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# Does Exogenous Melatonin Improve Quality of Sleep in Patients Experiencing Sleep Disturbances Secondary to Chronic Diseases?

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**Does Exogenous Melatonin Improve Quality of Sleep in  
Patients Experiencing Sleep Disturbances Secondary to  
Chronic Diseases?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

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Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **Abstract**

**Objective:** The objective of this selective EBM review is to determine whether or not “Does exogenous melatonin improve quality of sleep in patients experiencing sleep disturbances secondary to chronic diseases?”

**Study Design:** Three Randomized, placebo-controlled studies (RCT) published in 2010, 2013 and 2008.

**Data Sources:** All RCTs searched and located using PubMed database.

**Outcomes Measured:** Clinical outcome for all three articles using quality of sleep or quality of life questionnaires such as the Leeds Sleep Evaluation. All of which evaluated POEMs, and were self reported by participants.

**Results:** In a randomized control study (RCT) by Serfaty et al, sleep quality improved by lessening time needed to get to sleep, but was not specific to either the experimental or placebo group. The RCT by Russcher et al. also indicated that there was no significant increase in quality of life for participants given exogenous melatonin. Only the RCT by Koch et al. showed significant improvement in quality of sleep with the use of melatonin in participants by decreasing time needed to fall asleep, increasing sleep time and improving overall quality of sleep.

**Conclusions:** The data obtained was insufficient to conclusively support the use of exogenous melatonin to alleviate sleep disturbances secondary to chronic disease. Two of the three RCTs included in this systematic review were not able to show significant data in support of the positive effects of exogenous melatonin on sleep patterns.

**Keywords:** melatonin, depression, and hemodialysis

## **Introduction**

Melatonin plays an important role in the sleep regulation of human beings. It is a hormone that modulates sleep/wake cycles and can greatly diminish quality of life if levels are disturbed. It is one of the main external indicators of time during sleep/wake cycles and is stimulated by darkness and inhibited by light.<sup>1</sup> Many diseases such as chronic kidney disease and depression can cause sleep disturbances due to changes in circadian rhythms. More specifically, affective disorders such as depression affect circadian rhythms by modulating melatonin levels.<sup>1</sup> In patients suffering from chronic kidney disease, hemodialysis can impede the nocturnal rise in melatonin concentration.<sup>2</sup> Exogenous melatonin is widely available for purchase as an over the counter supplement in the United States, and is fairly inexpensive. This paper analyzes three randomized controlled studies that study the effects of exogenous melatonin on sleep disturbances caused secondarily due to chronic diseases.

Sleep disturbances consume a great deal of healthcare resources worldwide every year. Although there is not much data regarding the number of healthcare visits per year caused by sleep disturbances, one article noted that patients reporting less than 5 hours of sleep per night had the highest healthcare utilization when compared to other groups with better quality of sleep.<sup>3</sup> The same article also noted that sleep complaints are underreported by patients, and underdiagnosed by physicians, and therefore the healthcare utilization due to sleep disturbances is much higher than reported.<sup>3</sup> Although not specific to patients suffering from chronic diseases, one study noted that general sleep disturbances and associated health effects cost an estimated \$450 million dollars annually in Australia alone.<sup>4</sup> Due to the large impact of sleep disturbances on the depletion of healthcare resources, the efficacy of exogenous melatonin as a treatment for

sleep disturbances caused by they many different existing chronic disease is an important area of study.

Currently there are a wide variety of methods used to treat sleep disturbances. Good sleep hygiene should be considered the first and simplest method of helping to lessen such sleep disturbances. Some practices that may improve sleep hygiene include, having a regular sleep schedule, avoiding caffeinated beverages or smoking in the evening, adjusting your sleep environment to decrease stimuli, and only exercising at least 4-5 hours before scheduled sleep.<sup>5</sup> Other non-pharmacological approaches can also be therapeutic towards improving quality of sleep. One such approach is to use relaxation techniques such as progressive muscle relaxation and relaxation response therapy that should implemented right before each intended sleeping period.<sup>5</sup> Such relaxation techniques are simple to teach patients, and can be done independently. Cognitive behavioral therapy, which can be conducted traditionally through in person sessions or even via telephone or computer, may be an appropriate treatment for those individuals who need assistance and guidance. The most commonly used method to treat sleep disturbances are pharmacologic agents however. There are many different classes that can be utilized, including but are not limited to benzodiazepines, non-benzodiazepines, and melatonin agonists.<sup>6</sup> Some common benzodiazepines used are triazolam, lorazepam, tenazepam, and alprazolam. Non-benzodiazepines have newer, more advertised agents such as Zolpidem. Melatonin agonists agents include Ramelteon, and have shown to significantly improve general sleep latency.<sup>5</sup>

Overall many studies, including the three RCTs that this paper focuses on, evaluate the effects of exogenous melatonin on the many patient groups with disturbed circadian rhythms.<sup>1</sup> In some previous studies, short-term supplementation has been shown to alleviate problems, but the

studies included in this systematic review evaluate long term supplementation on patients with chronic disease and its results.

### **Objective**

The objective of this selective EBM review is to determine whether or not “Does exogenous melatonin improve quality of sleep in patients experiencing sleep disturbances secondary to chronic diseases?”

### **Methods**

This selective EBM review analyzed 3 randomized control studies that evaluated the aforementioned objective. The population criteria that were set for the purpose of this systematic review included the following: participants ages 18 and older, diagnosis of a chronic disease such kidney disease or major depression, and reported subjective findings of sleep disturbances. All three randomized controlled studies used exogenous melatonin as the intervention addressed, and used a placebo tablet for the comparison control group. The main outcome that is evaluated in this paper is quality of sleep based on sleep questionnaires values.

This writer used PubMed as the sole data source to find the three studies utilized in this paper, using keywords of melatonin, depression, and hemodialysis. The search parameters used were: English language, human species data, and published in peer reviewed journal in the past 10 years. Types of studies searched included only randomized control studies, which measured outcomes that could be classified as a POEM or Patient Oriented Evidence that Matters. Exclusion criteria included any studies in which participants used melatonin previously, studies that tested melatonin along with other pharmacological methods, or studies including participants not suffering from chronic diseases. The search conducted also verified that there are no previous Cochrane reviews or systematic reviews published on this objective, or any published by other

previous studies. All studies used in this paper used p-values to report statistics. The demographics and characteristics of the included studies can be seen in Table 1.

**Table 1 - Demographics & Characteristics of included studies**

Study	Type	# Pts	Age (yrs.)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Serfaty <sup>1</sup> (2010)	Double blind RCT	33	18-65	Diagnostic and Statistical Manual of Mental Disorders classification for major depression; a score of >17 on BDI; self reported sleep of 1 hour less than normal at least 3 days per week	Another axis 1 diagnosis, delusions or hallucinations, ECT within 6 months, hypnotic medications, recent change in dose or type of psychotropic medication within 4 weeks, history of ETOH abuse	2	Slow release exogenous melatonin (6 mg)
Russcher <sup>2</sup> (2013)	Double blind RCT	67	18-85	Patient in age group with >3 months of hemodialysis with adequate dialysis efficacy; subjective sleep problems at baseline; mean sleep onset latency > 15 min.	Current melatonin use, Known hypersensitivity to melatonin, severe psychological or neurological disease, unstable angina pectoris, NYHA class IV heart failure, pregnancy, participation in another clinical trial 1 month prior to start of this study	25	3 mg IR melatonin QD at 22:00 hrs.
Koch <sup>6</sup> (2008)	Double blind RCT	20	18-85	Pts in age group on stable hemodialysis (> 3 months)	Pts with prior use of melatonin, use of hypnotics that could not be stopped, or severe psychological or neurological disease.	4	Melatonin 3 mg QD at 22:00 hrs.

## **Outcomes Measured**

Outcomes measured in the three studies included in this paper were POEMS. In the Serfaty et al. RCT, subjective measures of sleep were collected using the Leeds Sleep Evaluation Questionnaire which measured: getting to sleep, quality of sleep, awakening from sleep and behavior following waking.<sup>1</sup> In the Russcher et al. RCT study, sleep-wake characteristics were measured from the Dutch sleep disorders questionnaire which recorded estimated sleep time, daytime function, sleep onset latency, wake periods during the night, feeling rested during daytime, and subjective sleep quality.<sup>2</sup> In the Koch et al. RCT study, sleep disturbances were measured by quality of life questionnaire.<sup>6</sup>

## **Results**

In the study by Serfaty et al., out of the 203 interviewed potential participants, 33 patients were recruited to the study.<sup>1</sup> 16 of the participants were referred to the study by their general practitioner, 13 were identified by databases, and 4 were self referred.<sup>1</sup> Two participants dropped out immediately due to feeling much better. Participants were randomly assigned to one of two groups, which was done by independent coordinator ensuring a double-blind trial.<sup>1</sup> The LSEQ tested many parameters for sleep and determined that sleep improved for whole group, but not specifically to the experimental group with melatonin. General Linear Modeling was used in this study to measure the differences between the placebo and melatonin groups which showed that there was a significant reduction in time getting to sleep ( $F = 6.6$ ,  $d.f. = 3.2$ ,  $P < 0.001$ ) and improved quality of sleep ( $F = 4.8$ ,  $d.f. = 3.6$ ,  $P < 0.002$ ) with melatonin.<sup>1</sup> Other than the previous two values mentioned, no other significant differences in sleep were seen in either group.<sup>1</sup>

In the Serfaty RCT, some patients reported adverse effects in both the melatonin and placebo groups. The adverse effects reported are shown in Table 2.

**Table 2 – Adverse Effects seen in Serfaty RCT<sup>1</sup>**

Melatonin Group		Placebo group	
Adverse Effect	# of patients affected	Adverse Effect	# of patients affected
Vivid dreams	2	Poor sleep	2
Daytime Somnolence	1	Daytime Somnolence	1
Fuzzy feeling	1	Vivid Dreams	1
		Headaches	1

The Russcher et al. RCT included sixty-seven daytime hemodialysis patients, forty-two of whom completed the study.<sup>2</sup> Twenty-five patients did not complete the study, reasons for which can be seen in Table 3. This RCT sought patients who had been on hemodialysis for at least 3 months, and reported subjective sleep problems with a minimum mean sleep onset latency of > 15 minutes.<sup>2</sup> Quality of life was the main topic investigated in this study, using a questionnaire that was independently filled out by the participants on a daily basis after sleep periods. After analyzing the questionnaire data, the researchers concluded that there was no discernable differences in vitality between the melatonin and placebo groups over the 12 months (difference -1.9%, 95% CI – 12.6, 8.7).<sup>2</sup> Some incidental differences were found which illustrated increased general mental health (difference 9.3%, 95% CI -0.1, 18.7, P = 0.052), and decreased physical functioning (-11.4%, 95 CI -12.6, 8.7) in the melatonin group over 12 months.<sup>2</sup> All other parameters tested by the quality of life questionnaire did not differ between melatonin and placebo groups. No side effects of melatonin were reported.<sup>2</sup>

**Table 3 – Patient Dropouts in Russcher et al. RCT<sup>2</sup>**

Melatonin Group		Placebo group	
Reason for leaving	# of patients	Reason for leaving	# of patients
Died	3	Died	3
Transplantation	3	Transplantation	3
Withdrawal	4	Withdrawal	6
Nocturnal dialysis	1	Nocturnal dialysis	1
		Home dialysis	1

The RCT by Koch et al. had a total of twenty-four participants at baseline, but 20 participants remained at the end of the 18-week period.<sup>6</sup> Of the 4 participants lost, two patients died, one withdrew from having dialysis, and one was removed due to non-compliance.<sup>6</sup> Throughout the course of the study, no adverse effects of melatonin were reported.

Koch et al. evaluated quality of sleep using a sleep questionnaire that analyzed daytime function and subjective sleep experience. The results of the questionnaire from patients undergoing hemodialysis are summarized in Table 4. The data illustrated that less time was necessary to fall asleep for patients on daytime dialysis when using melatonin over the placebo group ( $P = 0.04$ ).<sup>6</sup> Overall sleep time increased as well on nights after dialysis ( $P=0.01$ ), and nighttime awakenings decreased after dialysis ( $P=0.03$ ).<sup>6</sup> No adverse effects were reported.

**Table 4 – Sleep Questionnaire results from Koch et al.<sup>6</sup>**

Parameters	Median Placebo	Median Melatonin
Daytime napping (min)	30	0
Sleep onset latency (min)	45	15
Wake periods (min)	30	25
Sleep time (min)	345	480

## **Discussion**

Of the three RCT studies incorporated in this paper, only the Koch et al. RCT showed significant improvement due to the use of supplemental exogenous melatonin in those suffering with chronic diseases. The RCT by Serfaty et al. did not show any significant difference in sleep quality between both the melatonin and placebo groups, despite very similar demographic

factors, depression severity, and randomization. Serfaty et al. also discusses a limitation in which the values from the sleep diary/questionnaire could be unreliable as they may not have always been accurately reported by the patients.<sup>1</sup> It can be recommended in this RCT that such subjective findings be recorded or collected by a third party instead of having patients answer the questionnaires independently. The RCT by Russcher et al. also did not show any significant positive effects of using exogenous melatonin. The authors found that there was no improved quality of life based on the quality of life questionnaire it utilized, but did suggest using a higher dosage of melatonin could produce more favorable results.<sup>2</sup> Limitations of the Russcher study also include the higher than expected drop out rate of participants (37%), as this could have affected the data in a negative manner. The authors only expected to have a 25% drop out rate, and argued that the results obtained could be due to the study's loss of power rather than the inefficacy of exogenous melatonin to alleviate sleep disturbances.<sup>2</sup>

As this selective EBM review analyzes the efficacy of exogenous melatonin on sleep disturbances secondary to chronic disease, future research should be done on the effect of exogenous melatonin on diseases other than CKD and depression. The search conducted by this author on PubMed did not reveal many RCTs regarding the efficacy of exogenous melatonin in general, and future RCTs and researchers should seek out other chronic diseases that can impact the circadian rhythms of humans.

### **Conclusion**

After reviewing each of the three RCT studies discussed in this systematic review, there is not enough data for a conclusive decision on if exogenous melatonin is effective in alleviating sleep disturbances in those suffering from chronic diseases. Although all three RCTs incorporated in this paper had rigorous methodology and adequate sample sizes, 2/3 studies did

not find significant results supporting a positive change in sleep patterns in participants. The Koch et al. RCT did show definitive results that indicated exogenous melatonin improved quality of sleep by reducing time needed to get to sleep, increase in sleep time, and improvement in sleep quality. Limitations of this systematic review include one study that had a high number of withdrawals (25), biases of the participants filling out the subjective sleep questionnaires themselves, and the overall use of the standard dose of melatonin versus a larger dose. Therefore, further research should be conducted on the benefit of melatonin on patients suffering from chronic kidney disease, but should also include many different types of dialysis rather than only patients undergoing daytime treatments. Future studies can also investigate more long-term effects of melatonin and the effects of a larger doses of melatonin, as all three RCTs in this paper utilized traditional doses of melatonin and did not exceed a timeline of 12 months.

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