate)														
Ebrahimi-Monfared M	2017	Double-blind, placebo-controlled, parallel design	105	Melatonin valproate placebo	3 mg 200 mg	2	Attack frequency	4.2±1.2	<.05	<.05	3.8±1.1	2.5±1.3	2.3±1.5	/
							Intensity	7.4±1.4	<.05	<.05	6.0±3.2	3.5±2.6	3.4±1.7	NS
							Duration	19.7±18.5	<.05	<.05	14.1±8.1	8.7±12.4	8.8±9.4	/
							Number of analgesics	7.3±3.2	<.05	<.05	4.1±1.1	2.1±2	2.0±0.5	NS
							Responders			<.05	7 (20%)	12 (34.28%)	13 (37.14%)	/
							MIDAS	15.8±5.1	<.05	<.05	12.1±4.2	8.9±2.2	8.3±1.2	NS
Conclusion: melatonin was superior to placebo and as effective as sodium valproate. (amitriptyline)														
Razieh Fallah	2018	Single-blind, controlled, parallel design	80 (children)	Melatonin amitriptyline	0.3 mg/kg 1 mg/kg	3	Attack frequency	16.25±7.6	<.05			9.03±4.47	4.28±2.68	<.05
							Intensity	6.23±1.65	<.05			4.03±1.54	2.25±1.21	<.05
							Duration	2.16±1.54	<.05			1.41±0.41	0.56±0.51	<.05
							Number of analgesics	12.78±3.33	<.05			7.22±2.81	6.11±2.7	.5
							Responders					25 (62.5%)	33 (82.5%)	<.05
							MIDAS	32.27±9.23	<.05			23.38±9.51	8.28±3.75	<.05
Conclusion: melatonin was inferior to amitriptyline.														
Peres MF	2004	Uncontrolled	34	Melatonin	3 mg	3	Attack frequency	7.6±3.2	<.05			3.0±3.1		
							Intensity	7.4±1.3	<.05			3.6±2.7		
							Duration	19.8±19.8	<.05			8.8±12.4		
							Responders					25 (73.5%)		
Conclusion: melatonin was effective in migraine prevention.														
Plasencia-García BO	2015	Uncontrolled	6 (Comorbidity depression)	Agomelatine	25/50 mg	4	Attack frequency	3.8±1.8	<.05			0.7±1.0		
							VAS	9.0±0.9	<.05			2.0±1.4		
							MASRS	26.7±3.7	<.05			1.2±1.2		
Conclusion: melatonin was effective in migraine prevention.														
Bougea A	2016	Uncontrolled	37	Circadin	4 mg	6	Attack frequency	4.72±0.73	<.05			2.18±0.84		
							HIT-6	63.51±5.43	<.05			44.37±23.94		
Conclusion: melatonin was effective in migraine prevention.														

HIT-6 = Headache Impact Test-6, MADRS = Montgomery-Asberg Depression Rating Scale, MIDAS = Migraine Disability Assessment Score, NS = not significant, PSQI = Pittsburgh Sleep Quality Index, VAS = Visual Analogue Scale.

[*] Based on the difference between baseline and end of study in melatonin group.

[†] Based on the difference between melatonin and placebo.

[‡] Based on the difference between melatonin and other medication.

[§] Combined baseline values, there was no difference in baseline characteristics between groups in each study.

[‖] Patients with a higher than 50% improvement in headache frequency or number of migraine headache days.

[¶] *P* values were not provided in articles.

Moreover, melatonin was also unable to prove itself better than other main preventive drugs (amitriptyline or valproic acid) because of the conflicting results. Though it was reported not different from amitriptyline or valproic acid in Goncalves study (number of headache days 4.6 ± 2.3 vs. 5.0 ± 2.5, intensity 3.6 ± 3.5 vs. 3.5 ± 3.5, duration 10.9 ± 9.5 vs. 9.8 ± 10.5, number of analgesics taken 2.9 ± 1.7 vs. 3.2 ± 2.0) and in Mohsen Ebrahimi-Monfared study (AF 2.5 ± 1.3 vs. 2.3 ± 1.5, duration 8.7 ± 12.4 vs. 8.8 ± 9.4, severity 3.5 ± 2.6 vs. 3.4 ± 1.7, number of analgesics taken 2.1 ± 2.0 vs. 2.0 ± 0.5, MIDAS score 8.9 ± 2.2 vs. 8.3 ± 1.2), melatonin was considered less effective than amitriptyline in Razieh Fallah study (AF 9.03 ± 4.47 vs. 4.28 ± 2.68, intensity 4.03 ± 1.54 vs. 2.25 ± 1.21, duration 1.41 ± 0.41 vs. 0.56 ± 0.51, MIDAS score 23.38 ± 9.51 vs. 8.28 ± 3.75, P values $<.05$).

3.3. Adverse events

Totally, 5 articles reported 33 adverse events in 213 subjects who received melatonin therapy. Adverse effects were sleepiness ($n=16$), fatigue ($n=4$), increase in libido ($n=3$), dizziness ($n=2$), epigastralgia ($n=2$), nervousness ($n=1$), nightmares ($n=1$), pruritus ($n=1$), dry mouth ($n=1$), constipation ($n=1$), and alopecia ($n=1$).

In controlled trials, there were 24 adverse events in melatonin group in all, compared to 23 adverse events in placebo group and 63 adverse events in other preventive drugs group.

4. Discussion

The purpose of this study is to offer a systematic review of melatonin's therapeutic role in migraine prevention. By far, there is still a paucity of studies, and melatonin's effectiveness for migraine remains unclear with current limited literature. Further clinical investigations are warranted in the future.

4.1. Therapeutic efficacy

Current experimental evidence cannot claim a confirmed beneficial role of melatonin for migraine prophylaxis because placebo-controlled trials presented conflicting results. In Goncalves and Mohsen Ebrahimi-Monfared studies, melatonin was superior to placebo while it was found to be not different from placebo in Alstadhaug study. Various possible reasons may explain for the disparate outcomes, including different melatonin dose (3 mg vs. 2 mg) and formulation (immediate-release vs. prolonged-release), therapy duration (3 months and 2 months vs. 2 months), trial design (parallel design vs. cross-over design), sample size (176 and 105 vs. 48), and outcome measures (headache days and attack frequency vs. attack frequency). Above all, the placebo response is high in Alstadhaug study, beyond that in modern, properly powered placebo-controlled trials for migraine prevention. Therefore, the negative result is possible under- powering.

There seem to be a strong relationship between melatonin and headache relief according to the data in controlled and uncontrolled studies. In observational studies, compared to baseline, migraine was significantly improved, ranging from 51% to 83%. Although uncontrolled design cannot eliminate interferences such as periodic remission of migraine and patients' psychological factors, the great improvements seem impossible to be caused completely by the interferences; hence, it may indicate melatonin's effectiveness for migraine. In controlled studies, the headache improvements were 32%–56%, compared to baseline. Thus, given all the above, it is very likely that melatonin can benefit migraine in prophylaxis.

Similarly, compared to other preventive medications, melatonin's effectiveness seems unclear as well. In Goncalves and Mohsen Ebrahimi-Monfared studies, melatonin was not different from amitriptyline or valproic acid, while in Razieh Fallah study, amitriptyline was considered to be more effective. The differences between the trials are age (adults vs. children), melatonin dose (3 mg vs. 0.3 mg / kg), trial design (double-blind design vs. single-blinded design), preventive medications type and dose (amitriptyline 25 mg and sodium valproate 200 mg vs. amitriptyline 1 mg/kg), sample size (176 and 105 vs. 80), and therapy duration (3 months and 2 months vs. 3 months). Specially, the study conducted by Razieh Fallahl is a single-blinded trial on children migrainers lacking placebo-controlled group; therefore, investigators may affect final outcomes consciously or unconsciously due to their own anticipations during the periods of collecting information from children's parents and/or processing data.

4.2. Formulation, dose, and duration

Present melatonin formulations commonly include immediate-release melatonin, prolonged-release melatonin, and melatonin receptor agonists (Agomelatine, Ramelteon, and Tasimelteon). In this review, 7 studies examined immediate-release melatonin 3 mg, Agomelatine 25 mg, and prolonged-release melatonin 2 mg and 4 mg for migraine prevention. The findings were immediate-release melatonin 3 mg was effective in both placebo-controlled and uncontrolled trials, Agomelatine 25 mg was effective in uncontrolled trial, prolonged-release melatonin 2 mg was not effective in placebo-controlled trial, while 4 mg was effective in uncontrolled trial.

The sustained release design of prolonged-release melatonin made its efficacy could last up for 8 h.[35] A prolonged-release melatonin has received approval from European Medicines Agency (EMA) for insomnia in patients over 55 years old, and prolonged-release melatonin 2 mg was proved to be effective in clinical trials and recommended for insomnia patients[36–38]; thus, 2 mg may not be an enough dose for migraine preventive therapy, which may additionally and partly explain the negative outcome in Alstadhaug study.

Currently, Tasimelteon and Ramelteon have not been extensively studied. Both Ramelteon and Tasimelteon are nonselective melatonin receptor agonists. Tasimelteon, as the sole agonist who has a higher affinity for MT2 receptor than MT1 receptor (the others have higher affinities for MT1 receptor),[39] may be promising in migraine prophylaxis. Published data have underlined the importance of MT2 receptor in insomnia, anxiety, depression, pain, and central nervous system (CNS) neurodegenerative diseases as MT2 receptor mainly exists in the CNS.[40] For Ramelteon, one of its metabolites, M-II, has remarkably 20 to 100-fold higher overall systemic exposure than Ramelteon.[41] Despite its low-binding affinity for melatonin receptors, M-II may offer a similar "prolonged-release" efficacy for Ramelteon. More studies are needed to specify appropriate formulations and doses of melatonin for migraine in the future.

Treatment duration in this review varies from 2 to 6 months. Melatonin displayed ineffective in the 2-month trial in Alstadhaug study; therefore, 2 months may not be a sufficient duration for migraine prevention. As a result, treatment for migraine may require a long continuing period and 3 months or

more seem suitable. Significant improvement could be achieved instantly in some sensitive patients, though.

4.3. Adverse effects

A total of 213 subjects reported 33 adverse events, the most frequent was sleepiness, then fatigue and libido increase, all the adverse events were mild and tolerable. Melatonin's excellent safety and tolerability have been appreciated by lots of literature. Even at very high doses, melatonin was reported outstandingly safe causing no serious adverse events.

However, emerging literature is illustrating that some severe or critical situations can be induced by melatonin. Agomelatine, one kind formulation of melatonin medications, is a nonselective melatonin receptor agonist as well as a serotonergic 5-HT2C antagonist, which is considered to add extra antidepressant and anxiolytic efficacy to Agomelatine.[7] In 2008, EMA-approved Agomelatine in adult major depression. Agomelatine is thought to have idiosyncratic and specific injurious on liver, and its mechanism is still unknown.[42] Furthermore, the considerable intra- and inter-individual variability of its bioavailability also contributes, as the bioavailability is much higher in females and elderly people.[42] It is reported that significant liver transaminases increases (>3× upper limits of normal) occurred in 1%–10% patients who taking Agomelatine, and rare cases of serious hepatic reactions, such as cytolytic hepatitis and jaundice, were present in 0.01–0.1% patients.[43,44] In a systematic review, the rate of Agomelatine-associated liver injuries was 4.6%, compared to 2.1% in placebo group and no more than 2% in other antidepressants.[45] Agomelatine's liver toxicity has already been warned by EMA who recommends liver function must be monitored and regularly tested prior to administration, after 6, 12, 24 weeks, and even later.[46,47] Administration of Agomelatine needs to be carefully evaluated and monitored by clinicians, especially in patients with risks of liver injury (baseline hepatobiliary disorders, such as gallbladder disorder, cholecystitis, choledocholithiasis, and hepatic steatosis) or those who already present impaired liver function at the beginning.[45,48] Other types of melatonin medications are rarely reported harmful to liver.

Pineal gland plays a significant role in gonads' activities of both sexes. Hence, as a hormone generated from pineal gland, melatonin is highly related to reproductive system.[49] It is found that 6-month administration of melatonin decreased semen quality in healthy men.[50] Another 1-year study in chronic insomnia patients reported significant decline of free testosterone in male patients.[51] Of note, melatonin's influence on reproductive system appears to have sex-dependent differences. In an animal experiment, melatonin prompted onset of puberty in female rats, but delayed sexual maturity in male rats.[52] In humans, menstruation duration in women was prolonged by nearly 1 day after 1-year treatment.[51] Consequently, long-term use of melatonin may require special attention on adverse effects for reproductive system, particularly in children and adolescents whose reproductive system has not been fully developed.

Melatonin may aggravate autoimmune diseases via stimulating immune systems.[6] It is reported that the symptoms in rheumatoid arthritis patients deteriorated due to melatonin.[53] Another case report recorded melatonin-induced autoimmune hepatitis in an insomnia patient.[54]

In brief, despite its excellent safety profile, melatonin is unlikely to be completely safe. The above possible severe adverse events should not be ignored, and additional studies are needed to clarify melatonin's safety issues.

5. Conclusion

The literature examining melatonin's effectiveness in migraine prophylaxis is growing, but remains limited; hence, meta-analysis was not feasible. By far, there are only 4 high-quality controlled clinical trials, but they reported some conflicting results. However, the two negative outcomes in Alstadhaug study not different from placebo and in Razieh Fallah study inferior to amitriptyline are possible under-powering due to methodological shortcomings, one was crossover design and presented high placebo response, the other was single-blinded design with possible bias caused by investigators. Besides, the probable insufficient medicine dosage and therapy duration may also partly explain melatonin's ineffectiveness in Alstadhaug and colleagues study. Observational studies provided evidence to support melatonin's effectiveness for migraine. As a result, through lack of confirmed evidence, melatonin is very likely to benefit migraine in prophylaxis, and it may have a similar efficacy to other main preventive medicine. More studies of perfect design in methodology, pharmacology, and therapeutics are desirable to explicate the specific role of melatonin in migraine therapy.

Different formulations and doses of melatonin medications have been examined in studies. Immediate-release melatonin 3 mg was confirmed as effective, melatonin receptor agonist (Agomelatine) 25 mg and prolonged-release melatonin 4 mg were observed effective in uncontrolled studies. Given the special characteristic of each formulation, more studies are required to establish optimal choice of formulation and dosage of melatonin medications for migraine prevention. Moreover, melatonin displayed ineffective in the 2-month trial, thus 3 months or more may be a suitable duration for migraine therapy.

Given the published data, though melatonin is generally safe, the few severe adverse effects caused by melatonin should not be ignored, which mainly include liver injuries, reproductive system dysfunctions, and immunostimulation. Melatonin-associated liver injuries are highly related to one type of formulations particularly, Agomelatonin, owing to its additional serotonergic 5-HT2C antagonist characteristic. Agomelatine's liver toxicity has already been warned by EMA who recommends regular monitoring before and during the treatment. Reproductive system dysfunctions in children and adolescents need special attention because their reproductive systems have not been fully developed, particularly in those who taking long-term melatonin therapy. By stimulating immune systems, melatonin may aggravate autoimmune diseases.

In conclusion, melatonin is a very promising alternative for migraine prophylaxis, future studies are needed to achieve a deeper awareness of melatonin therapy in migraine. Despite its excellent safety profile, melatonin is not completely safe, and more studies are wanted into melatonin's safety issues.

Author contributions

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