European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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REVIEW

The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: A systematic review and meta-analysis

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Received 11 March 2014; received in revised form 27 June 2014; accepted 10 August 2014

KEYWORDS
Melatonin;
Chronobiology;
Depression;
Treatment;
Prophylaxis

Abstract
Circadian- and sleep disturbances may be central for understanding the pathophysiology and treatment of depression. The effect of melatonin on depression/depressive symptoms has been investigated previously. This systematic review assesses the current evidence of a therapeutic- and prophylactic effect of melatonin in adult patients against depression or depressive symptoms. A search was performed in The Cochrane Library, PubMed, EMBASE and PsycINFO for published trials on November 14th 2013. Inclusion criteria were English language, RCTs or crossover trials. Our outcome was measurement of depression/depressive symptoms with a validated clinician-administered or self-rating questionnaire. PRISMA recommendations were followed and the Cochrane risk-of-bias tool used. Ten studies in 486 patients were included in the final qualitative synthesis and four studies, 148 patients, were included in two meta-analyses. Melatonin doses varied from 0.5–6 mg daily and the length of follow-up varied from 2 weeks to 3.5 years. Three studies were done on patients without depression at inclusion, two studies in patients with depression and five studies included a mixture. Six studies showed an improvement in depression scores in both the melatonin and placebo groups but there was no significant difference. One study showed a significant prophylactic effect and another found

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http://dx.doi.org/10.1016/j.euroneuro.2014.08.008

Please cite this article as: Hansen, M.V., et al., The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: A systematic.... European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.08.008

a significant treatment effect on depression with melatonin compared to placebo. The two meta-analyses did not show any significant effect of melatonin. No serious adverse events were reported. Although some studies were positive, there was no clear evidence of a therapeutic- or prophylactic effect of melatonin against depression or depressive symptoms.

1. Introduction

Depression is a common mental disorder and WHO estimates that more than 350 million people of all ages suffer from depression worldwide (www.who.int - 2013). Depression is the leading cause of disability worldwide, and is a major contributor to the global burden of disease (www.who.int-2013). The antidepressants most commonly used today are thought to exert their actions based upon the classical mono-amine deficiency hypothesis (Belmaker and Agam, 2008). New approaches are in focus because the clinical effects of antidepressants used today can take up to two or more weeks to emerge, early discontinuaton rates are high, full remission rates are low and side effects are common (Malhi et al., 2013; Papakostas, 2008, 2010).

Circadian rhythms have been shown to be fundamentally disturbed in patients with depression (Germain and Kupfer, 2008) and insomnia and early-morning awakening are prominent symptoms of clinical depression (Germain and Kupfer, 2008; Srinivasan et al., 2009), suggesting a close link between the melatonergic system and depressed mood (Malhi and Kuiper, 2013; Pandi-Perumal et al., 2009; Srinivasan et al., 2009). Addressing the chronobiology of mood disorders with novel melatonin-based therapies, such as agomelatine has shown significant antidepressant effects with a favorable adverse effect and safety profile (Hickie and Rogers, 2011; Koesters et al., 2013). However, it is not known whether the antidepressant action of agomelatine is a synergistic effect or independently linked to the MT1/MT2 receptor binding properties or to the affinity to the 5-HT_{2c} serotonin receptor (de Bodinat et al., 2010).

Major depressive disorder (MDD) was proposed as the "low melatonin syndrome" in 1979 (Wetterberg, 1979); a concept that focuses on low melatonin secretion as a biological marker of depression. As a consequence of this theory many studies investigating the secretion of melatonin in depression have followed (Srinivasan et al., 2009), although the results are ambiguous with findings of decreased and increased secretion (Srinivasan et al., 2009). Melatonin itself is known to promote sleep, and synchronization and entrainment of the circadian clock; all effects that could contribute to the possible antidepressant effect (Boyce and Hopwood, 2013). In addition, exogenous melatonin has shown anti-depressant-like effects in animal models (Binfare et al., 2010; Detanico et al., 2009; Raghavendra et al., 2000). Since the first clinical study investigating the antidepressant effect of exogenous melatonin in humans in 1976 (Carman et al., 1976) showing negative effects, several other studies have been conducted with both positive and negative findings and therefore no clear evidence of the effect of melatonin on mood has been concluded (Bellipanni et al., 2001; Dalton et al., 2000; Danilenko and Putilov, 2005; Del et al., 2013; Fava et al., 2012; Jean-Louis et al., 1998; Lewy et al., 1998).

The aim of this systematic review and meta-analysis was to assess the current evidence of a therapeutic- and prophylactic effect of melatonin in adult patients against depression or depressive symptoms.

2. Experimental procedures

This systematic review was conducted following The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009), except that no formal review protocol was published.

2.1. Eligibility criteria

We used the following PICO (P: population, I: intervention, C: comparator/control, O: outcomes) (Liberati et al., 2009) when constructing the eligibility criteria and the search strategy; P: humans, adults +18 years, I: melatonin, C: to placebo or other active treatment and O: depression, depressive symptoms, mood disorders.

English language, randomized controlled trials (RCT) (with an inactive placebo or active treatment control group) or randomized crossover trials assessing the treatment or prophylactic effect of melatonin for depression or depressive symptoms were included. Our outcome was the measurement of depression, regardless of whether this was assessed as a primary, secondary or tertiary outcome in the studies. The outcome measure had to be either a validated clinician-administered or self-rating questionnaire with known psychometric properties and with a main focus on diagnosing and/or measuring depression. Results had to be reported in the manuscript in mean (SD) or median (IQR/range). The patient group had to have a depression or be predisposed in some way to the development of a depression or depressive symptoms (i.e. patients with chronic illnesses, cancer or sleep disturbances) and therefore studies on healthy volunteers were not included. In addition, inclusion was not restricted to a specific dose of melatonin or route or timing of administration, nor restricted to the primary and secondary outcomes otherwise being assessed in the studies.

Exclusion criteria were: other study designs than RCT or crossover, studies without results in figures or numbers, melatonin not given as an intervention, depression or depressive symptoms not being measured, language not English, an unclear (too general or not specific for depression) measurement instrument used (i.e. VAS for mood or MOS-SF-36) or if the effect of melatonin could not be isolated from other interventions (trials with co-intervention bias i.e. melatonin given together with buspirone, sleep deprivation, or light therapy).

2.2. Information sources and the search

The Cochrane Library, PubMed, EMBASE and PsycINFO were searched for published trials on November 14th 2013 with the following search strategy:

((melatonin) AND (depression OR depressive disorders OR mood disorders OR depressive symptoms) AND (therapeutics OR treat* OR effect*)).

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When constructing the search terms, words from the PICO were used in MESH term searches to find words to expand and improve the search strategy. Truncation was used to cover different word endings. Limits used when searching the databases were as follows:

PubMed: humans, 19+ years, randomized controlled trial, clinical trial and controlled clinical trial
The Cochrane Library: no limits
EMBASE: humans, adults <18 to 64 years> or aged >65+ years, all clinical trials
PsycINFO: humans, adults 18+years, treatment outcome/clinical trial.

No limits were set for language, so all records identified were manually screened with regard to being English. No limits were set with regard to the years of publication. The reference list of all included studies was manually reviewed to identify additional relevant studies. No search was performed for ongoing trials or unpublished studies and no contact with the study authors was made.

2.3. Study selection

All records identified by the database searches were manually screened for duplicates. Based on a screening of all the titles/abstracts, studies that were clearly not relevant were excluded. Full-text articles of the remaining studies were assessed for eligibility by two independent authors (MVH, AKD). Disagreements on inclusion were resolved by discussion between the two authors.

2.4. Data collection

Information about participant characteristics, intervention details, outcome measures and adverse effects was extracted independently by two authors (MVH, AKD) using a predesigned data form. Studies including patients with a depression at inclusion were classified as "treatment" and studies including patients without a depression at the time of inclusion as "prophylactic". Outcome data were extracted from the text, tables and figures. For the studies included in the meta-analyses, data needed to be presented as mean (SD), otherwise data were converted to this format ($SD = SEM \times \sqrt{n}$). Furthermore, geometrical mean was assumed as mean. When data were presented as changes in a score, the actual score was calculated by adding/subtracting the changes to/from the baseline value for the two groups. If the time of measurement was not exactly the same in the different studies, the closest possible time was chosen. If a cross-over trial was included in a meta-analysis all intervention measurements from the 2 groups were analyzed as if the trial were a parallel group trial, as suggested by The Cochrane Handbook for Systematic Review of Interventions (Higgins et al., 2011). Data on adverse events were only recorded for the melatonin group alone.

2.5. Data synthesis

We performed the data synthesis and statistical analysis using Review Manager software (Review Manager (RevMan) [Computer program], Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.). Since the population was

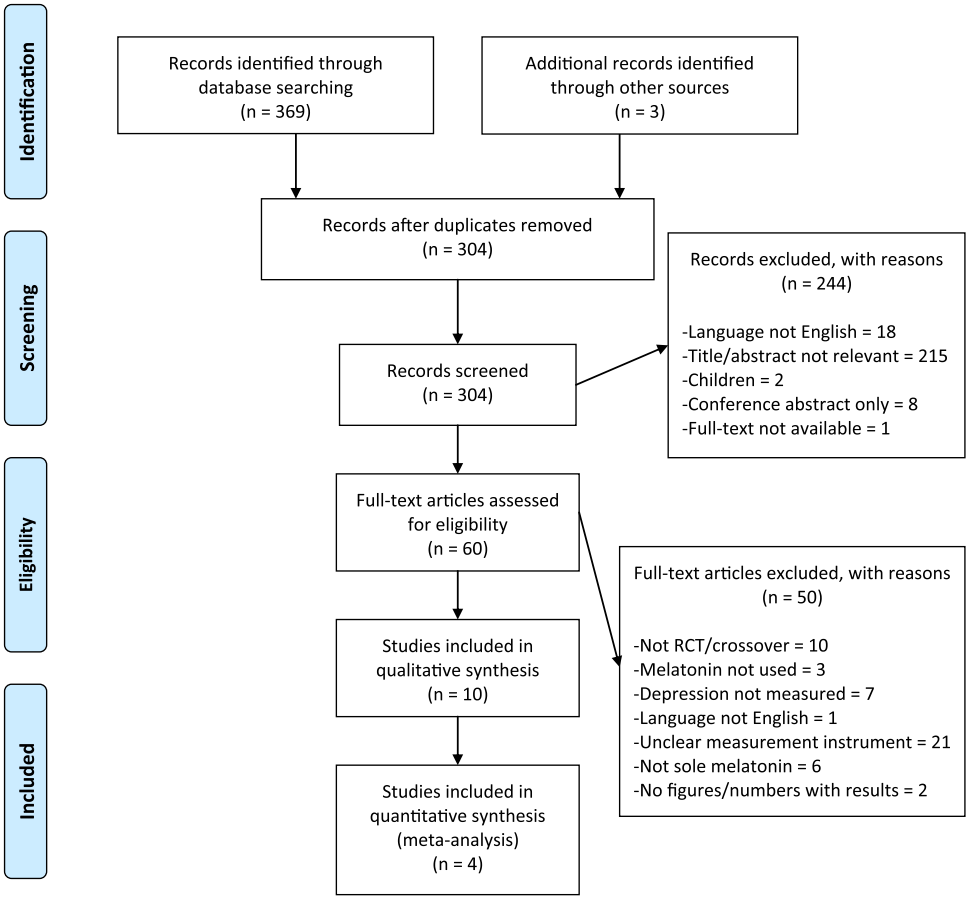

Figure 1 PRISMA flow diagram.

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varied, we included all types of age groups, dosing regimens, diseases and study sizes. Due to this variation, a random-effects model was suitable for the meta-analysis. Separate meta-analyses were performed if the following three criteria were met: the studies used the same rating scale for depression/depressive symptoms, the studies were either therapeutic or prophylactic and it was possible to extract data needed for the meta-analyses directly from the text, tables or figures. Accordingly, we were able to perform two meta-analyses: melatonin vs. placebo using Beck Depression Inventory, and Hospital Anxiety and Depression Scale. We analyzed data from the questionnaires as continuous data using an inverse variance method and presented these as mean differences when outcome measures were on the same scale. We expressed the overall results for our primary outcome as effect size with 95% confidence intervals. We assessed statistical heterogeneity with the I^2 statistic, thereby estimating the percentage of total variance across studies that was due to heterogeneity rather than chance.

We were not able to assess publication bias or small study effects in a qualitative manner using a funnel plot, as there were less than 10 studies included in the meta-analyses.

2.6. Risk of bias

The two authors (MVH, AKD) also assessed the methodological quality of the included studies by using the Cochrane risk-of-bias tool, consisting of 6 items (Higgins et al., 2011). Two items assessed the strength of the randomization process in preventing selection bias in the assignment of participants to the interventions; adequacy of sequence generation and allocation concealment. The third item assessed the influence of performance bias (blinding of participants and personnel) and the fourth item assessed detection bias (blinding of outcome assessors). The fifth item assessed attrition bias and whether incomplete outcome data were adequately addressed. The sixth item assessed whether selective reporting exists (reporting bias) and this item requires a comparison of published data with a trial protocol. Trial protocols for all included studies were searched for in two databases: www.clinicaltrials.gov and WHO's Trial Search (http://apps.who.int/trialsearch/). Randomized cross-over trials were separately assessed for risk of bias with regard to whether statistical consideration was given to the carry-over and/or period-effect (Hills and Armitage, 1979) of this study design.

3. Results

The database searches identified 372 records. After removal of duplicates, 304 titles/abstracts were screened, and 60 full-text articles were subsequently assessed for eligibility. Of these full-text articles, 50 were excluded due to various reasons (Figure 1) and 10 studies (Chojnacki et al., 2011; Garzon et al., 2009; Hurtuk et al., 2011; Kripke et al., 2006; Rahman et al., 2010a; Riemersma-van der Lek et al., 2008; Serfaty et al., 2010; Song et al., 2005; Lu et al., 2005; Williams et al., 2002) were included in the final qualitative synthesis, of which it was possible to include 4 studies (Chojnacki et al., 2011; Lu et al., 2005; Serfaty et al., 2010; Song et al., 2005) in 2 meta-analyses (Figures 2 and 3). Table 1 summarizes participant characteristics, study design and intervention details and Table 2 summarizes outcome measures and adverse effects of the included studies.

Of the 10 studies included, 5 were randomized placebo-controlled trials (Chojnacki et al., 2011; Kripke et al., 2006; Riemersma-van der Lek et al., 2008; Serfaty et al., 2010; Song et al., 2005) and 5 were randomized crossover trials (Garzon et al., 2009; Hurtuk et al., 2011; Lu et al., 2005; Rahman et al., 2010a; Williams et al., 2002). The number of included patients ranged from 17–189, melatonin doses varied from 0.5 mg to 6 mg daily and the length of follow-up varied from 2 weeks to 3.5 years. Three studies were done on patients without depression at the time of inclusion (prophylactic) (Garzon et al., 2009; Lu et al., 2005; Song et al., 2005), 5 studies included a mix of patients with/without depression at inclusion (Kripke et al., 2006; Hurtuk et al., 2011; Rahman et al., 2010a; Riemersma-van der Lek et al., 2008; Williams et al., 2002) and two studies (therapeutic) included only patients with depression (mild/moderate depression on Beck Depression Inventory Diagnostic and Statistical

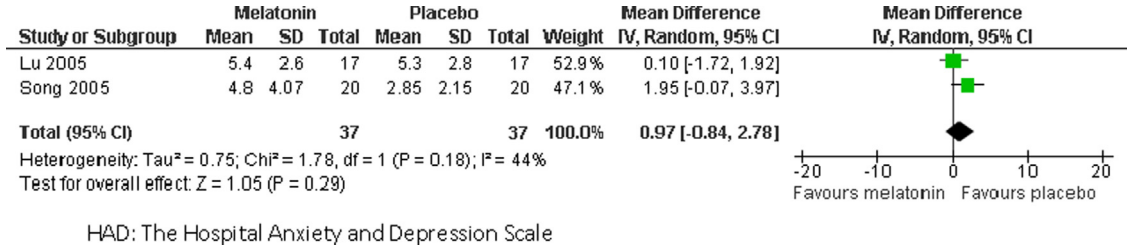

Figure 2 Forest plot – HAD. HAD: The Hospital Anxiety and Depression Scale.

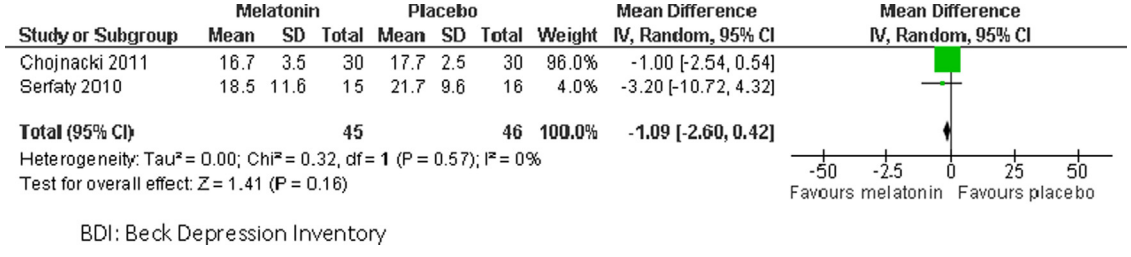

Figure 3 Forest plot – BDI. BDI: Beck Depression Inventory.

Table 1 Participant characteristics, study design and intervention details.

Author	Country	Population n (randomized ptt)	Age[a]	Sex (M/F) %	Study design	Patient group/ disease	Melatonin dose	Melatonin timing/duration	Other treatment	Depression at time of inclusion
Kripke DF 2006	USA	20 (30)	Mean 59 (range 51-69)	0/100	RCT - 3 arms	Postmenopausal with hot flushes	0.5 mg p.o	2.5-3 h before bedtime and upon awakening for 4 weeks	None	A mixture YES (4)
Chojnacki C 2011	Poland	60 (64)	MEL: Mean 35.6±11.4	37/63	RCT	Ulcerative colitis	5 mg p.o.	At bedtime for 12 months	Mesalazine 2 g daily	YES
Hurtuk A 2011	USA	61 (84)	Mean 57.8±10.4	70/30	RCT crossover	Chronic tinnitus	3 mg p.o.	Nightly for 30 days	None	A mixture YES (6)[b]
Serfaty MA 2010	UK	31 (33)	MEL: Mean 38.1 (SD 11.6)	13/87	RCT	MDD and early morning awakening	6 mg p.o.	At bedtime for 4 weeks	Treatment as usual	YES
Rahman SA 2010	Canada	20 (20)	DSPS+dep.: 31.5± 7.2 DSPS - dep.: 36.2±15.7	65/35	RCT - 4 arms, crossover	Delayed Sleep Phase Syndrome ± depressive symptoms	5 mg p.o	Between 19-21:00 for 4 weeks, 1 week wash-out and 4 weeks	None	A mixture YES (8)
Garzón C 2009	Spain	18 (22)	Men: Mean 75.8 Women: Mean 74.3	32/68	RCT crossover	Older adults - history of sleep complaints	5 mg p.o	At bedtime (app. 23:00) for 8 weeks, 2 week washout, then crossover 8 weeks	Hypnotics (n=14)	NO
Riemersma-van der Lek, RF 2008	Nether-lands	189 (189)	Mean 85.8 (SD 5.5)	10/90	RCT, 2×2 factorial	Residents of assisted care facilities, 87% had dementia	2.5 mg p.o	1 h before bedtime for maximum 3.5 years	Bright light	A mixture Some ptt (n=34) on anti-depressants
Song GH 2005	Singapore	40 (42)	MEL: Mean 27.15 (SEM 1.95)	40/60	RCT	Irritable bowel syndrome with sleep disturbances	3 mg p.o	At bedtime for 2 weeks	None	NO
Lu WZ 2005	Singapore	17 (24)	MEL: Mean 41.2	0/100	RCT crossover	Irritable bowel syndrome	3 mg p.o	Nocte for 8 weeks one arm, 4 week washout, 8 weeks other arm	None	NO
Williams G 2002	UK	30 (42)	Mean 44.5 (SD 11.1)	43/57	RCT crossover	Chronic fatigue syndrome	5 mg p.o	Evening - 4×12 weeks (MEL, phototherapy, PLC, washout)	Photo-therapy	A mixture (Borderline score)

MEL: melatonin, PLC: placebo, RCT: Randomized controlled trial, M: male, F: female, App.: approximately, Ptt: patients, DSPS: Delayed Sleep Phase Syndrome, Dep: depression.
[a]Reported as available in the demographic data; for all patients, for MEL group only, for DSPS±depression or for men/women.
[b]The number of randomized patients (n=61) does not equal the distribution of depression and/or anxiety at inclusion (yes:no) 6:42 in the table.

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Table 2 Outcome measures and adverse effects.

Author	Primary outcome of study	Depression: measurement instrument	Self-reported or clinician administered	Points of measurement: when?	Overall effect of melatonin on depression or depressive symptoms: ↑↓→	Results if a positive effect of MEL was found	Adverse effects -reported in the MEL group[a]
Kripke DF 2006	LH suppression and relief of hot flashes	CES-D and QIDS-SR	Self-reported	Baseline and after 5 weeks (end of study)	→(both CES-D & QIDS)	N/A	Mild sleepiness
Chojnacki C 2011	Activity of inflammatory process and sustaining remission	BDI	Self-reported	Baseline, 3, 6, 9, 12 months	→	N/A	Headaches
Hurtuk A 2011	Suppression of chronic tinnitus	BDI	Self-reported	Baseline, 30 days and 8, 12 weeks	→	N/A	None
Serfaty MA 2010	Improvement in sleep (sleep length - actigraphy)	BDI and 21-item HDRS	Self-reported and clinician administered	Baseline, 1,2,3,4 weeks, washout	→	N/A	Poor sleep, vivid dreams, day time sleepiness, fuzzy feeling
Rahman SA 2010	Amelioration of depressive symptoms	HDRS-17 and CES-D	Clinician administered and self-reported	Baseline, second night and last day of treatment in both phases	↓ (in DSPS group with depression)	Mean (HDRS-17+dep.: baseline 13.4 MEL: 6.0 PLC:13) (CESD +dep.: baseline 33.5 MEL:19 PLC: 25) $p<0.05$	Not reported
Garzón C 2009	Northside Hospital Sleep Medicine Institute Test and ability to discontinue hypnotic drug treatment	GDS	Self-reported	Baseline, 10 weeks, 20 weeks	↓	Mean GDS: Baseline 7.33 PLC: 7.06 MEL: 5.61 ($p=0.043$)	None
Riemersma-van der Lek, RF 2008	Progression of cognitive decline	CSDD	Clinician administered (interview of patients and caregivers)	Baseline, 6 weeks, 6 months, 1 year, 1.5 years, 2 years	→	N/A	None
Song GH 2005	Bowel symptoms, rectal sensitivity, sleep disturbances	HAD	Self-reported	Baseline and 2 weeks	→	N/A	Not reported
Lu WZ 2005	Bowel symptoms, sleep patterns, psychological profile	HAD	Self-reported	Baseline, 8 weeks, 20 weeks	→	N/A	Daytime sleepiness
Williams G 2002	Symptoms of CFS and quality of life	HAD	Self-reported	Last week of all four 12 weeks periods	→	N/A	Not reported

CES-D: The Center for Epidemiological Studies Depression Scale, QIDS-SR: Quick Inventory of Depressive Symptomatology self-rating version, BDI: Beck Depression Inventory, HDRS (17 and 21-item): Hamilton Depression Rating Scale, GDS: Yesavage Geriatric Depression Scale, CSDD: Cornell Scale for Depression in Dementia, HAD: The Hospital Anxiety and Depression Scale, →, ↓, ↑: no difference between groups, significant decrease, significant increase in depression/depressive symptoms, MEL: melatonin, PLC: placebo, Dep.: depression, CFS: Chronic fatigue syndrome, N/A: not applicable.

[a]No significant difference compared to placebo.

Manual of Mental Disorders (4th edition) diagnosis of MDD, respectively) (Chojnacki et al., 2011; Serfaty et al., 2010). Eight different scales were used to measure depression; The Center for Epidemiological Studies Depression Scale (CES-D), Quick Inventory of Depressive Symptomatology self-rating version (QIDS-SR), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS 17 and 21-item), Yesavage Geriatric Depression Scale (GDS), Cornell Scale for Depression in Dementia (CSDD) and The Hospital Anxiety and Depression Scale (HAD). Seven studies used only self-rating scales (Chojnacki et al., 2011; Garzon et al., 2009; Hurtuk et al., 2011; Kripke et al., 2006; Lu et al., 2005; Song et al., 2005; Williams et al., 2002), 2 studies used both a self-rating and a clinician-administered rating scale (Serfaty et al., 2010; Rahman et al., 2010a) and 1 study only used a clinician-administered scale (Riemersma-van der Lek et al., 2008). Only one of the studies had amelioration of depressive symptoms as a primary outcome (Rahman et al., 2010a).

3.1. Effect of melatonin

Six studies (Chojnacki et al., 2011; Hurtuk et al., 2011; Kripke et al., 2006; Lu et al., 2005; Serfaty et al., 2010; Song et al., 2005) showed an improvement in depression scores in both the melatonin and placebo groups but there were no significant differences between the two groups. Two studies did not show an effect of melatonin on depression scores and since the results from the placebo group were not clearly reported, it is not known whether an effect was found in this group (Riemersma-van der Lek et al., 2008; Williams et al., 2002).

One randomized crossover study with 18 non-depressed elderly patients evaluating the effect of 5 mg melatonin on sleep, and behavioral disorders showed a significant improvement ($p=0.043$) measured by the GDS (mean baseline: 7.33, mean melatonin: 5.61, mean placebo: 7.06) in the melatonin group compared to baseline and placebo after 8 weeks of treatment (Garzon et al., 2009). Another randomized crossover study also using 5 mg melatonin for 4 weeks in 20 patients with Delayed Sleep Phase Syndrome showed a significant improvement ($p<0.05$) in depression measured by HDRS-17 (data extracted from figure: mean baseline: 13.4, mean melatonin: 6.0, mean placebo: 13.0) and CES-D (data extracted from figure: mean baseline: 33.5, mean melatonin: 19.0, mean placebo: 25.0) compared to placebo and baseline, although this was only in the group with depression at inclusion ($n=8$) (Rahman et al., 2010a).

3.2. Meta-analyses: (Figures 2 and 3)

One meta-analysis (Figure 2) included 2 studies; one RCT (Song et al., 2005) and one randomized cross-over trial (Lu et al., 2005), in patients with irritable bowel syndrome who did not have a depression at the time of inclusion. Depression was measured by The Hospital Anxiety and Depression Scale (HAD). One other study (Williams et al., 2002) also used HAD but since data were not reported for placebo, it was not possible to include this study in the meta-analysis. To be able to extract data from the 2 studies we chose the closest time-points for measurement of depression/depressive symptoms; after 2 and 8 weeks of treatment respectively. This meta-analysis did not show a significant effect of melatonin versus placebo on HAD score (Relative effect 0.97, 95% confidence interval (CI) −0.84 to 2.78).

Another meta-analysis (Figure 3) included 2 other studies (Chojnacki et al., 2011; Serfaty et al., 2010) in patients with ulcerative colitis and MDD with early-morning awakening respectively. In both studies patients had a depression at the time of inclusion and depression was measured by Beck Depression Inventory (BDI). The closest time-points chosen to extract data were 3 months and 5 weeks respectively. This metaanalysis did not show a significant effect of melatonin versus placebo on BDI (Relative effect −1.09, 95% confidence interval (CI) −2.60 to 0.42).

3.3. Risk of bias

Overall findings are presented in the risk of bias summary (Figure 4). Selection bias was low as all studies adequately described the method used to generate the random sequence. Five studies were unclear with regard to the

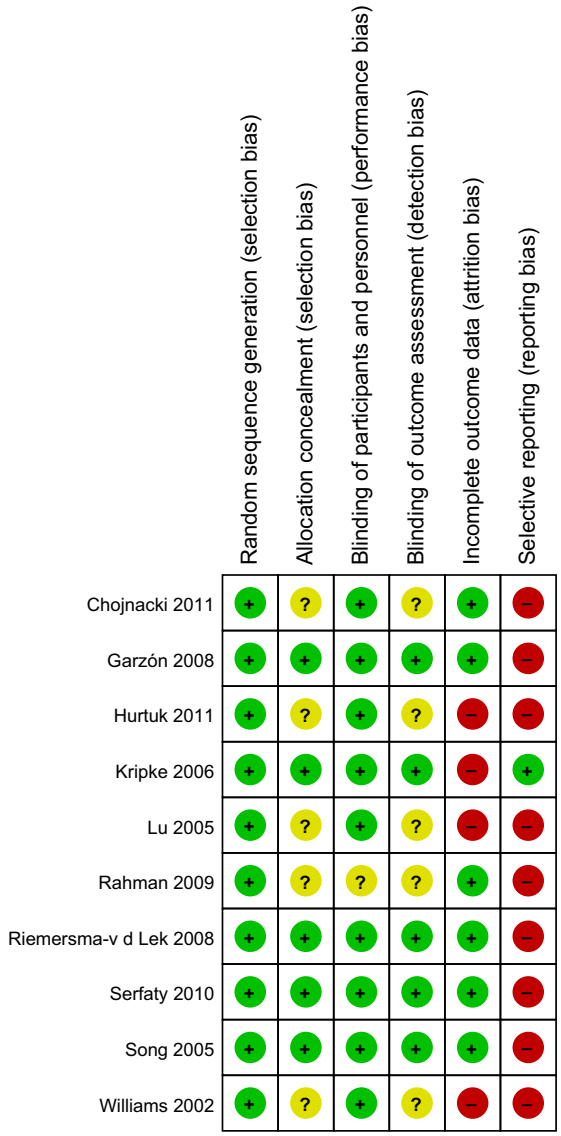

Figure 4 Risk of bias table.

allocation concealment (Chojnacki et al., 2011; Hurtuk et al., 2011; Lu et al., 2005; Rahman et al., 2010a; Williams et al., 2002). Blinding of participants and personnel was adequately described in all studies, except one (Rahman et al., 2010a) and blinding of outcome assessors was adequately described in 5 studies (Garzon et al., 2009; Kripke et al., 2006; Riemersma-van der Lek et al., 2008; Serfaty et al., 2010; Song et al., 2005). Four studies had a high risk of attrition bias (Hurtuk et al., 2011; Kripke et al., 2006; Lu et al., 2005; Williams et al., 2002) with many randomized patients who dropped out or were excluded, and who were not adequately accounted for. There was a high risk of reporting bias as only one study (Kripke et al., 2006) had an available protocol. The outcomes reported in this protocol (NCT00288262) were in complete accordance with what was reported in the article, giving this study (Kripke et al., 2006) a low risk of reporting bias. Of the five cross-over trials (Garzon et al., 2009; Hurtuk et al., 2011; Lu et al., 2005; Rahman et al., 2010a; Williams et al., 2002), two of them had a high risk of bias with regard to the statistics (Garzon et al., 2009; Rahman et al., 2010a).

3.4. Adverse events

Three studies (Garzon et al., 2009; Hurtuk et al., 2011; Riemersma-van der Lek et al., 2008) did not report any adverse events in the melatonin group and 3 studies (Rahman et al., 2010a; Song et al., 2005; Williams et al., 2002) did not report on adverse effects at all. In the remaining 4 studies (Chojnacki et al., 2011; Kripke et al., 2006; Lu et al., 2005; Serfaty et al., 2010) mild daytime sleepiness, headaches, poor sleep, vivid dreams and a fuzzy feeling were reported as adverse effects in the melatonin groups but there was no significant difference compared to placebo.

4. Discussion

This present systematic review does not support routine administration of melatonin for treatment or prophylaxis of depression, although two small studies (one prophylactic and one treatment) did find an effect compared to placebo and no studies found the opposite. The ten included studies were rather small with regard to number of included patients and heterogeneous with regard to type of patients included, melatonin dose, timing and duration of intervention, outcome measurement instrument and timing of measurement.

It is noteworthy, that six of the included studies showed an improvement of depression in both the melatonin and placebo groups over the course of time, showing that a placebo-response is probably present (Walsh et al., 2002; Rutherford and Roose, 2013). The placebo-response in antidepressant trials has risen over the last decades, leading to a reduction in the medication-placebo differences (Rutherford and Roose, 2013; Walsh et al., 2002). Consequently, it is becoming increasingly difficult to demonstrate a significant benefit of a putative antidepressant, such as melatonin, over placebo (Rutherford and Roose, 2013). This could be an explanation why an overall evident effect of melatonin was not found in this review including studies from 2005–2011 and future studies taking the placebo-response into consideration are necessary. Furthermore our review did not include any studies in patients with severe, elongated depression needing hospitalization; this population possibly contributing to a larger response rates of antidepressants against placebo (Rutherford and Roose, 2013; Walsh et al., 2002).

This review solely included studies using validated clinician-administered or self-rating questionnaires with known psychometric properties and a specific main focus on diagnosing and/or measuring depression. This was done to improve both the internal and external validity of this review. Consequently, it made comparability within the review possible and gave the opportunity to complete meta-analyses. Finally there is a greater clinical relevance of the results by making comparability and generalizability of the results an option in respect to other previous or future clinical studies on depression and depressive symptoms. However, in the context of the remaining literature with studies using other non-specific questionnaires/rating scales to assess mood and depression, melatonin has shown a positive effect in some studies (Bellipanni et al., 2001; Fava et al., 2012; Jean-Louis et al., 1998; Lewy et al., 1998; Lissoni et al., 1995, 2000; Suresh Kumar et al., 2007). Whether the positive effect of melatonin found in these excluded studies is due to the non-specific measuring instrument of mood/depression used or due to co-intervention with a possible add-on effect of melatonin in some of the studies is not known, but should be an issue for future investigations.

An aspect that could have confounded the results of this review is the inclusion of cross-over trials as seasonal variation (Kasper et al., 1989) and spontaneous fluctuations, especially spontaneous improvement, in mood and depression over time are evident (Rutherford et al., 2012; Rutherford and Roose, 2013). We chose to include randomized cross-over trials in our review, as they constitute a large group of the available evidence and furthermore, we assessed the carry-over effect to be minimal due to the short half-life of melatonin (Cardinali et al., 2012). This leaves only the aspect of the period effect as a risk of bias, which we judged did not have enough effect to exclude the evidence from these studies in the review. When including both an RCT and a randomized cross-over trial in a meta-analysis, we also knew it would give rise to a unit-of-analysis issue, but since the results from the randomized cross-over trial approximate those from the RCT in a comparable population (Song et al., 2005), we accepted the conservative estimate (Higgins et al., 2011).

Presently, we do not find the evidence on this topic adequate and comprehensive enough and in light of the heterogeneity of the included studies and the quality of the evidence being low, we believe further studies are warranted. The first question that arises for these future studies is to determine whether a possible effect of melatonin is confined to those patients who are depressed or if melatonin is also applicable as prophylaxis. One study has shown that low endogenous melatonin secretors who do not have the normal nocturnal peak in secretion are more likely to have depressive symptoms and subsyndromal depression (Rahman et al., 2010b), which could support the rationale of treatment with melatonin to prevent the

Please cite this article as: Hansen, M.V., et al., The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: A systematic.... European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.08.008

development of depression. If melatonin has a treatment effect on depression, it must also be evaluated whether melatonin only has an effect in those patients who exhibit a clear chronobiological disturbance in their depression (Boyce and Hopwood, 2013; Malhi and Kuiper, 2013). Furthermore, whether melatonin could have a possible synergistic effect when given together with other antidepressants (Hirsch-Rodriguez et al., 2007), or other treatments such as bright light (Riemersma-van der Lek et al., 2008), tamoxifen (Lissoni et al., 1995), 5-methoxytryptamine (Lissoni et al., 2000) or buspirone (Fava et al., 2012) and thereby be used as an add-on must be investigated. In view of the longer half-life and much higher potencies of the different melatonin agonists, such as ramelteon, future studies are also warranted with melatonin in higher doses before the relative effect of melatonin can be clarified (Cardinali et al., 2012). As many of the included studies were relatively small in size, larger studies should be conducted to exclude the possibility of a type II error. Furthermore, future studies should be performed as RCTs in order to rule out any bias related to the carry-over and period effect linked to cross-over trials.

In summary, this systematic review does not support routine administration of melatonin for treatment or prophylaxis against depression until further data are available. Thus, further studies are warranted.

Role of funding source

This work was supported by Grants from the University of Copenhagen, The Dagmar Marshalls Foundation and The Foundation of Poul Martin Christiansen and Spouse. These abovementioned funders have had no influence on the design and conduct of the study; collection, management analysis, and interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. All these activities are done by the authors.

Contributors

All authors had full access to all the data in the study and take responsibility for the integrity of the data, the accuracy of the data analysis and had final responsibility for the decision to submit for publication. All authors have agreed to be accountable for all aspects of the work and have all approved the final version of the manuscript to be published. Furthermore following contributions were made:

MVH: guarantor for the study, planned the study, designed the study, initiated the study, collected the data, analyzed and interpreted the data, prepared the first draft of the manuscript, revised and coordinated revision of the manuscript.
AKD: planned the study, designed the study, initiated the study, collected the data, analyzed and interpreted the data, revised the manuscript.
IH: planned the study, designed the study, revised the manuscript.
JR: planned the study, designed the study, revised the manuscript.
IG: planned the study, designed the study, revised the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

None.

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Please cite this article as: Hansen, M.V., et al., The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: A systematic.... European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.08.008