Sleep Medicine Reviews (2005) **9**, 41–50

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SLEEP MEDICINE reviews

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CLINICAL REVIEW

Effects of exogenous melatonin on sleep: a meta-analysis

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KEYWORDS
Melatonin; Sleep; Insomnia; Meta-analysis

Summary Exogenous melatonin reportedly induces drowsiness and sleep, and may ameliorate sleep disturbances, including the nocturnal awakenings associated with old age. However, existing studies on the soporific efficacy of melatonin have been highly heterogeneous in regard to inclusion and exclusion criteria, measures to evaluate insomnia, doses of the medication, and routes of administration. We reviewed and analyzed (by meta-analysis) available information on effects of exogenous melatonin on sleep. A MEDLINE search (1980 to December 2003) provided English-language articles, supplemented by personal files maintained by the authors. The analysis used information derived from 17 different studies (involving 284 subjects) that satisfied inclusion criteria. Sleep onset latency, total sleep duration, and sleep efficiency were selected as the outcome measures. The study effect size was taken to be the difference between the response on placebo and the mean response on melatonin for each outcome measured. Melatonin treatment significantly reduced sleep onset latency by 4.0 min (95% CI 2.5, 5.4); increased sleep efficiency by 2.2% (95% CI 0.2, 4.2), and increased total sleep duration by 12.8 min (95% CI 2.9, 22.8). Since 15 of the 17 studies enrolled healthy subjects or people with no relevant medical condition other than insomnia, the analysis was also done including only these 15 studies. The sleep onset results were changed to 3.9 min (95% CI (2.5, 5.4)); sleep efficiency increased to 3.1% (95% CI (0.7, 5.5)); sleep duration increased to 13.7 min (95% CI (3.1, 24.3)).

Introduction

The extensive reporting about melatonin in lay publications has encouraged very many people to consume this hormone, sometimes on a daily basis, often with the goal of improving sleep quality.[1] In humans, the circadian rhythm of melatonin release from the pineal gland is highly synchronized with

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doi:10.1016/j.smrv.2004.06.004

the habitual hours of sleep, and the daily onset of melatonin secretion is well correlated with the onset of the steepest increase in nocturnal sleepiness ('sleep gate').[2] Serum melatonin levels were reported to be significantly lower (and the time of peak melatonin values was delayed) in elderly subjects with insomnia, compared with age-matched subjects with no insomnia.[3]

There are also a number of reports that physiological doses of melatonin (i.e. doses which elevate plasma melatonin within its normal nocturnal range), or pharmacologic doses, induce drowsiness and sleep, and may ameliorate sleep disturbances.[4,5] Unfortunately, the studies described in existing publications on melatonin's efficacy have utilized different inclusion and exclusion criteria, different outcome measures to evaluate insomnia, different doses of the hormone, and different routes and timing of its administration. Adding to this complexity, there continues to be considerable controversy over the meaning of the discrepancies that sometimes exist between subjective and objective (polysomnographic) measures of good and bad sleep.[6] In an attempt to respond to these problems we have therefore integrated information derived from 17 studies[3,7–22] which fulfill the criteria described below, using meta-analysis. To our knowledge, while several reviews have examined the effects of melatonin on sleep and insomnia, none has provided a quantitative meta-analysis of these effects, as presented below.

Material and methods

The meta-analysis is based on data reported in peer-reviewed scientific journals. Studies that included at least six adult subjects with no severe disabling systemic disease; were randomized and double blinded; involved placebo-controlled clinical trials; and used objective measures of sleep evaluation were eligible for inclusion in the meta-analysis. Both crossover and parallel group designs were included but case reports were excluded (Appendix A). We identified 17 studies (Table 1) which met the inclusion criteria. Summary information on 284 subjects (means and standard errors) was collected and analyzed.

The studies

Studies differed considerably in terms of the subjects examined (Table 1). Seven of the trials were conducted on healthy normal volunteers; six studied insomniacs; one studied artificially induced insomnia; one studied a combination of institutionalized and independently living insomniacs, one studied schizophrenics, and one studied Alzheimer's disease patients. The age and sex distributions of subjects also differed. The drug formulations, and the doses provided, varied substantially among studies.

Generally, polysomnography was used to record sleep outcome measurements, except for 6 studies (Table 1—studies 3, 10, 11, 13, 15 and 17) which used actigraphy or the index finger switch depression method.

A variety of outcome measurements was investigated. Sleep onset latency, total sleep duration, and sleep efficiency were selected as the outcome measures for our meta-analysis because they were the most frequently recorded. Inadequate presentation of results in some of the 17 papers presented a problem for our review, and two studies were not included in the final analysis for this reason (studies 2 and 6). Sleep onset latency was defined as the time between lights out and polysomnographic or actigraphic evidence of sleep onset. Total sleep duration was the total time spent asleep subsequent to sleep onset. Sleep efficiency was the ratio of total sleep time to total time in bed. All studies included in the meta-analysis recorded at least one of these three outcome measures. Sleep onset latency was the most frequently recorded outcome, 13 of the studies recording this parameter. Total sleep duration was recorded in nine studies and sleep efficiency in eight studies.

Four recent publications on melatonin and sleep,[23–26] were excluded from this meta-analysis (Appendix A). The reasons for exclusions are as follows: Baskett et al.[23] did not report means and standard errors; Stone et al.[24] did not report standard errors; the study by Shirakawa et al.[25] was not blinded (though it was placebo-controlled); and Leppamaki et al.[26] considered only subjective outcomes. Two of these studies[25,26] described beneficial effects of melatonin on sleep; two found no effects.[23,24]

The analysis

The study effect size was taken to be the difference between the mean response on placebo and the mean response on melatonin for each outcome measured. Estimated effect size for each study (i) was taken as: $Y_i = \bar{x}_{pi} - \bar{x}_{ti}$, where $\bar{x}_{pi}$ and $\bar{x}_{ti}$ denote the mean responses on placebo and melatonin, respectively.

Inadequate reporting of results in some of the papers presented difficulties. Such papers reported

Table 1 A summary of the characteristics and designs of the 17 studies included in the meta analysis.

Study	First author (year)	Design	Treatment	Duration	Measured	Conditions	Subjects (M, F)	Age (SEM) [range]	Type
1	Attenburrow (1996)	Crossover	Placebo/0.3 mg/ 1.0 mg Orally	Three nights each trt arm	Polysomnography	Home-nighttime	15 (4,11)	53.9 [41–67]	Healthy normals
2	Cramer (1974)	Crossover - no washout	Placebo/50 mg i.v injection	1 day each trt arm	Polysomnography	Laboratory-Daytime	15 (15)	Young	Healthy normals
3	Dollins (1994)	Crossover 5 × 5 Latin square	Placebo/0.1 0.3 mg/ 1.0 mg/10 mg Orally	1 day each trt arm	Index finger switch depression method	Laboratory-Daytime	20 (20)	3.5 (4.22) [18–24]	Healthy normals
4	Hughes (1997)	Crossover	Placebo/1 mg/10 mg/ 40 mg Orally	1 day (4 h period)	Polysomnography	Laboratory-Daytime	8 (8)	not given [18–30]	Healthy normals
5	James (1987)	Crossover	Placebo/1 mg/5 mg Orally	3 weeks each trt arm	Polysomnography	Laboratory-Nighttime	10 (7,3)	29.9 [21–40]	Healthy normals
6	Waldhauser (1990)	Parallel	Placebo vs. 80 mg Crystalline Orally	1 night	Polysomnography	Laboratory-Nighttime	20 (10,10)	26.4 (1.1)	Artificial insomnia
7	Zhdanova (1995)	Crossover 3 × 3 Latin Square	Placebo/0.3 mg/1 mg Orally,6,8,9PM	1 night	Polysomnography	Laboratory-nighttime	6 (6)	26.5 (1.3)	Healthy normals
8	Zhdanova (1996)	Crossover 3 × 3 Latin Square	Placebo/0.3 mg/1 mg Orally	1 night	Polysomnography	Laboratory-Nighttime	12 (12)	28.5 (1.8)	Healthy normals
9	Dahlitz (1991)	Crossover	Placebo/5 mg orally	4 weeks each trt arm	Polysomnography	Laboratory-Nighttime	8 (8)	Not given	Insomniacs
10	Garfinkel (1995)	Crossover	Placebo/2 mg control release	3 weeks each trt arm	Actigraphy	Home-Nighttime	12 (7,5)	76 (2.3) [68–93]	Insomniacs
11	Haimov (1995)	Crossover	Placebo/2 mg sustained/2 mg fast release	1 week each trt arm	Actigraphy	Laboratory-Nighttime	8 (4,4), 18 (6,12)	73.1 (3.9), 81.1 (8.9)	Independent and institutionalized insomniacs
12	James (1990)	Crossover-no washout	Placebo/1 mg/5 mg orally	1 week each trt arm	Polysomnography	Laboratory-Nighttime	10 (4,6)	33.4 [20–57]	Insomniacs
13	Wurtman (1995)	Latin Square	Placebo/0.3 mg orally	3 nights	Not given	Not given-Nighttime	9	Not given [51–78]	Insomniacs
14	Hughes (1998)	Crossover	Placebo/0.5 mg Immediate 0.5 mg controlled release	2 weeks each trt arm	Actigraphy and Polysomnography	Home and Laboratory	14 (5.9)	70.3 (1.87) [57–79]	Insomniacs
15	Shamir (2000)	Crossover	Placebo/2 mg controlled release	3 weeks each trt arm	Actigraphy	Home nighttime	19	77	Schizophrenic insomniacs
16	Zhdanova (2001)	Crossover	Placebo/0.1 mg/ 0.3 mg/3 mg	1 week each trt arm	Polysomnography	Home and laboratory	30	Over 50	Healthy normals and insomniacs
17	Singer (2003)	Parallel	Placebo/2.5 mg (slow-release)/10 mg	2 months each trt arm	Actigraphy	Home	103	77.4 (8.9)	Alzheimer's patients with sleep disturbance

only the mean response and associated standard errors for each dose, and not the standard error of the mean for differences between doses. In the absence of the correct standard errors (which would have taken into account the matched nature of the designs used), a conservative unpaired analysis was used, calculating standard errors for the standard error of Y_i on the basis of assumed independence of the data for different treatment allocations, as follows.

$$\mathrm{SEM}(Y_i) = \sqrt{(\mathrm{SEM_{pi}})^2 + (\mathrm{SEM_{ti}})^2},$$

(where $\mathrm{SEM_{pi}}$ = Standard Error of the Mean for Placebo and $\mathrm{SEM_{ti}}$ = Standard Error of the Mean for Treatment).An approximate 95% confidence interval for the effect size for study *i* is given by

$$[Y_i - 1.96(\mathrm{SEM}(Y_i)), Y_i + 1.96(\mathrm{SEM}(Y_i))].$$

The estimated overall effect size is

$$\bar{Y} = \frac{\sum W_i Y_i}{\sum W_i},$$

where W_i are weights defined as

$$W_i = \frac{1}{(\mathrm{SEM_{pi}})^2 + (\mathrm{SEM_{ti}})^2}.$$

The standard error of the estimated overall effect size is given by

$$\mathrm{SEM}(\bar{Y}) = \frac{1}{\sqrt{\sum W_i}}.$$

An approximate 95% confidence interval for the underlying effect size is given by $[\bar{Y} - 1.96(\mathrm{SEM}(\bar{Y})), \bar{Y} + 1.96(\mathrm{SEM}(\bar{Y}))]$.

The characteristics of the studies are different and hence there was no reason necessarily to expect the effect size to be homogeneous. However, the primary objective of the analysis was to identify directional effects, and hence it was considered useful to base the primary analysis on a common overall estimate of effect size.

Meta-analysis of effect sizes is simplest if a single dose is compared to placebo. In the studies included in this meta-analysis a variety of dosing strategies was used, ranging from placebo versus a single dose to placebo versus four doses. The dose response relationships in 11 of the studies (see Refs. 17,18) support the existence of a plateau effect, with maximum effect generally being achieved at low doses (e.g. 0.3 mg) and maintained or diminished at higher doses.[18] This relationship supports the comparison of the highest dose versus placebo as the basis for the meta-analysis, and all results reported in this document are based on such comparisons.

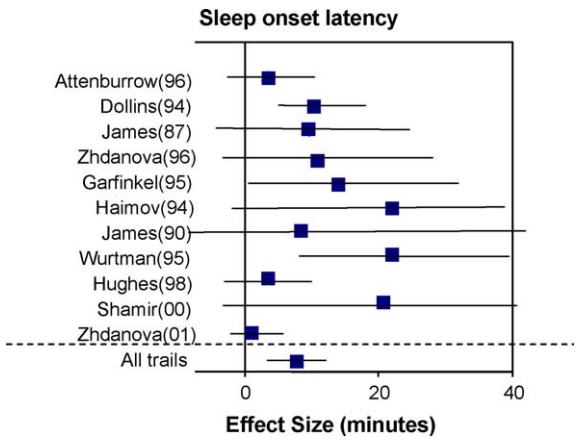

Figure 1 Effects of exogenous melatonin on sleep onset latency. Intervals are 95% confidence intervals for the mean effect.

We also tested the heterogeneity of effect size by comparing the statistic Q defined below to the χ^2 distribution with I−1 degrees of freedom, where *I* is the total number of studies included in the meta-analysis. The null hypothesis of no interstudy variation is rejected if $Q > \chi^2_{I-1}$ test statistic.

$$Q = \sum W_i Y_i^2 - \frac{(\sum W_i Y_i)^2}{\sum W_i}.$$

Results

Summary statistics and overall *P*-values for comparisons among treatment groups were abstracted from the source publications and are displayed graphically in Figs. 1–3. These data are the source data for the conduct of the meta-analysis.

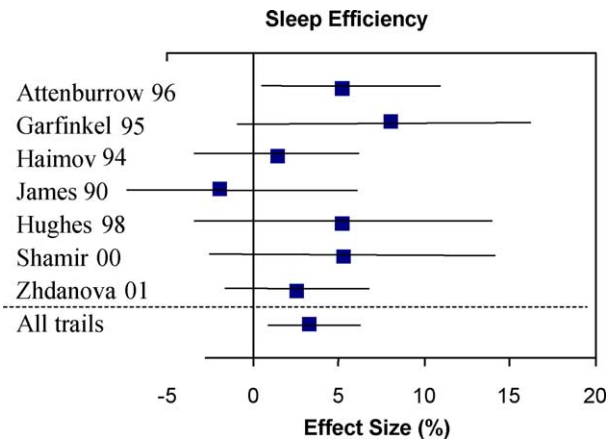

Figure 2 Effects of exogenous melatonin on sleep efficiency. Intervals are 95% confidence intervals for the mean effect.

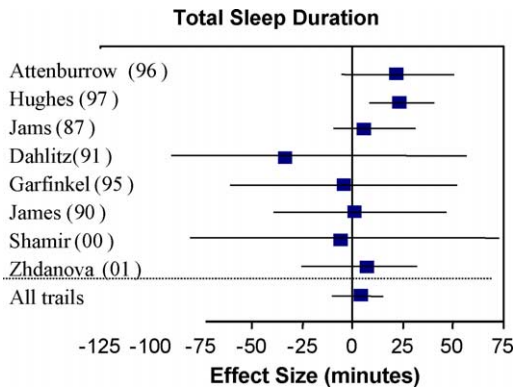

Figure 3 Effects of exogenous melatonin on total sleep duration. Intervals are 95% confidence intervals for the mean effect.

Sleep onset latency

The analysis was undertaken twice for this outcome measure. Initially all 13 studies which had included data on sleep onset latency were pooled. On average, sleep onset latency time was reduced significantly by melatonin, by 4.0 min, 95% confidence interval (2.5, 5.4). However, it was evident that study 7 might have exerted undue influence on the analysis because of outliers in the original dataset; therefore it was of interest to reanalyze the results omitting this study. Similarly, study 4 was removed because of the significant heterogeneity of the data. The revised analysis produced an estimated mean reduction in sleep onset latency of 7.5 min, 95% confidence interval (5.2, 9.9), (Fig. 1).

Sleep efficiency

The overall estimated mean effect of melatonin was to increase sleep efficiency significantly, by 2.2%, 95% confidence interval (0.2, 4.2), (Fig. 2).

Total sleep duration

On average, melatonin significantly increased total sleep duration by 12.8 min, 95% confidence interval (2.9, 22.8), (Fig. 3).

Evidence of heterogeneity

Heterogeneity was tested for all three outcomes and, as above, twice for sleep onset latency. For sleep onset latency: $Q = 52.0$ when compared to χ^2_{12} produced a significant result, indicating that the studies were heterogeneous with regard to this outcome measure (when outliers were omitted: $Q = 34.1$ which also produced a significant result). For total sleep duration: $Q = 4.3$ when compared to χ^2_8 produced an insignificant result, indicating that one cannot rule out the possibility that studies were homogeneous with regard to this outcome measure. For Sleep Efficiency: $Q = 7.5$ when compared to χ^2_7 failed to produce a significant result, indicating that the null hypothesis of homogeneity cannot be rejected for this outcome measure.

Dawson study

Dawson et al.[27] studied the effect of transbuccal administration of melatonin in elderly insomniacs. In this double-blind crossover study, subjects were randomized to melatonin or placebo for four nights, and then switched to the other treatment for four additional nights, following 3 days of washout. Averages and standard errors are reported in this article for each of the last two nights of melatonin and placebo. This study was not included in our meta-analysis because the mean difference in total sleep duration between the last two placebo nights was very large and statistically significant (108.1 min, $N = 12$, $P = 0.02$). If this discrepency is ignored, the two-night results are pooled for both treatments, and it is included in the meta-analysis, then the meta-analysis results remain statistically significant and become 14.6 $\pm$ 5.0 m, 4.0 $\pm$ 0.74 m, and 1.9 $\pm$ 1.0% for duration, onset latency, and efficiency, respectively, values which would not materially change the discussion or conclusions of the present article.

Discussion

This meta-analysis supports the hypotheses that melatonin decreases sleep onset latency, increases sleep efficiency, and increases total sleep duration. The pooled data were highly heterogeneous, possibly reflecting the fact that the melatonin preparations used in these individual studies varied in dose presented, and probably in quality, excipients, and purity as well. In addition, the study designs differed considerably from each other. Nevertheless, in spite of the heterogeneity of the data, the present meta-analysis does lend statistical support to the notion that melatonin preparations can improve sleep quality with regard to sleep onset latency, sleep efficiency, and sleep duration.

The definition of 'normal' sleep varies considerably within the general population. Some individuals may require relatively little sleep without characteristic symptoms of insomnia while others who sleep longer may complain of fatigue, daytime sleepiness, or irritability. In an attempt to evaluate the efficacy of soporific-hypnotics in treating insomnia several diagnostic classifications have been established. The 'European guidelines for clinical investigation of hypnotic medicinal products' defined five criteria to be used in evaluating the therapeutic efficacy of a soporific or hypnotic drug. These included: sleep onset latency, sleep efficiency, sleep duration, feeling of restorative sleep, and subsequent improved daytime functioning. In the present meta-analysis we analyzed melatonin's effects only on the first three of these criteria since they are more uniformly measurable and the most objective. There is a positive correlation between improvements in these sleep variables and the feeling of restorative sleep and the sensation of well being after awakening.[28]

Some studies which were not included in our meta-analysis (because they used only subjective methods of sleep evaluation) failed to find significant effects of exogenous melatonin on sleep (Appendix A).[29] However, the integrated data from the 17 studies included in this meta-analysis clearly indicate that specific melatonin preparations produce statistically significant benefits in sleep onset latency, sleep efficiency and sleep duration. Exogenous melatonin shortened the sleep onset latency by 4.0 min. The normal limits for latency to sleep are considered to be 15–20 min. Typically for research purposes sleep onset insomnia is defined as latency of 30 min or more. A reduction of about 5–10 min in sleep latency thus may be clinically significant. There was an improvement of 2.2% in sleep efficiency and sleep duration was prolonged by 12.8 min. The normal sleep efficiency is about 90–95%. A 3–4% increase in sleep efficiency usually reflects a decreased number of awakenings during sleep, shortened periods of wakefulness, or a reduction of sleep latency; all of these improve the overall quality of sleep. Prolongation of sleep duration is also an indication of improved sleep efficiency and continuity. Such improvements are associated with better achievements in various performance tests (such as attention score, concentration score, fine motor activity score, and reaction time score) and the sensation of improved well being during the day (see Ref. 19).

Of the 17 studies used in the above analysis, 15 involved healthy subjects who had no known relevant condition other than insomnia. One study[20] was on schizophrenics; the other[22] enrolled Alzheimer's disease patients. The analysis was redone omitting these two investigations, and the results were found to be similar to those discussed above. Sleep onset latency decreased to 3.9 min (95% CI (2.5, 5.4)); omitting studies 4 and 7 in addition to study 15 (which enrolled schizophrenics) led to an estimate of 7.4 min (95% CI (5.1, 9.8)), which is comparable to the estimate obtained by omitting studies 4 and 7 but including study 15. (Study 17 in Alzheimer's patients did not report sleep onset latency.) Sleep efficiency increased to 3.1% (95% CI (0.7, 5.5)); sleep duration increased to 13.7 min (95% CI (3.1, 24.3)).

Few studies have investigated the possible effects of exogenous melatonin on sleep architecture. Unlike benzodiazepines, melatonin is described in most studies[11,15] as producing no effects on stages 2 and 3–4 sleep. One study[17] found a tendency for prolonged stage 2 sleep and shorter stages 3–4 after consuming physiological (low) doses of melatonin, while stages 1 and REM sleep were unaffected. However, a subsequent study by the same group[18] failed to note any changes in sleep architecture. When pharmacological doses were used,[12] this tendency reached statistical significance. A 'hangover' effect, which is typical of most benzodiazepines, has not been reported for melatonin. In two of the reviewed studies where this phenomenon was specifically investigated no such effect was found.[4,21]

Available data on the sleep-promoting effects of modest increases in serum melatonin concentrations suggest that the hormone may have a physiological role in sleep initiation and maintenance. The present meta-analysis implies that exogenous melatonin might have some use in treating insomnia, particularly that associated in aged individuals with nocturnal melatonin deficiency[18] or with an abnormal pattern of melatonin secretion. The optimal dose and time of melatonin administration need further delineation.

Acknowledgements

These studies were supported in part by NIH Grants 5M01 RR1066-25 to the MIT Clinical Research Center, The National Institutes of Health (MH-28783), and from the Center for Brain Sciences and Metabolism Charitable Trust and the Women' Health Center, Hadassah–Hebrew University Medical Center.

Appendix A. Table of excluded articles

First author, title, reference	Reason(s) for exclusion
1. Kunz D Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. J Clin Endocrinol Metab. 2004 Jan;89(1):128–34	Inadequate outcome measures.
2. Paul MA, Impact of melatonin, zaleplon, zopiclone, and temazepam on psychomotor performance. Aviat Space Environ Med. 2003 Dec; 74(12):1263–70	Inadequate outcome measures
3. Fischer S, Melatonin acutely improves the neuroendocrine architecture of sleep in blind individuals. J Clin Endocrinol Metab. 2003 Nov;88(11):5315–20	Inadequate outcome measures blind people
4. Boeve BF Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003 Jul;4(4):281–4	Inadequate outcome measures
5. Baskett JJ, Does melatonin improve sleep in older people? A randomized crossover trial. Age Ageing. 2003 Mar;32(2):164–70	Inadequate statistical information
6. Stone BM, Hypnotic activity of melatonin. Sleep.2000 Aug 1;23(5):663–9	Inadequate statistical information
7. Shirakawa SI, Effect of melatonin on sleep and rectal temperature of young healthy evening types. Psychiatry Clin Neurosci. 2001 Jun;55(3):301–2	Not blinded
8. Leppamaki S, Effect of controlled-release melatonin on sleep quality, mood, and quality of life in subjects with seasonal or weather-associated changed in mood and behaviour. Eur Neuropsychopharmacol. 2003 May;13(3):137–45	Subjective outcomes
9. Asayama K, Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. J Nippon Med Sch. 2003 Aug;70(4):334–41	Not a peer reviewed journal
10. Cardinali, The use of melatonin in Alzheimer's disease. Neuroendocrinol Lett. 2002 Apr;23 Suppl 1:20–3	Inadequate statistical information
11. Cavallo A, Dose response to melatonin treatment for disordered sleep rhythm in a blind child. Sleep Med. 2002 Mar;3(2):159–61.	Case report. Child
12. Niederhofer H, Brief report: melatonin facilitates sleep in individuals with mental retardation and insomnia. J Autism Dev Disord. 2003 Aug;33(4):469–7	Inadequate subjects. Mental retardation
13. Smits MG, Melatonin improved health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2003 Nov;42(11):1286–93	Children
14. Paavonen EJ, Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. J Child Adolesc Psychopharmacol. 2003 Spring;13(1):83–95	Children

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Appendix A (*continued*)

First author, title, reference	Reason(s) for exclusion
15. Almeida Montes LG, Treatment of primary insomnia with melatonin: a double-blind, placebo-controlled, crossover study. J Psychiatry Neurosci. 2003 May;28(3):191–6	Inadequate outcome measures
16. Serfaty M. Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomized placebo controlled trial of low does melatonin for sleep disorders in dementia. Int J Geriatr Psychiatry. 2002 Dec;17(12):1120–7	Inadequate subjects. Subjects with severe dementia
17. Zhdanove IV, Geiger DA, Schwagerl AL, Leclair OU, Killiany R, Taylor JA, Rosene DL, Moss MB, Madras BK. Melatonin promotes sleep in three species of diurnal nonhumam primates. Physiol Behav. 2002 Apr 1;75(4):523–9	Non-human
18. Ross C, Melatonin treatment for sleep disorders in children with neurodevlopmental disorders: an observational study. Dev Med Child Neurol. 2002 May;44(5):339–44	Children
19. Satoh K, Mishima K Hypothermic action of exogenously administered melatonin is dose-dependent in humans Clin Neuropharmacol. 2001 24(6):334–40	Inadequate outcome measures
20. Sharkey KM, Effects of melatonin administration on daytime sleep after simulated night shift work. J Sleep Res. 2001 Sep; 10(3): 181–92	Night shift sleep. Inadequate outcome measures
21. Brusco LI, Effect of melatonin in selected populations of sleep-disturbed patients. Biol Signals Recept. 1999 Jan–Apr; 8(1–12): 126–31	Open label study
22. Matsumoto M. The hypnotic effects of melatonin treatment on diurnal sleep in humans. Psychiatry Clin Neurosci. 1999 Apr; 53(2): 243–5	Diurnal sleep
23. Jan JE, Melatonin treatment of sleep-wake cycle disorders in children and adolescents. Dev Med .Child Neurol. 1999 Jul; 41(7): 491–500	Children
24. Zhdanova IV, Wurtman RJ, Wagstaff J. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. J Pediatr Endocrinol Metab. 1999 Jan–Feb; 12(1): 57–67	Children
25. Kunz D, Bes F, Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord. 1999 May; 14(3): 507–11	Open label study
26. Skene DJ, Lockley SW, Arendt J, Melatonin in circadian sleep disorders in the blind. Biol Signals Recept. 1999 Jan–Apr; 8(1–2): 90–5	Review
27. Jean-Louis G, Zizi F, von Gizycki H, Taub H, Effects of melatonin in two individuals with Alzheimer's disease. Percept Mot Skills. 1998 Aug; 87(1): 331–9	Fewer than six subjects

Appendix A (*continued*)

First author, title, reference	Reason(s) for exclusion
28. Jean-Louis G, von Gizycki H, Zizi F, Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment. J Pineal Res. 1998 Oct; 25(3): 177–83.	Not placebo controlled
29. Wright SW, Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. Ann Emerg Med. 1998 Sep; 32(3 Pt 1): 334–40	Night shift work
30. Van Den Heuvel CJ, Kennaway DJ, Dawson D. Effects of daytime melatonin infusion in young adults. Am J Physiol. 1998 Jul; 275(1 Pt 1): E19–26	Inadequate outcome measures
31. Nagtegaal JE, Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. J Sleep Res. 1998 Jun; 7(2): 135–43	Inadequate outcome measures
32. Okawa M, Melatonin treatment for circadian rhythm sleep disorders. Psychiatry Clin Neurosci. 1998 Apr; 52(2): 259–60	Not placebo controlled
33. Jan JE, Melatonin treatment of chronic sleep disorders J child Neurol. 1998 Feb; 13(2): 98.	Children
34. Lushington K, Daytime melatonin administration in elderly good and poor sleepers: effects on core body temperature and sleep latency. Sleep. 1997 Dec; 20(12): 1135–44	Inadequate outcome measures
35. Jan JE, The treatment of sleep disorders with melatonin. Dev Med Child Neurol. 1994 Feb; 36(2): 97–107	Children
36. Ferini-Strambi L, Effect of melatonin on sleep microstructure: preliminary results in healthy subjects. Sleep. 1993 Dec; 16(8): 744–7	Combination of melatonin and benzodiazepines
37. MacFarlane JG, The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. Biol Psychiatry. 1991, 15; 30(4): 371–6	Subjective assessment of sleep Inadequate outcome measures

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