INPLASY

Melatonin or melatonin receptor agonist for treatment of functional dyspepsia: a systematic review and meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 April 2024 and was last updated on 19 April 2024.

INTRODUCTION

Review question / Objective Are melatonin or melatonin receptor agonists effective for symptomatic relief of functional dyspepsia?

Condition being studied Functional dyspepsia (FD) is a functional gastrointestinal disease, which is diagnosed by one or more of the symptoms, including the discomfort of fullness after a meal, discomfort of early satiety, upper middle abdominal pain, and burning sensation in the upper middle abdomen. The symptoms appear for at least 6 months before diagnosis, and the symptoms are more than 3 months standard.
The prevalence of FD is relatively high. It is 8%-23% in Asia, while about 40% of adults suffer from functional dyspepsia in Western countries. In addition, FD seriously reduces the work efficiency of patients, affects their quality of life, and brings a heavy economic burden. According to the surveys, the cost of treating patients with FD in the United States was about 18.4 billion US dollars in 2009.
The consensus points out that melatonin or melatonin receptor agonists could be used to relieve functional dyspepsia symptoms. However, there is no systematic review to systematically evaluate the effectiveness and safety of melatonin or melatonin receptor agonists for the treatment of FD. However, there is no systematic review to systematically evaluate the efficacy and safety of massage for the treatment of FD.

METHODS

Search strategy #1 (epigastric pain syndrome [Title/Abstract]) OR (postprandial distress syndrome [Title/Abstract]) OR dyspepsia[MeSH Terms] OR (functional dyspepsia [Title/Abstract])

OR indigestion [Title/Abstract] OR indigestive [Title/Abstract]
#2 (melatonin[MeSH Terms]) OR (melatonin[Title/Abstract]) OR (MTL[Title/Abstract]) OR (pineal hormone[Title/Abstract]) OR (N-acetyl-5-methoxytryptamine[Title/Abstract]) OR (melatonin mt1 receptor[MeSH Terms]) OR (melatonin mt2 receptor[MeSH Terms]) OR (melatonin receptor[MeSH Terms]) OR (melatonin receptor agonist[Title/Abstract]) OR (agomelatine[Title/Abstract]) OR (ramelteon[Title/Abstract]) OR (tasimelteon[Title/Abstract]) OR (TIK 301[Title/Abstract]) OR (MT1 melatonin receptor[Title/Abstract]) OR (MT2 melatonin receptor[Title/Abstract])
#3 #1AND #2.

Participant or population We will include researches involving people with functional dyspepsia according to any diagnostic criteria, of both genders and any age. Patients with other types of diseases, such as severe cardiac dysfunction, severe hepatic dysfunction, severe kidney dysfunction, endocrine disease, cholecystitis, pancreatitis, and peptic ulcer, will be excluded.

Intervention We will include melatonin and melatonin receptor agonist, including agomelatine, ramelteon, and tasimelteon. Melatonin and melatonin receptor agonist will not be combined traditional Chinese therapy; however, they may be used alone, or in combination with conventional medical treatment, such as acid suppression agents, prokinetics agents, H. Pylori eradication, and Histamine 2-receptor antagonists (H2RAs), and so on.

Comparator The control intervention will include: no treatment, placebo, and conventional medical treatment, such as acid suppression agents, prokinetics agents, H. Pylori eradication, and H2RAs, and so on. Co-invention will be allowed as long as all arms of the randomized allocation received the same co-invention.

Study designs to be included Randomized, parallel clinical trials will be included irrespective of blinding, publication status and language. Randomized cross-over trials will be included only if the trial reported a wash-out period to eliminate any carry-over effect. Quasi-randomized trials and controlled clinical trials without randomization will be excluded.

Eligibility criteria No.

Information sources We will search the following electronic databases from their inception dates to March 2024 for potentially relevant studies, and languages will be restricted to Chinese and English only.
China National Knowledge Infrastructure (CNKI);
Wangfang Database;
Chinese Science Technology Journal Database (VIP);
China BioMedical Literature Service System (SinoMed);
Cochrange Library, including the trials registers of the Cochrane Gut Review Group and the Cochrane Central Register of Controlled Trials (CENTRAL);
Pubmed;
Embase;
CINAHL Complete;
Ovid;
Science Direct On Site (SDOS);
SpringerLink;
Wiley InterScience.

We will also search the following trial registers:
The Chinese Clinical Trial Registry (https://www.chictr.org.cn/);
International Standard Randomized Controlled Trial Number Registry (www.controlled-trials.com);
US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov);
World Health Organization International Clinical Trials Registry
(www.who.int/ictrp/en/).

In addition, the reference lists of all identified studies will also be searched to find any further relevant trials for inclusion.

Main outcome(s) The main outcome measures sought at the end of treatment and at maximal follow-up after completion of the treatment will be global improvement of symptoms (patient-reported and/or clinician-evaluated) and quality of life.

Additional outcome(s) (1)Number of recurrent episodes; (2)Subtypes of the predominant symptom: the discomfort of fullness after a meal, discomfort of early satiety, upper middle abdominal pain, and burning sensation in the upper middle abdomen; (3)Cost-effectiveness; (4)Number and type of adverse events. Two types of adverse events were analyzed, serious adverse events and adverse events not considered serious. The serious adverse events were any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability, are congenital anomalies/birth defects or events that may

jeopardize the patient or required intervention to prevent one of the former serious adverse events. All other adverse events will be considered non-serious. (5)Gastrointestinal hormones. We will observe the changes in gastrointestinal hormones, including ghrelin, motilin, gastrin, etc.. in functional dyspepsia patients' blood after treatment. (6)Circadian rhythm indicators (e.g. sleep rhythm, etc.). (7)Psychological states: including depression and anxiety.

Data management Two review authors (QY He and N Dai) will independently extract the following study characteristics and outcome data from included studies by using standard data extraction forms and checking them. Data from trials in duplicate will be included only once. Any disagreement will be resolved through discussion. In addition, if any information in a given study is missing or unclear, we will try to contact the authors of the study for more specific information.
Methods: study design, total duration of study, number of study centers and location, study setting, withdrawals, date of study.
Participants: number, mean age, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria.
Interventions: name of intervention, schedule, comparison, concomitant medications.
Outcomes: primary and secondary outcomes specified and collected, time points reported.
Notes: funding for the trial, notable conflicts of interest of trial authors.
One review author (N Dai) will enter the data from the data extraction forms into Review Manager (RevMan5.4, 2021), and another author (QY He) will check it.

Quality assessment / Risk of bias analysis
Assessment of risk bias in included studies
Two authors (QY He and N Dai) will independently assess the risk of bias for each study using the Cochrane risk-of-bias 2.0 (ROB 2) tool. Any disagreements will be resolved by consensus.
We will assess the following domains.
Bias arising from the randomization process;
Bias due to deviations from the intended interventions;
Bias due to missing outcome data;
Bias in the measurement of the outcome;
Bias in the selection of the reported result;
Overall bias.
We will assess each potential source of bias as 'high,' 'low,' or 'some concerns' as described in the Cochrane Handbook for Systematic Reviews of Interventions. We will summarize the 'Risk of bias' judgments across different studies for each of the domains listed. We will present a 'Risk of bias' summary figure and a 'Risk of bias' graph to illustrate these findings.

Strategy of data synthesis Melatonin or melatonin receptor agonists will be compared with no treatment, placebo, or conventional medical treatment individually regardless of route of administration, dose, or preparation. We will undertake a meta-analysis only if we consider that the participants, interventions, comparisons, and outcome assessment are similar enough to ensure that an answer would be clinically meaningful. Otherwise, we will present a qualitative synthesis to describe the results across the included studies. Dichotomous data will be presented as relative risk (RR) and continuous outcomes as standardized mean difference (SMD), both with 95% confidence intervals (CI). Analyses will be performed by intention-to-treat where possible. For dichotomous outcomes, patients with incomplete or missing data will be included in a sensitivity analysis by counting them as treatment failures to explore the possible effect of loss to follow-up on the findings ('worst-case' scenario).
Assessment of heterogeneity
Heterogeneity will be tested for using I2 with significance being set at $P<0.10$. Where there was statistically significant heterogeneity, the random effects model would be used. According to the Cochrane Handbook 5.1.0, we will interpret the I2 statistic as follows:
0% to 50%: may represent mild heterogeneity;
50% to 75%: may represent moderate heterogeneity;
75% to 100%: may represent severe heterogeneity.
We will identify $I2>50\%$ as substantial heterogeneity, and explore it by prespecified subgroup analysis and sensitivity analyses.

Assessment of reporting biases
If we pool more than 10 trials, we will create and examine a funnel plot to explore possible publication biases. The asymmetry of the funnel plot will be assessed statistically. When a funnel plot is not symmetric, publication bias will be considered as only one of some possible explanations.

Subgroup analysis If sufficient data are available, we will carry out the subgroup analyses to reveal any effect that might explain any heterogeneity, including dosage of melatonin or melatonin receptor agonist, types of FD (epigastric pain syndrome and postprandial distress syndrome), diagnostic criteria, participants ages and treatment duration (less than four weeks versus four weeks and greater than four weeks).

We will assess differences between subgroups with the I2 statistic to test for subgroup interactions.

Sensitivity analysis Sensitivity analysis was intended to be conducted so that robustness could be tested, including quality of trials (high or low), and funding (commercial or uncommercial).

Language restriction No.

Country(ies) involved China.

Keywords Melatonin; melatonin receptor agonist; functional dyspepsia; systematic review; meta-analysis; intervention.

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