

# Melatonin for the treatment of gastroesophageal reflux disease; protocol for a systematic review and meta-analysis

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## Abstract

**Background:** Melatonin generated in the gastrointestinal tract has mucosal protective effect with inhibiting gastric acid secretion, while increasing gastrin release, which in turn stimulates the contractility of lower esophageal sphincter. Gastroesophageal reflux disease (GERD) is also known to have association with sleep disturbance. However, melatonin or melatonin receptor agonist has not been included in the treatment of GERD. This study aimed to evaluate the efficacy of melatonin for the treatment of GERD.

**Methods:** We will search the core databases [MEDLINE (through PubMed), the Cochrane Library, and Embase] from their inception to December 2018 by 2 independent evaluators. The P.I.C.O. is as follows; Patients: who have GERD, Intervention: melatonin or melatonin receptor agonist treatment, Comparison: patients without melatonin or melatonin receptor agonist treatment, Outcome: clinical indices (or crude number or proportion of improvement) for the evaluation of symptomatic improvement which enable comparison of efficacy between patients with melatonin or melatonin receptor agonist and the control group. All types of study design will be sought with full-text will be included. The risk of bias will be assessed using the ROBINS-I tool. Descriptive data synthesis is planned and quantitative synthesis will be used if the included studies are sufficiently homogenous. Publication bias will be assessed with quantitative analyses if more than 10 articles are enrolled.

**Results:** The results will provide evidence for the efficacy of melatonin or melatonin receptor agonist for the treatment of GERD.

**Conclusion:** This study will provide evidence of melatonin or melatonin receptor agonist treatment for GERD.

**Abbreviations:** LES = lower esophageal sphincter, GERD = gastroesophageal reflux disease.

**Keywords:** gastroesophageal reflux, melatonin, reflux esophagitis

## 1. Introduction

Melatonin, which is mainly generated in the pineal gland has a role for regulation of sleep–wake cycles and circadian rhythms.<sup>[1]</sup> The synthesis of this hormone shows diurnal/nocturnal fluctuations with low concentrations during the daytime and significant increase during the darkness and seasonal fluctuations with

decrease in autumn and winter.<sup>[1–3]</sup> This hormone has been used to treat sleep disorders or reducing the effect of jet lag promoting the reset of sleep–wake cycles.<sup>[4]</sup> Seasonally related depression has been also one of the diseases treated with melatonin.<sup>[3]</sup> In addition to pineal gland, many other organs including gastrointestinal tract, retina, extraorbital lacrimal gland, or bone marrow cells are known to produce melatonin and melatonin receptors also have been discovered in various organs including gastrointestinal tract.<sup>[5–7]</sup>

Melatonin generated in the gastrointestinal tract has mucosal protective effect. It prevents the formation of acute gastric injury and accelerates healing of chronic ulcers with increasing the activity of nitric oxide synthase and cyclooxygenase, which results in the increase of nitric oxide, prostaglandin E<sub>2</sub>, and mucosal blood flow.<sup>[2]</sup> It also maintains esophageal mucosal integrity with inhibiting gastric acid secretion, while stimulating duodenal bicarbonate secretion and increasing gastrin release, which in turn stimulates the contractility of lower esophageal sphincter (LES). All these actions have potential for protecting the esophageal mucosa by minimizing contract with acid, bile, or pepsin in animal studies.<sup>[2,8–10]</sup>

Gastroesophageal reflux disease (GERD) is known to have close association with sleep disturbance. Poor quality of sleep is one of the risk factors for GERD symptoms and nocturnal symptom such as night-time heartburn also lowers the quality of sleep and makes it difficult to fall asleep.<sup>[11]</sup> Treatment of GERD has shown improvement of symptoms not only for night-time heartburns, but also for poor quality of sleep.<sup>[12]</sup> Although this bidirectional influence between sleep disorders and GERD, the

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Access to data: All investigators will have access to the final dataset.

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evidence about therapy for targeting of sleep disorders in patients with GERD or both conditions have been scarce. Proton pump inhibitors have been mainly used and recommended for the treatment of GERD; however, melatonin or melatonin receptor agonist has not been included in the treatment of GERD.<sup>[13–16]</sup> This study aimed to evaluate the efficacy of melatonin or melatonin receptor agonist for the treatment of GERD.

## 2. Methods

This systematic review and meta-analysis will fully adhere to the principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-P) checklist.<sup>[17]</sup> This study was registered at PROSPERO (<https://www.crd.york.ac.uk/prospero>) on November 2018 (registration number, CRD42018118516) before study was initiated. The approval of institutional review board was exempted due to the characteristics of this study (collecting and synthesizing data from published studies).

### 2.1. Literature searching strategy

MEDLINE (through PubMed), the Cochrane library, and Embase will be searched using common keywords associated with melatonin or melatonin receptor agonist for the treatment of GERD (from inception to December 2018) by 2 independent evaluators (CSB, and YJY). Medical Subject Heading or Emtree keywords will be selected for searching electronic databases. The abstracts of all identified studies will be reviewed to exclude irrelevant publications. Full-text reviews will be performed to determine whether the inclusion criteria are satisfied in the remaining studies, and the bibliographies of relevant articles will be rigorously reviewed to identify additional studies. Disagreements between the evaluators will be resolved by discussion or

consultation with a third evaluator (GHB). The detailed searching strategy is described in Table 1.

### 2.2. Selection criteria

We will include studies that met the following criteria: patients: who have GERD; intervention: melatonin or melatonin receptor agonist treatment; comparison: patients without melatonin or melatonin receptor agonist treatment; outcome: clinical indices (or crude number or proportion of improvement) for the evaluation of symptomatic improvement which enable comparison of efficacy between patients with melatonin or melatonin receptor agonist and the control group; study design: all types including randomized, prospective, retrospective studies or case studies; studies of human subjects; and publications in English; full-text publications. Studies that met all of the inclusion criteria will be sought and selected. The exclusion criteria are as follows: review articles; guidelines, consensus documents or expert position papers; comments, letters, brief reports, proceedings, or protocol studies; publications with incomplete data; and meta-analysis articles. Studies meeting at least 1 of the exclusion criteria will be excluded from this analysis.

### 2.3. Methodological quality

The methodological quality of the included publications will be assessed using the Risk Of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool.<sup>[18]</sup> The ROBINS-I tool contains 7 domains, including “bias due to confounding” and “bias in selection of participants into the study” at pre-intervention, “bias in classification of intervention” at intervention and “bias due to deviations from intended interventions,” “bias due to missing data,” “bias in measurement outcomes,” and “bias in selection of the reported result” at post-intervention.<sup>[12]</sup> Each domain is

**Table 1**

#### Searching strategy to find the relevant articles.

Database: MEDLINE (through PubMed)

- #1 "melatonin"[tiab] OR "melatonin agonist"[tiab] OR "melatonin receptor agonist"[tiab] OR "melatonin"[Mesh] OR "ramelteon"[tiab] OR "Rozerem"[tiab] OR "tasimelteon"[tiab] OR "Hetlioz"[tiab] OR "Circadin"[tiab] OR "Agomelatine"[tiab] OR "TIK-301"[tiab] OR "Receptors, Melatonin"[Mesh]
- #2 "reflux esophagitis"[tiab] OR "GERD"[tiab] OR "gastroesophageal reflux disease"[tiab] OR "Gastroesophageal Reflux"[Mesh] OR "erosive reflux disease"[tiab] OR "erosive esophagitis"[tiab] OR "nonerosive reflux disease"[tiab] OR "nonerosive esophagitis"[tiab] OR "NERD"[tiab]
- #3 #1 AND #2
- #4 #3 AND English[Lang]

Database: Embase

- #1 'melatonin':ab,ti,kw OR 'melatonin agonist':ab,ti,kw OR 'melatonin receptor agonist':ab,ti,kw OR 'melatonin'/exp OR 'melatonin receptor agonist'/exp OR 'ramelteon':ab,ti,kw OR 'rozerem':ab,ti,kw OR 'tasimelteon':ab,ti,kw OR 'hetlioz':ab,ti,kw OR 'circadin':ab,ti,kw OR 'agomelatine':ab,ti,kw OR 'tik-301':ab,ti,kw
- #2 'reflux esophagitis':ab,ti,kw OR 'GERD':ab,ti,kw OR 'gastroesophageal reflux disease':ab,ti,kw OR 'reflux esophagitis'/exp OR 'Gastroesophageal Reflux'/exp OR 'erosive reflux disease':ab,ti,kw OR 'erosive esophagitis':ab,ti,kw OR 'nonerosive reflux disease':ab,ti,kw OR 'nonerosive esophagitis':ab,ti,kw OR 'NERD':ab,ti,kw OR
- #3 #1 AND #2
- #4 #3 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [english]/lim

Database: Cochrane Library

- #1 melatonin:ab,ti,kw or melatonin agonist:ab,ti,kw or melatonin receptor agonist:ab,ti,kw or ramelteon:ab,ti,kw or rozerem:ab,ti,kw or tasimelatonin:ab,ti,kw or hetlioz:ab,ti,kw or circadin:ab,ti,kw or agomelatine:ab,ti,kw or tik-301:ab,ti,kw
- #2 MeSH descriptor: [melatonin] explode all trees
- #3 MeSH descriptor: [receptors, melatonin] explode all trees
- #4 #1 or #2 or #3
- #5 reflux esophagitis:ab,ti,kw or GERD:ab,ti,kw or gastroesophageal reflux disease:ab,ti,kw or erosive reflux disease:ab,ti,kw or erosive esophagitis:ab,ti,kw or nonerosive reflux disease:ab,ti,kw or nonerosive esophagitis:ab,ti,kw or NERD:ab,ti,kw
- #6 MeSH descriptor: [Gastroesophageal Reflux] explode all trees
- #7 #5 or #6
- #8 #4 and #7

determined to exhibit low-, moderate-, serious-, or critical risk of bias. No information category will be used only when insufficient data are reported to permit a judgement.<sup>[18]</sup> Overall risk of bias judgement is determined based on the interpretation of each domain level and low risk indicates that the study is comparable to a well-performed randomized trial for all domains being evaluated. Moderate risk of bias indicates the evidence of study is sound for a nonrandomized study but not comparable to a randomized trial (low or moderate risk of bias for all domains). Serious risk of bias indicates the presence of important problems (serious risk of bias in at least one domain, but not at critical risk of bias in any domain). Critical risk of bias indicates the study is problematic to provide any useful evidence (critical risk of bias in at least one domain).<sup>[18]</sup>

Two of the evaluators (CSB and YJY) will independently assess the methodological qualities of all the included studies, and any disagreements between the evaluators will be resolved by discussion or consultation with a third evaluator (GHB).

#### 2.4. Data extraction and primary and modifier-based analyses

Two evaluators (CSB and YJY) will independently use the same data fill-in form to collect the primary summary outcome and modifiers in each study, and disagreements between the 2 evaluators will be resolved by discussion or consultation with a third author (GHB).

The primary outcome of this study is the efficacy of melatonin or melatonin receptor agonist for the treatment of GERD. Efficacy can be defined as improvement in the global patient assessment, the visual analog scale of symptoms, indices for the evaluation of symptomatic improvement, such as the Nepean Dyspepsia Index, or any other validated tools indicating overall symptom of patients.<sup>[19]</sup> The following data will also be extracted from each study, whenever possible; study design, age or ethnicity of enrolled population, sample size, published year, diagnostic method of GERD and assessment tool of outcome (efficacy of melatonin or melatonin receptor agonist treatment).

Narrative (descriptive) synthesis is planned and quantitative synthesis will be used if the included studies are sufficiently homogenous. The common effect size will be extracted from each study, whenever possible and we will also perform sensitivity analyses and meta-regression using the modifiers identified during the systematic review to confirm the robustness of the main result and to identify the reason of heterogeneity.

#### 2.5. Statistical analysis

Comprehensive Meta-Analysis Software (version 3, Biostat; Borenstein M, Hedges L, Higgins J and Rothstein H. Englewood, NJ) will be used for this meta-analysis. Heterogeneity will be determined using the  $I^2$  test developed by Higgins, which measures the percentage of total variation across studies.<sup>[20]</sup>  $I^2$  will be calculated as follows:  $I^2 (\%) = 100 \times (Q - df) / Q$ , where  $Q$  is Cochran's heterogeneity statistic, and  $df$  signifies the degrees of freedom. Negative values for  $I^2$  will be set to zero, and an  $I^2$  value over 50% was considered to be of substantial heterogeneity (range: 0%–100%).<sup>[21]</sup> Pooled-effect sizes with 95% confidence intervals (CIs) will be calculated using the DerSimonian and Laird random effects model meta-analysis and sensitivity analyses will be performed using the Mantel-Haenszel fixed-effect model meta-analysis.<sup>[22]</sup> These results will be confirmed by the  $I^2$  test. Significance will be set at  $P = .05$ . Publication bias will be

evaluated using Begg's funnel plot, Egger's test of the intercept, Duval and Tweedie's trim and fill, and Begg and Mazumdar's rank correlation test.<sup>[23–27]</sup>

### 3. Discussion

This is the protocol of a systematic review and meta-analysis for the efficacy of melatonin or melatonin agonist for the treatment of GERD. The pathogenesis of GERD is complex and sleep deprivation is one of the risk factors of GERD. Sleep disturbance is associated with worsening of symptoms by modulating esophageal perception thresholds for pain in patients with symptomatic erosive esophagitis<sup>[28]</sup> and nocturnal symptoms of GERD are also known to lower the quality of sleep.<sup>[11]</sup> Treatment of GERD has shown improvement of symptoms not only for nighttime heartburns, but also for poor-quality of sleep.<sup>[12]</sup>

Although this bidirectional relationship between sleep disorders and GERD, previous studies about sedative for the treatment of GERD have shown conflicting results. Benzodiazepine has shown worsening of symptoms of GERD by reducing the LES pressure, esophageal peristalsis and gastric emptying.<sup>[29–32]</sup> Alprazolam also led to nocturnal symptoms although no significant effect on LES pressure or esophageal motility but interfering with normal nocturnal acid clearance mechanisms triggered by arousal from sleep due to alprazolam-induced central nervous system depression.<sup>[33,34]</sup> However, visceral analgesics (pain modulator) such as tricyclic antidepressants, selective serotonin uptake inhibitors, serotonin-norepinephrine reuptake inhibitors or trazodone also have been recommended in patients with refractory GERD who have a physiologic reflux and positive symptom association.<sup>[35]</sup>

In contrast to the sedative agents which suppresses normal acid clearance mechanisms triggered by arousal from sleep, melatonin generated by the enterochromaffin cells in the stomach and intestinal tract (including melatonin agonists) induces sleep through activation of melatonin receptors and has shown esophageal mucosal protective effect by minimizing contract with acid, bile, or pepsin reflux in animal studies.<sup>[2,8–10]</sup> Improvement of sleep quality by melatonin or melatonin receptor agonists is also expected as one of the mechanisms of alleviating symptoms of GERD by raising perception threshold for pain.<sup>[28]</sup>

This study will provide evidence of melatonin or melatonin receptor agonist for the treatment of GERD.

#### Author contributions

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#### References

- [1] Karasek M, Winczyk K. Melatonin in humans. *J Physiol Pharmacol* 2006;57(suppl 5):19–39.

- [2] Konturek SJ, Konturek PC, Brzozowski T. Melatonin in gastroprotection against stress-induced acute gastric lesions and in healing of chronic gastric ulcers. *J Physiol Pharmacol* 2006;57(suppl 5):51–66.
- [3] Klupińska G1, Wisniewska-Jarosińska M, Harasiuk A, et al. Nocturnal secretion of melatonin in patients with upper digestive tract disorders. *J Physiol Pharmacol* 2006;57(suppl 5):41–50.
- [4] Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* 2002;2:CD001520.
- [5] Vijayalaxmi, Thomas RC, Reiter RJ, et al. Melatonin: from basic research to cancer treatment clinics. *J Clin Oncol* 2002;20:2575–601.
- [6] Pandi-Perumal SR, Srinivassan V, Maestroni GJ, et al. Melatonin: nature's most versatile biological signal? *FEBS J* 2006;273:2813–36.
- [7] Ekmekcioglu C. Melatonin receptors in humans: biological role and clinical relevance. *Biomed Pharmacother* 2006;60:97–108.
- [8] Patrick L. Gastroesophageal reflux disease (GERD): a review of conventional and alternative treatments. *Altern Med Rev* 2011;16:116–33.
- [9] Konturek SJ, Zayachkivska O, Havryluk XO, et al. Protective influence of melatonin against acute esophageal lesions involves prostaglandins, nitric oxide and sensory nerves. *J Physiol Pharmacol* 2007;58:361–77.
- [10] Konturek SJ, Konturek PC, Brzozowski T, et al. Role of melatonin in upper gastrointestinal tract. *J Physiol Pharmacol* 2007;58(suppl 6):23–52.
- [11] Yamamichi N, Mochizuki S, Asada-Hirayama I, et al. Lifestyle factors affecting gastroesophageal reflux disease symptoms: a cross-sectional study of healthy 19864 adults using FSSG scores. *BMC Med* 2012;10:45.
- [12] Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. *Am J Gastroenterol* 2011;106:421–31.
- [13] Hunt R, Armstrong D, Katelaris P, et al. World Gastroenterology Organisation Global Guidelines: GERD global perspective on gastroesophageal reflux disease. *J Clin Gastroenterol* 2017;51:467–78.
- [14] Jung HK, Hong SJ, Jo YJ, et al. Updated guidelines 2012 for gastroesophageal reflux disease. *Korean J Gastroenterol* 2012;60:195–218.
- [15] Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–28. quiz 329.
- [16] Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. *J Gastroenterol* 2016;51:751–67.
- [17] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
- [18] Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- [19] Bang CS, Kim JH, Baik GH, et al. Mosapride treatment for functional dyspepsia: a meta-analysis. *J Gastroenterol Hepatol* 2015;30:28–42.
- [20] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- [21] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [22] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- [23] Sterne JA, Egger M. Funnel plots for detecting bias in metaanalysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046–55.
- [24] Sutton AJ, Abrams KR, Jones DR, et al. *Methods for Meta-analysis in Medical Research*. Chichester: Wiley; 2000.
- [25] Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in metaanalysis. *Biometrics* 2000;56:455–63.
- [26] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [27] Egger M, Davey Smith G, Schneider M, et al. Bias in metaanalysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [28] Schey R, Dickman R, Parthasarathy S, et al. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. *Gastroenterology* 2007;133:1787–95.
- [29] Rushnak MJ, Leevy CM. Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. *Am J Gastroenterol* 1980;73:127–30.
- [30] Rubin J, Brock-Utne JG, Dimopoulos GE, et al. Flunitrazepam increases and diazepam decreases the lower oesophageal sphincter tone when administered intravenously. *Anaesth Intensive Care* 1982;10:130–2.
- [31] Inada T, Asai T, Yamada M, et al. Propofol and midazolam inhibit gastric emptying and gastrointestinal transit in mice. *Anesth Analg* 2004;99:1102–6.
- [32] Jha LK, Fass R, Gadam R, et al. The effect of ramelteon on heartburn symptoms of patients with gastroesophageal reflux disease and chronic insomnia: a pilot study. *J Clin Gastroenterol* 2016;50:e19–24.
- [33] Singh S, Bailey RT, Stein HJ, et al. Effect of alprazolam (Xanax) on esophageal motility and acid reflux. *Am J Gastroenterol* 1992;87:483–8.
- [34] Mungan Z, Pınarbaşı Şimşek B. Which drugs are risk factors for the development of gastroesophageal reflux disease? *Turk J Gastroenterol* 2017;28:S38–43.
- [35] Boeckxstaens G, El-Serag HB, Smout AJ, et al. Symptomatic reflux disease: the present, the past and the future. *Gut* 2014;63:1185–93.