Melatonin as add-on treatment for epilepsy (Review)

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[Intervention Review]

Melatonin as add-on treatment for epilepsy

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ABSTRACT

Background

Epilepsy is one of the most common chronic neurologic disorders. Despite the plethora of antiepileptic drugs (AEDs) currently available, 30% of patients continue having seizures. This group of patients requires a more aggressive treatment, since monotherapy, the first choice scheme, fails to control seizures. Nevertheless, polytherapy often results in a number of unwanted effects, including neurologic disturbances (somnolence, ataxia, dizziness), psychiatric and behavioral symptoms, and metabolic alteration (osteoporosis, inducement or inhibition of hepatic enzymes, etc.). The need for better tolerated AEDs is even more urgent in this group of patients. Reports have suggested an antiepileptic role of melatonin with a good safety profile.

Objectives

To assess the efficacy and tolerability of melatonin as add-on treatment for epilepsy.

Search methods

We searched the Cochrane Epilepsy Group Specialized Register (May 2012), the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4 of 12, *The Cochrane Library* 2012), and MEDLINE (1946 to April 2012). The bibliographies of any identified study were searched for further references. We handsearched selected journals and conference proceedings. No language restrictions were imposed. In addition, we contacted melatonin manufacturers (i.e. Nathura) and original investigators to identify any unpublished study.

Selection criteria

Randomized controlled trials; double, single, or unblinded trials; parallel group or cross-over studies. People with epilepsy regardless of age and sex, including children and adults with disabilities. Administration of melatonin as add-on treatment to any AED(s) compared to add-on placebo or no add-on treatment.

Data collection and analysis

Review authors independently selected trials for inclusion according to predefined criteria, extracted relevant data, and evaluated the methodologic quality of trials. The following outcomes were assessed: at least 50% seizure reduction, seizure freedom, adverse events, and quality of life.

Main results

Four publications, with a total of 102 participants (90 aged under 18 years), were included. Two different comparisons were available: 1. melatonin versus placebo and 2. melatonin 5 mg versus melatonin 10 mg. Despite our primary intention, due to insufficient information on outcomes, we were unable to perform any meta-analysis, but summarized data narratively. Two studies were randomized, double-blind, cross-over, placebo-controlled trials and two were randomized, double-blind, parallel, placebo-controlled trials. Only one study provided the exact number of seizures during the trial compared to the baseline: none of the patients with seizures during the trial had a change in seizure frequency compared with the baseline. Adverse events were systematically evaluated in only one study (no adverse events observed). Only one study systematically evaluated quality of life, showing no statistically significant improvement in quality of life in the add-on melatonin group.

Authors' conclusions

Included studies were of poor methodologic quality, and did not systematically evaluate seizure frequency and adverse events, so that it was impossible to summarize data in a meta-analysis. It is not possible to draw any conclusion about the role of melatonin in reducing seizure frequency or improving quality of life in patients with epilepsy.

PLAIN LANGUAGE SUMMARY

The use of melatonin as an adjunctive treatment for epilepsy

Epilepsy is one of the most common chronic neurologic disorders, and despite several antiepileptic drugs being available, 30% of patients continue having seizures. Reports have suggested an antiepileptic role of melatonin with a good safety profile. Four trials representing 102 participants were included in the present review. Two different comparisons were available: 1. melatonin versus placebo and 2. melatonin 5 mg versus melatonin 10 mg. Included trials were of poor methodologic quality, and did not systematically evaluate seizure frequency, seizure freedom and adverse events. Only one study systematically reported seizure frequency occurring during the trial compared to the baseline, and only one trial evaluated the direct influence of melatonin on quality of life. It is not possible to draw any definitive conclusions about the role of melatonin in reducing seizure frequency or improving the quality of life in people with epilepsy.

BACKGROUND

Epilepsy is defined as the occurrence of at least two unprovoked epileptic seizures (Commission ILAE 1989). It is one of the most common neurologic disorders: in Western countries the incidence in adults is 50/100,000 per year (Hauser 1998) with a prevalence of 5/1000 to 10/1000 (Goodridge 1983; McDonald 2000). In children from birth to 15 years of age, the incidence is 5/10,000 to 7/10,000 per year and prevalence 5/1000, the differences being mainly due either to benign epilepsy syndromes that remit spontaneously or to severe pathologies with neurologic involvement causing death.

Despite the plethora of antiepileptic drugs (AEDs) developed since the introduction of phenobarbital in 1912, 30% continue having seizures (Annegers 1979; Camfield 1996; Cockerell 1995; Elwes 1984; Goodridge 1983; McDonald 2000; Shorvon 1982). This group of patients requires a more aggressive treatment, since monotherapy, the first choice scheme, fails to control seizures. Nevertheless, polytherapy often results in a number of unwanted effects, including neurologic disturbances (somnolence, ataxia, dizziness), psychiatric and behavioral symptoms, and metabolic alteration (osteoporosis, inducement or inhibition of hepatic enzymes, etc.). The need for better tolerated AEDs is even more urgent in this group of patients.

Research has suggested an antiepileptic role of melatonin, an indolamine synthesized from tryptophan in the pineal gland and released in a circadian pattern (Brzezinski 1997). In clinical practice, melatonin is used to treat sleep-wake cycle disorders, mainly jet lag syndrome and shift worker disturbances (Herxheimer 2003; Herxheimer 2005; Revell 2006), as well as for the treatment of sleep disorders in children with neurologic and developmental problems (Cortesi 2010; Weiss 2010).

Both in vitro and in vivo studies have suggested an antiepileptic activity of melatonin (Anton-Tay 1974; Fauteck 1999; Je 1996; Mevissen 1998; Molina-Carballo 1997), mediated by an antiox-

idant effect (Kabuto 1998), an increase in γ-aminobutyric acid (GABA) concentration (Niles 1987) and GABA receptor affinity (Acuna-Castroviejo 1986), or a reduction of the N-methyl-D-aspartate (NMDA) excitatory effect (Munoz-Hoyos 1998). In contrast, a proconvulsant effect of melatonin has been reported by one author (Sheldon 1998). Although studies investigating the long-term effects of melatonin are still lacking, high melatonin doses have so far proved safe (Seabra 2000).

In this review we investigated the efficacy of add-on melatonin in patients with epilepsy.

OBJECTIVES

To evaluate the efficacy and tolerability of melatonin as add-on therapy in patients with epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomized controlled trials.
2. Double, single, or unblinded trials.
3. Parallel group or cross-over studies.

Types of participants

People with epilepsy, defined as with at least two unprovoked seizures, diagnosed by a physician, regardless of age, sex, ethnicity, and diagnosis, including children and adults with disabilities.

Types of interventions

Administration of melatonin as add-on treatment to any AED(s) compared to add-on placebo or no add-on treatment.

Types of outcome measures

Primary outcomes

At least a 50% reduction in frequency of seizures of any type

The proportion of patients with a 50% or greater reduction in seizure frequency during the treatment period compared to the pre-randomiszation baseline period.

Seizure freedom

The proportion of patients with a complete cessation of seizures during the treatment period.

Adverse events

The proportions of patients with adverse events reported in included studies.

Secondary outcomes

An improvement in quality of life

The proportion of patients reported to have a better quality of life according to validated questionnaires (e.g. Quality of Life in Childhood Epilepsy (QOLCE), United States Quality of life in Cchildhood eEpilepsy (USQOLCE), Short Form 36 questions (SF-36) health profile including quality of life, etc.)

Search methods for identification of studies

Electronic searches

We searched the following databases:

1. Cochrane Epilepsy Group Specialized Register (3 May 2012),
2. The Cochrane Central Register of Controlled Trials (CENTRAL Issue 4 of 12, *The Cochrane Library* 2012) using the search strategy outlined in Appendix 1,
3. MEDLINE (Ovid, 1946 to April week 4, 2012) using the search strategy outlined in Appendix 2.

Searching other resources

The bibliographies of any included studies that were identified were searched for further references. We handsearched selected journals and conference proceedings. No language restrictions were imposed. In addition, we contacted melatonin manufacturers (i.e. Nathura) and original investigators to identify any unpublished study.

Data collection and analysis

Selection of trials

Review authors (FB and ADF) independently assessed trials for inclusion. Any disagreement was resolved by discussion.

Assessment of methodologic quality

Review authors (FB and ADF) independently assessed the methodologic quality of all the included studies and recorded the findings. We noted following methodology aspects: study design, type of control, method of allocation, concealment, completeness of follow-up. We used preprinted selection forms to evaluate methodologic quality.

Data extraction

One review author (FB) extracted the data onto a prespecified data extraction form, and the other author (ADF) independently checked the data. Pilot testing of data collection forms were performed to improve reliability. Data reported by published sources were used in this trial.

Data analysis

We extracted the following data for trials meeting our inclusion criteria.

Methodologic/trial design

(a) Method of generation of random list
(b) Method of concealment of randomization
(c) Blinding methods

Patients' covariates

(a) Age
(b) Sex
(c) Seizure type
(d) Epileptic syndrome
(e) Presence of neurologic signs/intellectual disabilities
(f) Electroencephalogram (EEG)
(g) Neuroradiology (computerized tomography (CT), magnetic resonance imaging (MRI))
(h) Duration of disease prior to treatment
(i) Monotherapy versus polytherapy before randomizations

Outcomes data

(1) Fifty per cent or greater reduction in seizure frequency: proportion of participants with at least 50% or greater reduction in seizure frequency at the end of the study (numerator)/number of participants at prerandomization baseline period (denominator).
(2) Seizure freedom: proportion of participants achieving total cessation of seizures (numerator)/number of participants at prerandomization baseline period (denominator).
(3) Incidence of adverse events of any type: number of adverse events (numerator)/total number of participants at prerandomization baseline period (denominator).
(4) Improvement in quality of life as assessed by validated and reliable rating scales (quality of life rating scores).

Data analysis plan

We sought data on the number of participants in the treatment groups and with each outcome, irrespective of compliance or completeness of follow-up, in the articles or requested from the authors in order to undertake an intention-to-treat analysis.
Despite our primary intention, due to insufficient information on outcomes, we were unable to perform any meta-analyses.
We therefore planned:
(a) to extract data from the trials or calculate from the primary data supplied by the authors,
(b) to summarize efficacy (seizure frequency and seizure freedom) data narratively,
(c) to document tolerability (incidence of individual adverse events) narratively,
(d) to summarize quality of life data narratively.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 28 potentially relevant studies. After careful evaluation, 24 studies were excluded from the review. The main reasons for exclusion were: not relevant outcomes, not relevant participants, adverse events unclear/not stated, no comparison with placebo or other drug (see Excluded studies; Characteristics of excluded studies).
Four publications for a total of 102 patients (mostly children) fulfilled the inclusion criteria of the present review. Two publications (Coppola 2004; Hancock 2005) were randomized, double-blind, cross-over, placebo-controlled trials and two (Gupta 2004a; Gupta 2004b) were randomized, double-blind, parallel, placebo-controlled trials.

Included studies

See: Characteristics of included studies

Coppola 2004

Coppola 2004 was a randomized, double-blind, cross-over, placebo-controlled trial conducted in subjects aged over 12 months, with mental retardation with/without seizures, and diagnosed with wake-sleep disorders. Thirty-two patients were enrolled in the study, seven patients (28%) were lost to the study. Twenty-five patients (16 males, nine females), ages from 3.6 to 26 years (mean 10.5 years), mostly (18/25) with epileptic seizures, completed both melatonin and placebo phases. Patients were randomized to oral synthetic fast-release melatonin or placebo. Phase 1 (melatonin or placebo) lasted four weeks and, after a cross-over period of one week, each patient entered phase 2 (melatonin or placebo), which lasted four weeks. Melatonin was initiated at the daily dose of 3 mg, at nocturnal bedtime. In case of inefficacy, melatonin dose could be titrated up to 9 mg during the following two weeks in increments of 3 mg/week, unless the patient was unable to tolerate it. The dose of pre-existing medication was maintained throughout the trial. At the end of phase 2, responders to melatonin entered an open-label phase of two months. Seizure freedom and seizure frequency were reported without clearly specifying the exact number of seizures; authors stated only that out of the 11 seizure-free patients before starting the study, nine remained unchanged on melatonin treatment. No overall significant change with regards to seizure control was found with melatonin. Melatonin was well tolerated in all patients and no adverse effects were reported.

Gupta 2004a

Gupta 2004a was a randomized, double-blind, parallel, placebo-controlled trial. It was conducted in children with epilepsy ages 3 to 12 years on carbamazepine monotherapy to evaluate the effects of add-on melatonin administration on the quality of life using a parental questionnaire (Sleep Behavior Questionnaire). Children had to be seizure-free for at least the last six months before enrollment. Of the 31 patients enrolled, 13 (mean age 8.3 years) randomly received add-on melatonin, whereas 15 (mean age 8.1 years) received add-on placebo. Two patients in the placebo group and one in the melatonin group were lost to follow-up. The questionnaire was administered before add-on melatonin/placebo and four weeks after (28 to 32 days). No data on seizure freedom or seizure frequency were reported. No adverse events warranting discontinuation of the therapy were reported.

Gupta 2004b

Gupta 2004b was a subsequent study performed by the same investigators (Gupta 2004b). It was a randomized, double-blind, placebo-controlled trial. It was also conducted in children with an epilepsy, ages 3 to 12 years on valproate monotherapy to evaluate the effect of add-on melatonin on quality of life using a parental questionnaire (QOLCE). Children had to be seizure-free for six months before enrollment. Of the 31 patients enrolled, 16 (mean age 7.4 years) randomly received add-on melatonin, whereas 14 (mean age 6.6 years) received add-on placebo. One patient in the placebo group was lost to follow-up. The questionnaire was administered before add-on melatonin/placebo and four weeks after (28 to 32 days). No data on seizure freedom or seizure frequency were reported. No adverse events warranting discontinuation of therapy were reported.

Hancock 2005

This was a randomized, double-blind, controlled, cross-over trial investigating the response to oral melatonin using two dose regimens in patients with sleep disorders associated with tuberous sclerosis complex (Hancock 2005). Eight outpatients with tuberous sclerosis complex and sleep disorder (ages 18 months to 31 years) received either 5 or 10 mg of melatonin. All patients were epileptic and on concurrent AEDs, and all had mental retardation and behavioral difficulties. The trial consisted of following phases: an initial two-week baseline period to confirm the sleep disorder and familiarize the patient or caregiver with the requirements of the trial with no treatment; a two-week period of treatment with either 5 or 10 mg of melatonin; a two-week washout period with no treatment; and a two-week period of treatment with the alternative dose of melatonin (i.e. 5 mg after 10 mg or 10 mg after 5 mg). Sleep latency, total sleep time, number of awakenings, and seizure frequency were recorded in sleep and seizure diaries. No evidence of a dose effect between 5 and 10 mg was seen with respect to any outcome measure. The exact number of seizures occurring during the trial, compared to baseline, was given. None of the children who had seizures during the trial had a change in seizure frequency compared with the baseline period before melatonin treatment at either dose. Trials duration (including follow-up) was six weeks. During the study three out of seven patients who completed the study remained seizure-free. No side effects were reported or observed. Quality of life was not considered as an outcome.

Participants

We included four studies with a total of 102 patients (90 participants aged under 18 years). One study was conducted in children, adolescents, and young adults with wake-sleep disorder and mental retardation, most of them on chronic AED therapy (Coppola 2004). The principal investigator of Coppola 2004 indicated by mail (December 2011) that 21 out of 25 patients who completed the study were aged under 18 years. Two studies were conducted by the same group of investigators on pediatric populations (Gupta 2004a; Gupta 2004b). When contacted by mail (29 December 2011), authors of one trial that also included adults (Hancock 2005) specified that all participants enrolled (included patients lost to follow-up) except one were aged under 18 years old.

One study (Coppola 2004) was conducted in patients with or without epilepsy. This study is included but we analyzed only data from patients with epilepsy. One study was conducted in patients with tuberous sclerosis complex and sleep disorder (children and adults) (Hancock 2005). In this trial, all participants had epilepsy and were on concurrent AEDs.

Three studies compared the efficacy of melatonin versus placebo (Coppola 2004; Gupta 2004a; Gupta 2004b), whereas Hancock 2005 compared two different doses of melatonin (5 mg versus 10 mg).

Adverse events

Apart from one study (Hancock 2005), adverse events were not systematically reported.

Quality of life

Based on the protocol's requirement and the data collected from the included studies, the only validated quality-of-life scale adopted in the included studies was the QOLCE (Gupta 2004b). One study (Gupta 2004a) included the evaluation of sleep quality as an outcome; however this trial was excluded as the questionnaire used assessed sleep quality alone, and not the overall quality of life.

Excluded studies

See: Characteristics of excluded studies

After careful evaluation, 24 studies were excluded from the review. The main reasons for exclusion were: non-relevant outcomes (Ardura 2010; Ashrafi 2010; Bazil 2000; Eisermann 2010; Elkhayat 2010; Guo 2009; Gupta 2006; Molina-Carballo 2007; Murck 1997; Paprocka 2010; Ross 2002; Schapel 1995; Yalyn 2006), non-relevant participants (McArthur 1998; McLellan 2002; Murck 1997; Smits 2000; Wassmer 2001), adverse events unclear/not stated (Gupta 2004c; Gupta 2004d), no comparison with placebo or other drug (Ardura 2010; Elkhayat 2010; Fauteck 1999; Guo 2009; Molina-Carballo 2007; Paprocka 2010; Peled 2001). Some studies were excluded for more than one reason. Two studies were conducted by the same authors (Gupta, Aneja, Kohli) and published within a short time (Gupta 2004b; Gupta 2005). Although evaluating different outcomes (sleep behavior, Gupta 2005; quality of life, Gupta 2004b), both studies were conducted in children with epilepsy on valproate monotherapy (same numbers of patients, same demographic characteristics) in the same period. Since patients included in Gupta 2005 were the same patients already included in trial of Gupta 2004b, we considered this trial (Gupta 2005) as a duplicate publication and therefore excluded it from the review, including only Gupta 2004b.

Risk of bias in included studies

See: Characteristics of included studies

Sequence generation was explicitly reported and adequately performed in two trials (Gupta 2004a; Gupta 2004b). In both studies randomization code lists were prepared by a statistician, not connected to the study, and the permutation of code numbers was computer generated for the treatment groups. In two publications (Coppola 2004; Hancock 2005) authors did not explicitly state how sequence generation was created. However, after contact (by mail, 29 December 2011), principal investigators of Hancock 2005 and Coppola 2004 indicated that allocation sequence was computer generated. Allocation concealment was adequate in three trials (Gupta 2004a; Gupta 2004b; Hancock 2005), whereas in one study it was unclear due to lack of information (Coppola 2004). In two studies (Gupta 2004a; Gupta 2004b) the placebo tablets were identical in shape, size, color, and packaging. In Hancock 2005, patients received identical capsules (principal investigator specified that the placebo was made by the company who supplied the melatonin). The principal investigator of the fourth study (Coppola 2004) was contacted by mail (29 December 2011), but no additional information to evaluate allocation concealment was provided. In all studies blinding was not explicitly reported. All studies reported reasons for lossof follow-up, although no study performed an intention-to-treat analysis. Only one study explicitly reported or systematically evaluated the presence of adverse events (Hancock 2005). In two trials (Gupta 2004a; Gupta 2004b) the completeness of outcome reporting was unclear: for each patient a daily diary was provided with the instruction to record any adverse events or unusual symptoms observed immediately; however, in the results section, the authors stated only that no adverse events warranting discontinuation of the therapy were observed.

Effects of interventions

Two different comparisons were available (melatonin versus placebo; melatonin 5 mg versus melatonin 10 mg), but only the former included more than one study.

Comparison 1: melatonin (any dose) versus placebo

Three trials evaluated melatonin versus placebo (Coppola 2004; Gupta 2004a; Gupta 2004b). The melatonin dose varied between trials. Despite our primary intention, due to insufficient information on each outcome, we were unable to perform a meta-analysis.

Primary outcomes

Seizure frequency (50% seizure reduction during the treatment period from baseline)

In one study (Coppola 2004) the authors stated that seizures occurred, without further specifying the exact number of seizures occurring in each group (melatonin/placebo). The principal investigator of this study was contacted by mail (29 December 2011), but no additional information was provided. In one trial (Gupta 2004a), which selected only patients seizure-free for at least six months before the beginning of the trial, all patients (13/13 on add-on melatonin, 16/16 on add-on placebo) remained seizure-free, so that a 50% seizure reduction rate during the treatment period from baseline could not be calculated. One study gave no data regarding this outcome (Gupta 2004b); this trial selected only patients seizure-free for at least six months before the beginning of the trial, so that 50% seizure reduction during the treatment period from baseline could not be calculated. The duration of trials (including follow-up) varied from four weeks (Gupta 2004a) to nine weeks (Coppola 2004).

Seizure freedom

Two studies (Coppola 2004; Gupta 2004a) reported data regarding seizure freedom. Additional data on this outcome were requested by mail for the third included study (Gupta 2004b), but not provided. In one trial (Gupta 2004a) all patients (13/13 on add-on melatonin, 15/15 on add-on placebo) remained seizure-free for eight weeks' follow-up. One study (Coppola 2004) described seizure freedom and seizure frequency without clearly specifying the exact number of seizures; authors stated only that out of the 11 seizure-free patients before starting the study, nine remained unchanged on melatonin treatment. The number on placebo (if any) who remained seizure free was not reported. The principal investigator of this study (Coppola 2004) was contacted by mail (29 December 2011), but no additional information to clarify such an aspect further was provided.

Adverse events

Although adverse events were not systematically evaluated, in one trial (Coppola 2004) no side effect was reported. In two trials (Gupta 2004a; Gupta 2004b) the completeness of outcome reporting was unclear. A daily diary was provided for each patient with the instruction to record any adverse events or unusual symptoms observed immediately. However, in the results section the authors stated only that no adverse events warranting discontinuation of the therapy were observed.

Secondary outcomes

Quality of life

Only one study (Gupta 2004b) systematically evaluated quality of life, showing no statistically significant improvement in quality of life in either group (valproic acid + melatonin group: intragroup P = 0.08; valproic acid + placebo group: intragroup P = 0.16). The authors performed no intergroup statistical evaluation between valproic acid + melatonin and valproic acid + placebo.
One study (Gupta 2004a) evaluated sleep quality alone, without focusing on global quality of life. One study did not provide quantitative or validated data (Coppola 2004). The authors stated only that "half the parents/caregivers preferred improved behavior and alertness in children who appeared more quiet and better disposed to rehabilitation treatment; familial environment improved concomitantly, as a consequence of a better quality of night time" (Coppola 2004).

Comparison 2: melatonin 5 mg versus melatonin 10 mg

This comparison was evaluated by one study (Hancock 2005).

Primary outcomes

Seizure frequency

The exact number of seizures occurring during the trial, compared to the baseline, was given. None of the four patients who had seizures during the trial (on either 5-mg or 10-mg melatonin) had a 50% seizure reduction during the treatment (on either 5-mg or 10-mg melatonin) period compared to baseline. The duration of the trial (including follow-up) was six weeks.

Seizure freedom

During the study three out of seven patients who completed the study remained seizure-free (on either 5 mg or 10 mg melatonin).

Adverse events

The caregivers were asked to record any illness the child had or any possible side effects experienced during the trial period. No adverse events were reported.

Secondary outcomes

Quality of life

Such an outcome was not considered.

DISCUSSION

Four trials were included in this systematic review. They were of poor methodologic quality and they did not systematically evaluate seizure frequency and adverse events, so that it was not possible

to summarize data in a meta-analysis. Although all included studies were reported as double-blinded, blinding was not explicitly reported in all trials. Only one study (Hancock 2005) systematically examined seizure frequency occurring during the trial, compared to the baseline. Apart from one trial (Hancock 2005), none of the included trials systematically evaluated seizure freedom and adverse events. Two trials (Gupta 2004a; Gupta 2004b) selected only patients who were seizure-free for at least six months before the beginning of the trial, so that 50% seizure reduction during the treatment period from baseline could not be calculated. From a clinical point of view, the reported follow-up duration of the included studies was not long enough to evaluate the antiepileptic efficacy of add-on melatonin, maybe because none of the trials was primarily designed to evaluate seizure freedom/reduction. Nevertheless, the relative high number of seizure-free patients reported in the included studies may be attributed to the fact that a large proportion of them was already recruited as seizure-free (three out of seven patients on either 5-mg or 10-mg melatonin in Hancock 2005, and all patients in Gupta 2004a and Gupta 2004b). Only one study explicitly reported the presence of adverse events (Hancock 2005), and only one trial (Gupta 2004b) evaluated the direct influence of melatonin on quality of life.

All studies included in the present review were primarily aimed to evaluate the effect of melatonin on wake-sleep disorders, thus not focusing on efficacy and tolerability of add-on melatonin as treatment for epilepsy. The fact that primary outcomes evaluated in the studies did not focus on seizure control is responsible for the lack of information regarding the efficacy of melatonin as add-on treatment for epilepsy. As a consequence of this lack of data, it is not possible to draw definite conclusions concerning efficacy and tolerability of melatonin as add-on treatment for epilepsy. Furthermore, it is impossible to evaluate whether a possible beneficial role of melatonin in epilepsy treatment is direct or indirect (i.e. seizure reduction as a consequence of an improvement in sleep quality).

AUTHORS' CONCLUSIONS

Implications for practice

It is not possible to draw any conclusions about the role of add-on melatonin in reducing seizure frequency or improving the quality of life or about the safety profile of this drug in people with epilepsy.

Implications for research

Further studies, especially large, well-conducted, randomized clinical trials with adequate follow-up, are required before reaching a definite conclusion concerning the efficacy and tolerability of melatonin as add-on treatment in patients with epilepsy. Studies should systematically evaluate and report adverse events.

ACKNOWLEDGEMENTS

None.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Coppola 2004

Methods	Randomized, double-blind, cross-over, placebo-controlled trial
Participants	Inclusion criteria: (i) mental retardation with/without epileptic seizures; (ii) age > 12 months; (iii) diagnosis of sleep disorder, defined according to DSM-IV criteria as the circadian rhythm sleep disorder; (iv) exclusion of medical issues such as gastroesophageal reflux, pain, or epileptic seizures mimicking sleep disorders; (v) persisting sleep disturbances despite maintaining appropriate sleep hygiene; (vi) informed consent by parents, caregivers, both Exclusion criteria: (i) progressive neurologic, systemic, or both diseases; (ii) age < 12 months; (iii) poor compliance from parents/caregivers with the study requirements before trial entry N: 32 (7 lost to follow-up); 25 completed the trial M: 16; F: 9 Age: 3.6 to 26 years (mean age 10.5 years) 18/25 patients were epileptic and on concurrent AEDs Type of seizures: complex partial (8), with secondary generalization (5), tonic-clonic (4) , tonic (3), drop-attacks (2), atypical absences (1), myoclonic seizures (2) Type of epilepsy: partial epilepsy (9); generalized symptomatic (5) or cryptogenic (1) epilepsy; multifocal epileptic encephalopathy (3). A genetic syndrome was diagnosed in 5 cases (20%); they were the following: Angelman syndrome; Saethre-Chotzen syndrome; 11p13 microdeletion; Leber amaurosis; CHARGE syndrome Concurrent AED treatment: monotherapy (11), bi-therapy (2;), and tri-therapy (5) Seizure frequency: seizure-free (7); sporadic (3); 1 to 3/month (3); > 1/week (2); > 1/day (3) Duration of the trial (including follow-up): 9 weeks
Interventions	Melatonin (fast release) compared with placebo (see text for more details)
Outcomes	Seizure freedom/seizure frequency: out of the 11 seizure-free patients before starting the study, 9 remained unchanged on melatonin; in the other 2, seizures reappeared after 1 month (1 Lennox-Gastaut syndrome; 1 partial seizures). Soon after discontinuing melatonin, seizures stopped in both these patients. Among the 7 uncontrolled patients during the baseline phase, 1 became seizure-free (1 secondarily generalized partial seizure) , 2 partially improved (1 partial seizure; 1 myoclonic seizure), and the other 2 were unchanged; the remaining 2 showed a seizure worsening 1 month after starting melatonin phase (1 cryptogenic generalized seizure; 1 secondary generalized partial seizure). In the latter patients, seizures decreased soon after melatonin withdrawal Adverse events: none reported Quality of life: not systematically evaluated. Authors stated that "half the parents/caregivers referred improved behavior and alertness in children who appeared more quiet and better disposed to rehabilitation treatment; familial environment improved concomitantly, as a consequence of a better quality of night time"

Coppola 2004 (*Continued*)

Notes	Not all patients were epileptic Seizure diaries were used to monitor the frequency and type of seizures Reasons for lost to follow-up (7 patients) are reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The permutation of code numbers was computer generated for the treatment groups (information provided directly from the principal Investigator)
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing to follow-up are reported. No intention-to-treat analysis was made
Selective reporting (reporting bias)	High risk	Authors stated that seizures occurred, without further specifying the exact number of seizures. Adverse events were not systematically evaluated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)

Gupta 2004a

Methods	Randomized, double-blind, parallel, placebo-controlled trial
Participants	Inclusion criteria: children of either sex, ages 3 to 12 years, carbamazepine monotherapy, confirmed diagnosis of epilepsy according to the International Classification of Epileptic Seizures, seizure-free for at least the last 6 months Exclusion criteria: children with a history of psychiatric or other progressive neurologic disorder, or a chronic hematologic, cardiac, hepatic, renal, or thyroid disorder N: 31 (3 lost to follow-up) M: 21; F: 7 Type of seizures: complex partial seizures (19); generalized tonic clonic seizures (6);

Gupta 2004a (*Continued*)

	simple partial seizures (3) Concurrent AED treatment: carbamazepine monotherapy Seizure frequency: all patients were seizure free for at least the last 6 months Duration of the trial (including follow-up): 8 weeks
Interventions	Melatonin (fast release) compared with placebo (see text for more details)
Outcomes	Seizure freedom: patients were followed up clinically for total 8 weeks during which all patients remained seizure free Adverse events: authors state that "no adverse event warranting discontinuation of the therapy was observed" Quality of life: not evaluated systematically. Sleep quality after add-on melatonin administration was assessed by a parental questionnaire, the SBQ
Notes	Reasons for lost to follow-up (3 patients) were reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization code list prepared by a statistician, not connected to the study. The permutation of code numbers were computer generated for the treatment groups
Allocation concealment (selection bias)	Low risk	The placebo tablets were identical in shape, size, color, and packaging
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing to follow-up are reported (the reason for 2 lost to follow-up not reported). No intention-to-treat analysis
Selective reporting (reporting bias)	High risk	For each patient, a daily diary was provided with the instruction to record any adverse events or unusual symptoms observed immediately. In results section, authors only state that "no adverse event warranting discontinuation of the therapy was observed"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)

Gupta 2004a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)

Gupta 2004b

Methods	Randomized, double-blind, parallel, placebo-controlled trial
Participants	Inclusion criteria: children of either sex, ages 3 to 12 years, valproate monotherapy, confirmed diagnosis of epilepsy according to the International Classification of Epileptic Seizures, seizure free for at least the last 6 months Exclusion criteria: children with a history of psychiatric or other progressive neurologic disorder, or a chronic hematologic, cardiac, hepatic, renal, or thyroid disorder N: 31 (1 lost to follow-up) M: 18; F: 12 Type of seizures: absence (8); complex partial (5); generalized tonic-clonic seizures (14) ; Lennox-Gastaut syndrome (3) Concurrent AED treatment: valproate monotherapy. Patient on sodium valproate (10 mg/kg/day) monotherapy for the last 6 months, and, at the time of inclusion in the study, with serum blood levels in the range 75 to 125 microgram/mL Seizure frequency: all patients were seizure free for at least the last 6 months Duration of the trial (including follow-up): 8 weeks
Interventions	Melatonin (fast release) compared with placebo (see text for more details)
Outcomes	Adverse events: authors state that "no adverse event warranting discontinuation of the therapy was observed" Quality of life: assessed by the QOLCE questionnaire. Valproic acid + melatonin group: intragroup P = 0.08; valproic acid + placebo group: intragroup P = 0.16
Notes	Reasons for lost to follow-up (1 patient) are reported Authors performed no intergroup statistical evaluation between valproic acid + melatonin and valproic acid + placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization code list prepared by a statistician, not connected to the study. The permutations of code numbers were computer generated for the treatment groups
Allocation concealment (selection bias)	Low risk	The placebo tablets were identical in shape, size, color, and packaging

Gupta 2004b (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing to follow-up are reported. No intention-to-treat analysis
Selective reporting (reporting bias)	High risk	For each patient, a daily diary was provided with the instruction to record any adverse events or unusual symptoms observed immediately. In results section, authors only state that "no adverse event warranting discontinuation of the therapy was observed"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)

Hancock 2005

Methods	Randomized, double-blind, cross-over, controlled trial
Participants	Inclusion criteria: confirmed diagnosis of tuberous sclerosis complex and sleep problems (Quine Sleep Index score of at least 6 out of a possible 8) Exclusion criteria: situational sleep disorder (a higher Quine score at home with a score of < 6 elsewhere) N: 8 (1 lost to follow-up) M: 4; F: 3 Age: 18 months to 31 years (median age 9 years) All patients were epileptic and on concurrent AEDs; 2 of them were well controlled All had mental retardation and behavioral difficulties Duration of the trial (including follow-up): 6 weeks
Interventions	Melatonin 5 mg versus melatonin 10 mg (see text for more details)
Outcomes	Seizure frequency: 4 patients had seizures during the trial, without change in the frequency (or type) of seizures compared with the baseline period before melatonin treatment at either dose Seizure freedom: 3 patients with well-controlled epilepsy remained seizure-free during the trial Adverse events: none reported

Notes	Seizure type was not reported Concurrent AEDs not reported. Seizure diaries were used to monitor the frequency and type of seizures Reasons for lost to follow-up (1 patient) were reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation made by the pharmacy using random number sequences
Allocation concealment (selection bias)	Low risk	Patients received identical capsules
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No lost to follow-up
Selective reporting (reporting bias)	Low risk	All data regarding outcomes of interest for this systematic review are reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not explicitly reported (insufficient information to permit judgment)

AED: antiepileptic drug; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; F: female; M: male; N: number; QOLCE: Quality of Life in Childhood Epilepsy; SBQ: Sleep Behavior Questionnaire.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ardura 2010	No comparison: melatonin not compared with placebo or other drug. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Ashrafi 2010	Not relevant outcome: melatonin was not used as AED

(*Continued*)

Bazil 2000	Not relevant outcome: melatonin was not used as AED
Eisermann 2010	Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Elkhayat 2010	No comparison: melatonin not compared with placebo or other drug. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Fauteck 1999	No comparison: melatonin not compared with placebo or other drug
Guo 2009	No comparison: melatonin not compared with placebo or other drug. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Gupta 2004c	Adverse events: outcome is unclear. Authors state only that "no adverse event warranting discontinuation of the therapy was observed"
Gupta 2004d	Adverse events: outcome is unclear. Authors state only that "no adverse event warranting discontinuation of the therapy was observed"
Gupta 2005	Duplicate publication of Gupta 2004b
Gupta 2006	Not relevant outcome: melatonin was not used as drug for epilepsy treatment
McArthur 1998	Not relevant participants: not epileptic patients
McLellan 2002	Not relevant participants: not epileptic patients
Molina-Carballo 2007	No comparison: melatonin not compared with placebo or other drug. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Murck 1997	Not relevant participants: not epileptic patients. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Paprocka 2010	No comparison: melatonin not compared with placebo or other drug. Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Peled 2001	No comparison: melatonin not compared with placebo or other drug
Ross 2002	Relevant outcomes: unclear. Authors evaluated only sleep quality using parent-completed sleep diary. Authors therefore did not use validated questionnaires in order to evaluate sleep quality
Schapel 1995	Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Smits 2000	Not relevant participants: not epileptic patients
Uberos 2011	Not relevant outcome: melatonin was not used as drug for epilepsy treatment
Van der Heijden 2007	Not relevant participants. Not relevant outcome: melatonin was not used as drug for epilepsy treatment

(*Continued*)

Wassmer 2001	Not relevant participants: not epileptic patients
Yalyn 2006	Not relevant outcome: melatonin was not used as drug for epilepsy treatment

AED: antiepileptic drug.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 28 January 2012.

Date	Event	Description
28 January 2012	Amended	Amended after peer-review

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 6, 2012

CONTRIBUTIONS OF AUTHORS

Alessandra Del Felice conceived the idea and development of the project. Alessandra Del Felice and Pietro Guaraldi designed the protocol. Alessandra Del Felice and Francesco Brigo assessed the studies for inclusion and extracted the data from the individual studies. Text of the final review was written by Francesco Brigo.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Drug Therapy, Combination [methods]; Epilepsy [*drug therapy]; Melatonin [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant; Young Adult