

Systematic review protocol

Title of the review	<i>Food supplements for sleep disorders: a systematic review</i>
First reviewer	<i>Dr Simone Guadagna</i>
Team of reviewers	<i>Dr Dionisio Franco Barattini Dr Serban Rosu Dr Roberto Piazza</i>
Supervisor/Project PI	<i>Dr Dionisio Franco Barattini</i>
Clinical Portfolio Group	“”
Project title (if different from review title)	“”

Support – please state if advice/training or personnel required at each stage	
SR overview	“”
Protocol development	<i>Advice gained from literature and Dr Barattini</i>
Literature searching	<i>Training from specific literature searching courses and also did literature review for PhD study and post doc activity</i>
Quality appraisal	<i>Advice gained from literature</i>
Data Extraction	“”
Synthesis	“”
Writing up	Course in Scientific writing at Kings College London, PhD thesis and various articles published.

1. Background to review

Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim

Insomnia is defined as dissatisfaction with sleep quality or quantity in addition to at least one other symptom among difficulty initiating sleep, difficulty maintaining sleep or early morning awakening with inability to return to sleep. Occasional insomnia is a very common disturb that has been reported to be experienced by about 30% of the U.S. general population. Sleep disorders have an important societal and economic impact, with a consequent reduction in labor productivity or increased risk of accidents. Chronic sleep dysfunction is also a risk factor for a variety of significant health problems, such as cardiovascular disease, diabetes, obesity, as well as bad mood and cognitive disfunction. Almost half of individuals with sleep problems had never taken any steps to resolving them, and the majority of respondents had not spoken with a physician about their problems. Of those individuals who had consulted a physician, drug prescriptions had been given to approximately 50% in Western Europe and the USA. The commonly used sleep aids based on benzodiazepine and non- benzodiazepine hypnotic drugs are often related to negative side effects such as daytime drowsiness, dependency, depression, hypnotic-withdrawal insomnia, and even excess mortality.

Moreover, there are limited data on long-term efficacy of hypnotic drugs. Given these concerns and an increasing patient preference for nonpharmacological treatment, it is important to offer patients with insomnia evidence-based nonpharmacologic alternatives that may improve their sleep.

As defined in the DSHEA, a dietary supplement is “a product (other than tobacco) intended to supplement the diet that bears or contains one or more dietary ingredients, including a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake”. A growing body of evidence have shown promising results for these compounds in supporting health and body functions. In particular, several dietary supplements are popularly used for sleep disorders, also in addition to other remedies (e.g. sleep hygiene and mind-body therapies). Moreover, no golden standard therapy is recommended to treat mild sleep disorders related to specific sleep stages (starting, maintaining and ending sleep).

Our aim in this study is to systematically review recent literature on food supplements and nutraceuticals administered orally and acting on sleep-related disorders. In particular we will differentiate the interventions and the outcomes of the studies according to the criteria of sleep disorders (difficulty in initiating or maintaining sleep, quality and quantity of sleep, waking up too early) and we will review the available clinical data of the 7 most studied natural products: valerian, lavender, melatonin, chamomile, hop, St. John's wort and hawthorn.

2. Specific objectives

1. *To summarize and comment the evidence on the efficacy of oral food supplements and nutraceuticals acting on sleep-related disorders.*
2. *To differentiate the interventions and the outcomes of the studies according to the criteria of sleep disorders (difficulty in initiating or maintaining sleep, quality and quantity of sleep, waking up too early).*

3. a) Criteria for including studies in the review

If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading

i. Population, or participants and conditions of interest	<i>Adult and pediatric subjects with occasional or chronic sleep disorders.</i>
ii. Interventions or exposures	<i>Oral food supplements or nutraceuticals used for sleep disorders.</i>
iii. Comparisons or control groups	<i>Placebo, not treated subjects or hypnotic drugs.</i>
iv. Outcomes of interest	<i>Subjective parameters of sleep quality and quantity: sleep diaries, Pittsburgh Sleep Quality Inventory (PSQI), Insomnia Severity Index (ISI), The Pre-Sleep Arousal Scale (PSAS). Objective parameters: registered by means of transportable home recorder systems</i>
v. Setting	<i>Hospitals and clinics</i>
vi. Study designs	<i>The inclusion criteria were randomized, double-blind, placebo-controlled trials, non-controlled trials and cohort studies.</i>

3. b) Criteria for excluding studies not covered in inclusion criteria

Any specific populations excluded, date range, language, whether abstracts or full text available, etc

We considered studies only on humans and written in English. We excluded non-relevant articles and works with no full text available.

4. Search methods	
<p>Electronic databases Please list all databases that are to be searched and include the interface (eg NHS, EBSCO, etc) and date ranges searched for each</p>	<p><i>PUBMED/MEDLINE, Google scholar.</i></p>
<p>Other methods used for identifying relevant research ie contacting experts and reference checking</p>	<p><i>Reference checking and hand searching of these.</i> <i>Contacting Authors to obtain the full text of the articles.</i></p>
<p>Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.</p>	<p>“”</p>

5. Methods of review	
<p>Details of methods Number of reviewers, how agreements to be reached and disagreements dealt with, etc.</p>	<p><i>Two main reviewers and a third to resolve any disagreements.</i></p>
<p>Quality assessment Tools or checklists used with references or URLs</p>	<p><i>Quality of studies will be assessed using the Jadad scale for quality rating (Jadad 1996). Risk of bias of individual studies will be considered both at study or outcome level. Parameters considered will be: hierarchy of clinical evidence, sample size, quality of data reported and statistical analysis</i></p>
<p>Data extraction What information is to be collected on each included study. If databases or forms on Word or Excel are used and how this is recorded and by how many reviewers</p>	<p><i>Data extraction form in Excel document. Zotero to be used to keep track of references. Major information collected will be: available oral food supplements and nutraceuticals for sleep disorders, efficacy of compounds on different phases of sleep (difficulty in initiating or maintaining sleep, quality and quantity of sleep, waking up too early). Reviewer 1 (SG) and 2 (DFB) will collect data in Excel and Word.</i></p>
<p>Narrative synthesis Details of what and how synthesis will be done</p>	<p><i>Narrative synthesis will be done considering the data extracted from selected articles. In particular we will discuss:</i></p> <ol style="list-style-type: none"> <i>1. Most studied oral food supplements and nutraceuticals for sleep disorders</i> <i>2. Efficacy of compounds on different phases of sleep (difficulty in initiating or maintaining sleep, quality and quantity of sleep, waking up too early)</i> <i>3. Quality of studies using the Jadad scale for quality rating</i> <i>4. Safety of natural products compared to hypnotic drugs</i>
<p>Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.</p>	<p><i>No meta-analysis will be conducted because of the great variability in treatments and clinical end points considered.</i></p>
<p>Grading evidence System used, if any, such as GRADE</p>	<p><i>Quality of studies will be graded using the Jadad scale for quality rating. Additionally, evidence will be graded as following:</i></p> <ol style="list-style-type: none"> <i>1. randomized, double-blind, placebo-controlled trials,</i> <i>2. non-controlled trials</i> <i>3. cohort studies.</i>

6. Presentation of results	
<p>Additional material Summary tables, flowcharts, etc, to be included in the final paper</p>	<p><i>PRISMA 2009 checklist</i> <i>PRISMA 2009 flow diagram</i> <i>Protocol</i> <i>Summary tables and flowcharts</i> <i>Graphs extracted from selected article</i></p>
<p>Outputs from review Papers and target journals, conference presentations, reports, etc</p>	<p><i>Data from the review will be presented at the Vitafoods 2019 conference.</i> <i>The review will be published in a peer-reviewed journal.</i></p>

7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	<i>1 month</i>
Literature searching	<i>1 month</i>
Quality appraisal	<i>1 month</i>
Data extraction	<i>1 month</i>
Synthesis	<i>1 month</i>
Writing up	<i>2 months</i>