Drug Saf (2013) 36:207–215
DOI 10.1007/s40264-013-0033-y

LEADING ARTICLE

Does Melatonin Affect Epileptic Seizures?

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Published online: 27 March 2013

Abstract Melatonin is widely used for sleep disorders in patients with a range of developmental disorders and neurodisabilities, who also frequently have epilepsy. The aim of our review was to examine published data to assess the evidence for melatonin affecting seizure control. The literature search revealed 26 papers apparently reporting an association between melatonin and epilepsy or seizures but seven of these did not provide relevant information. Of the three double-blind, randomised, controlled trials, two showed no overall worsening or improvement in seizures, and one recent trial reported a statistically significant reduction in seizures. The open studies reported conflicting results. The few studies on the effect of seizures on melatonin levels have reported that baseline melatonin levels may be low in patients with uncontrolled epilepsy and that levels increase markedly following seizures. The striking finding of this review is the paucity of relevant data from the remarkably small number of studies. These results allow no firm conclusions to be drawn, although it would seem reasonable to observe that there was no marked overall effect on seizures, neither improvement nor worsening. There is a need for large, well designed, randomised, double-blind, placebo-controlled trials to establish the role of melatonin in either predisposing to or decreasing the likelihood of seizures.

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1 Introduction

Melatonin is a hormone produced by the pineal gland. It plays an important role in the regulation of sleep and circadian rhythm. It can be taken by mouth and has been marketed extensively for sleep disorders. A high proportion of people with mental retardation also have sleep problems, for which melatonin is often prescribed. However, mental retardation is also a major risk factor for developing epilepsy and, in the absence of clear evidence-based guidance, concern has been expressed about prescribing melatonin in this population because of the possibility that it might precipitate or exacerbate seizures. There has also been reluctance to prescribe melatonin in anyone with a history of seizures, because of a perceived risk of seizure exacerbation. The purpose of this review was to examine published data to assess the evidence for melatonin affecting seizure control.

2 Methods

MEDLINE and EMBASE databases were searched from January 1990 to May 2012. The search strategy was as follows: 'melatonin and (epilepsy or seizure)'. The search revealed a total of 162 papers, 98 when limited to human data. We reviewed abstracts of the 98 papers. The following papers were excluded from this review: (i) papers reporting the role of melatonin exclusively on sleep in children with intellectual disabilities (in these papers role of melatonin with regard to seizures was not discussed); (ii) papers about use of melatonin in sleep electroencephalograms (EEGs); (iii) papers about circadian rhythms and melatonin; (iv) papers reporting utility of melatonin in conditions other than sleep and epilepsy, e.g. as an

antidepressant and in cancer. We also excluded papers that were not available in the English language but extracted any relevant information from the English abstract.

We found 26 papers apparently reporting an association between melatonin and epilepsy or seizures, but seven of these did not provide relevant, accessible information. The details of the seven studies that we did not discuss are as follows. One study was about melatonin and epileptic seizures in patients with acute intermittent porphyria. Three articles reviewed the therapeutics of melatonin, reporting on uses of melatonin in general, including favourable effects on seizures. Three articles were excluded because they were in Hungarian [13] or Spanish [30, 31]. These three papers were not available in English. We endeavoured to sort the results into the following three categories, but it should be noted that, because most of the studies were open, not placebo controlled, and involved small numbers, this task could not be performed with certainty.

1. Apparent induction, recurrence or worsening of seizures, with or without a prior diagnosis of epilepsy.
2. No clear worsening or improvement in seizures.
3. Apparent improvement of seizure control in patients with uncontrolled epilepsy.
4. The effect of seizures on melatonin levels was also examined.

3 Study Findings

3.1 Apparent Induction, Recurrence or Worsening of Seizures, With or Without a Prior Diagnosis of Epilepsy

Sheldon [1] described an apparent increase in seizures with oral melatonin in four out of five neurologically disabled young people with epilepsy. The whole group consisted of six patients, aged 9 months to 18 years, with multiple neurological deficits, who also had chronic sleep problems. Five out of the six had epilepsy: four had generalised tonic-clonic seizures and one had myoclonic seizures. Synthetic melatonin 5 mg was administered either orally or via gastrostomy at the patient's habitual bedtime. While taking melatonin, considerable improvement was observed in total sleep time, sleep continuity and sleep onset latency in five of the six patients. Four patients had increased or new seizure activity. All seizure activity returned to pre-treatment levels after discontinuing the melatonin. Three subjects were re-challenged with a smaller (1 mg) melatonin dose. The authors stated that the seizure activity again increased and returned to baseline after discontinuing the melatonin, although no details were given.

In a single open case report, Sandyk et al. [2], using magnetoencephalography (MEG) as an indirect measure of epileptiform activity, showed an increase in this activity in a 21-year-old woman with uncontrolled epilepsy who took 3 mg of melatonin before the investigation and who also had four brief 'major seizures', each lasting a few seconds on the same afternoon that she received the melatonin. At the time of the evaluation she was taking phenytoin, carbamazepine and sodium valproate.

3.2 No Overall Worsening or Improvement in Seizures

Jan et al. [3] published a study of the effect of melatonin on sleep disorders in 42 children, most of whom had multiple disabilities; 23 had epilepsy. The melatonin dose ranged from 2 to 12 mg. They commented that none had significant seizure exacerbations requiring discontinuation of the melatonin therapy, although they added that the antiepileptic medication had to be adjusted 'on occasion' after the melatonin was prescribed. Details of the patients with epilepsy were not provided in this paper. The authors also commented that they had encountered no significant adverse effects of melatonin in the total of 144 patients that they had treated, 42 % of whom had epilepsy, but again no details were provided.

Ross et al. [4] assessed the value of melatonin in 49 children with neurodevelopmental disorders and found that it was effective in treating sleep problems; 26 of the 48 evaluable subjects had epilepsy. The melatonin doses ranged from 2.5 to 10 mg. They found no clear worsening of seizures, but three parents reported an improvement in seizure frequency with the melatonin. They commented that the numbers were too small to draw any conclusions.

Coppola et al. [5] studied 25 subjects, aged 3.6–26 years, with mental retardation, most of whom (18/25) also had epileptic seizures. The patients were randomised to oral synthetic melatonin or placebo. The melatonin was effective in improving sleep in 24 of the 25 subjects, at the following doses: 3 mg/day in 7 patients (29.2 %), 6 mg/day in 11 (45.8 %), 9 mg in 5 (20.8 %) and 12 mg in 1 (4.2 %). In one patient, melatonin was ineffective at a daily dose of up to 12 mg. A genetic syndrome was diagnosed in five cases. The epilepsy was classified as follows: partial epilepsy (nine); generalised symptomatic (five); cryptogenic epilepsy (one) and multifocal epileptic encephalopathy (three). Before starting melatonin treatment, of the 18 patients who had epilepsy, 11 were taking antiepileptic drug (AED) monotherapy, two were taking two AEDs and five were taking three AEDs. The AED comedication was not modified during the trial. Of the 11 patients who were free of seizures before starting the study, nine remained seizure free. In the other two patients, seizures reappeared after 1 month (one with Lennox-Gastaut syndrome; one with partial seizures).

Soon after discontinuing melatonin, the seizures stopped in both these patients. Among the seven patients who had uncontrolled seizures during the baseline phase, when treated with melatonin one became seizure free, two partially improved and the two were unchanged; the remaining two had a deterioration in seizure control 1 month after starting melatonin. In these two patients, the seizures decreased soon after melatonin withdrawal. Melatonin was effective in treating the sleep disorder by reducing the time to sleep onset and improving the total duration of nocturnal sleep. However, the number of night awakenings did not appear to be altered. The authors concluded that melatonin had little effect on seizure frequency, although in some cases seizures either worsened or improved.

Gupta et al. [6] carried out a double-blind, randomised, placebo-controlled trial on the effect of add-on melatonin on sleep in 31 children aged 3–12 years with epilepsy that had been well controlled with sodium valproate monotherapy for at least 6 months. Children were randomised to receive melatonin ($n = 16$) or placebo ($n = 15$, one of whom was lost to follow-up). The dose of melatonin was 6 mg for children under 9 years who weighed less than 30 kg and 9 mg for children older than 9 years who weighed more than 30 kg. All the patients remained seizure free during the 8-week follow-up period. The percentage decrease in the median total sleep score was 24.4 (range 0.0–63.2) in the valproate plus melatonin group compared with 14.0 (2.2–18.8) in the valproate plus placebo group, the difference being statistically significant ($p < 0.05$). The median percentage decrease in the parasomnias score was 60 (range 0.0–70.8) in the valproate plus melatonin group compared with 36.4 (0.0–63.2) in the valproate plus placebo group, the difference being statistically significant ($p < 0.05$).

Elkhayat et al. [7] treated 37 children, aged 2–15 years, with melatonin. All 37 had epilepsy but 23 were classified as having 'intractable epilepsy'; the remaining 14 had controlled seizures. The children were treated with a range of AEDs: valproic acid (18), carbamazepine (17), clonazepam (9), topiramate (6), lamotrigine (5), phenytoin (4), phenobarbital (3) and vigabatrin (1). The initial melatonin dose was 3 mg but was decreased to 1.5 mg after two patients had an increase in seizures. The authors reported statistically significant improvements in various sleep parameters, including bedtime resistance, sleep duration, sleep latency, frequent nocturnal arousals, excessive daytime sleepiness, nocturnal enuresis, sleep talking, sleep walking, forcible teeth-grinding, sleep apnoea and the Epworth sleepiness scale. There was no improvement in seizure frequency, but seizure severity score improved on the Chalfont scale [8] (75.6 before melatonin and 41.5 while taking melatonin). Before the melatonin was administered, 95 % of the children had abnormal EEGs according to the classification of Stern and Engel [9], and only one patient had a normal EEG. The normal EEGs remained normal with melatonin, and three patients (13 %) who had an abnormal EEG before the melatonin was administered had a normal EEG while taking the melatonin. The seizure frequency deteriorated in three patients, resulting in withdrawal of the melatonin.

Andersen et al. [10] carried out a retrospective study of 107 children, aged 2–18 years, with autistic spectrum disorder, in whom melatonin was used for treatment of sleep problems. Epileptic seizures were documented in 21 children, although only four children were noted to have refractory epilepsy. Details of the medication in individual children were not provided, but 36 of 107 children were taking antiepileptic medication; it should be noted that this number is higher than the 21 children who were said to have had seizures, but some AEDs, including sodium valproate, carbamazepine and lamotrigine, are used as a mood-levelling medication in people who do not necessarily have seizures. The melatonin dose ranged from 0.75 to 6 mg. The authors found no increase in seizures with melatonin in children who had pre-existing epilepsy. There were no cases of new-onset seizures. Details of the epilepsy syndromes and degree of seizure control prior to commencing melatonin were not described in the paper.

Jones et al. [11] carried out a retrospective before and after observational study of 13 patients prescribed melatonin for sleep disturbances. The patients included 11 children (age 6–18 years) and two adults. All had severe learning disabilities and behavioural problems, 12 had autistic spectrum disorders and 11 had severe epilepsy. The dose of melatonin ranged from 2 to 6 mg nocte. Of the 13 patients, 11 slept better with melatonin. Of those with epilepsy, three had an increase in seizure rate, seven had a decrease in seizure rate and one had no observable difference. There was no statistically significant effect on seizure frequency.

3.3 Apparent Improvement of Seizure Control in Patients with Uncontrolled Epilepsy

Fauteck et al. [12] administered melatonin 5 or 10 mg to ten prepubertal children, aged 5 months to 12 years (five male, five female) who had various types of epilepsy (six with secondary Lennox-Gastaut syndrome and four with what the authors termed 'retardation syndrome of unspecific severity with therapy-resistant nocturnal cerebral convulsions'). Five of the six children received 10 mg of melatonin and one child received 5 mg. The types of antiepileptic medication were not stated, apart from the comment that none received carbamazepine and that one child was treated with phenobarbital (see later). All the children had 'severe sleeping-waking rhythm pathology'. Sleep and seizure control was improved

in six (three with Lennox-Gastaut syndrome) of the eight children. The mean daily seizure frequency, averaged over 7 days, decreased from about 8–12 seizures/day to 0–2 seizures/day. One child with Lennox-Gastaut syndrome who had been treated with phenobarbital monotherapy before the addition of melatonin discontinued this AED and, during the 6-month period on melatonin therapy, had only one tonic-clonic seizure. Few additional details were provided. In particular, results for the two children who did not improve were not presented.

Saracz and Rosdy [13] reported on the effect of melatonin in two children with refractory epilepsy who had been treated with various AEDs. Both the frequency of the seizures and the epileptiform abnormalities in the EEG decreased after the melatonin was commenced. The melatonin was stopped 3 months later, and the seizures increased again. Further details were not available because the paper was only available in English in abstract form.

Peled et al. [14] treated six children, aged 2–15 years, who had severe uncontrolled epilepsy, with 3 mg oral melatonin in addition to the antiepileptic medication for 3 months. Each child was being treated with at least two AEDs, including phenobarbital (four), vigabatrin (four), valproate (two) and one patient each on phenytoin, nitrazepam, carbamazepine, clobazam and acetazolamide. Four of these children had a history of infantile spasms and/or Lennox-Gastaut syndrome, one had lissencephaly with severe psychomotor retardation and spastic quadriplegia, and one had progressive myoclonic epilepsy with severe sleep disturbance. The parents kept seizure diaries for a month before treatment and during the treatment with melatonin. The seizures improved in five of the six. The mean seizure frequency decreased from 3.6 ± 3.9 to 1.5 ± 1.8/day while the children were taking melatonin ($p = 0.049$). The seizure frequency remained unchanged in the sixth subject but the EEG showed 'mild worsening'. In the other two patients in whom the EEG was monitored, there was a decrease in epileptiform activity. The notable characteristics of this group of children were the severity of the epilepsy and of the disability. The subject in whom the seizure control did not improve was by far the oldest at 15 years of age; the age range of the remaining children was 2–10 years.

Molina-Carballo et al. [15] reported that high-dose melatonin (20 mg in the morning, 80 mg and subsequently 100 mg in the evening) was the only therapy that was associated with seizure control in a 1-year-old girl with refractory severe myoclonic epilepsy of infancy over a period of 2 years. The seizure rate decreased from 15–20/day to zero. It was possible to decrease the antiepileptic medication to 'non-therapeutic levels': primidone 60 mg, clonazepam 0.3 mg and phenobarbital 4 mg, each given 12 hourly. When the melatonin was discontinued, the seizure frequency returned to the previous level.

Uberos et al. [16] studied ten children, aged 4–10 years, with severe epileptic disorders (three with West syndrome, two with Lennox-Gastaut syndrome, two with progressive myoclonic epilepsy, two with epileptic encephalopathy secondary to hypoxic-ischaemic encephalopathy and one with epilepsy secondary to cytomegalovirus infection). The patients were given a nightly dose of a placebo for 1 week; for the next 3 months, the placebo was replaced with a nightly dose of 3 mg of melatonin. At the end of each treatment period, the urinary excretion of 6-sulfatoxymelatonin (the hepatic metabolite of melatonin) and plasma levels of melatonin were recorded over a period of 24 h. The administration of melatonin daily for a period of 3 months produced circulating levels that were clearly higher than those obtained in the same patients during administration of the placebo. Sleep efficiency improved, with fewer night-time awakenings, when patients received melatonin. A reduction in the number of seizures was also observed in these patients. However, the authors provided no further details of the seizure control.

Goldberg-Stern et al. [17] recently published a small double-blind, placebo-controlled crossover trial examining the effect of melatonin on seizures. Twelve subjects (aged 9–32 years) with 'intractable' symptomatic or cryptogenic epilepsy who had partial and/or generalised seizures entered the trial, but data were only available on ten (aged 13–32 years). The subjects were randomly assigned to melatonin or placebo for 3 weeks, followed by a 1-week washout period, after which those who had previously received placebo were given melatonin and vice versa. The melatonin tablets were 10 mg, fast release, given 1 h before bedtime. The placebo tablets were identical in size and appearance, prepared by the same pharmacist. There was a statistically significant reduction in diurnal seizures with the melatonin, from a mean of 7.75 to a mean of 4.6 per day ($p = 0.034$, Wilcoxon test). Separate analysis of partial and generalised seizures or nocturnal seizures did not yield statistically significant results, although there was a reduction in mean frequency of partial seizures from 8.31 with placebo to 5.26 with melatonin ($p = 0.208$, Wilcoxon test). The authors stated that there was no seizure aggravation, but details of the seizure frequencies in the melatonin and placebo phases were not provided. Three of the ten patients continued taking the melatonin; the reason for this relatively small number was not given.

The studies reporting the apparent effects of melatonin on seizures, discussed above, are summarised in Table 1.

3.4 Effect of Seizures on Melatonin Levels

Yalyn et al. [18] compared the circadian rhythms and melatonin levels in 20 patients, aged 18–50 years, with diurnal complex partial seizures and nocturnal complex

Table 1 Apparent effect of melatonin on seizures

Author	Study details	Results	Comments
Sheldon [1]	Observational study of effect of melatonin on 6 children, aged 9 months to 18 years, with multiple neurological problems and sleep complaints. 5 of the children had epilepsy	Four pts had increased or new seizure activity while on melatonin. Considerable improvement in sleep observed	Small numbers
Sandyk et al. [2]	Single case report in 21-year-old woman with uncontrolled epilepsy	Four brief 'major seizures' after melatonin 3 mg before MEG	Single case report with possible confounding factors
Jan et al. [3]	23 children with epilepsy in a group of 42 children, 'mostly with multiple disabilities'	No significant seizure exacerbations	Open study
Ross et al. [4]	26 of 48 evaluable children with neurodevelopmental disorders had epilepsy	No clear worsening of seizures. Three parents reported improvement of seizure frequency	Open study
Coppola et al. [5]	Randomised control trial of 25 pts, aged 3.6–26 years with mental retardation. 18 out of 25 pts had epileptic seizures	Melatonin was effective in improving sleep disorder in pts. It had little effect on seizure frequency; seizures worsened in some cases and improved in others	Randomised controlled trial. Small number of pts
Gupta et al. [6]	Double-blind, randomised, placebo-controlled trial evaluating sleep behaviour in 31 children aged 3–12 years with controlled epilepsy	Sleep was observed to improve in the melatonin group. No seizures were precipitated by the melatonin	Response assessed by questionnaire
Elkhayat et al. [7]	Observed effect of melatonin on sleep and seizure frequency in 37 children aged 2–15 years with epilepsy. 23 had intractable epilepsy	Significant improvement in sleep parameters observed. Effect on seizure control was equivocal. No improvement in seizure frequency, but an improvement in seizure severity observed. There was an improvement in EEG findings after melatonin in three children	Open study. Significance of small number of improved EEGs uncertain
Andersen et al. [10]	Retrospective study of 107 children with autistic spectrum disorder. 21 children had epilepsy. Melatonin was used for treatment of sleep problems	No increase in seizure frequency and no cases of new onset seizures observed	Retrospective, open study. Details of epilepsy syndromes and degree of seizure control prior to commencing melatonin not described
Jones et al. [11]	Retrospective before and after observational study of 13 young people with severe learning disabilities and behavioural problems prescribed melatonin for sleep disturbances. 11 had severe epilepsy	Melatonin improved sleep. No demonstrable influence in seizure control was observed—seizure frequency decreased in some and increased in others	Small, open study. Details of type of epilepsy not available
Fauteck et al. [12]	10 children aged 5 months–12 years	Mean seizure frequency decreased from 8–12 to 0–2 seizures/day	Small, open study
Saracz and Rosdy [13]	Study of effect of melatonin in children with refractory epilepsy who had been treated with various AEDs	Frequency of seizures and epileptiform abnormalities on EEG decreased after melatonin was commenced	Study involved case reports. Further details not available as paper was available in English in abstract form
Peled et al. [14]	6 children aged 2–15 years with severe uncontrolled epilepsy, treated with 3 mg oral melatonin in addition to AEDs for 3 months	Seizures improved in 5 of 6 children	Small, open, study. Results obtained by parental questionnaire

Table 1 continued

Author	Study details	Results	Comments
Molina-Carbello et al. [15]	Study of effect of high-dose melatonin in a 1-year-old girl with refractory myoclonic epilepsy	Seizure frequency reduced remarkably while on melatonin	Single case report
Uberos et al. [16]	Evaluation of sleep-wake pattern, plasma melatonin levels and the urinary excretion of its metabolite among 10 children aged 4–10 years with severe epileptic disorders before and after a therapeutic trial with melatonin	Sleep efficiency was observed to improve when pts received melatonin. A reduction in number of seizures was also observed in these pts	Small, open study. Details of seizure control not available
Goldberg-Stern et al. [17]	A double-blind, placebo-controlled crossover trial of effect of melatonin on seizures in 12 subjects aged 9–32 years with uncontrolled epilepsy	Statistically significant reduction in diurnal seizures with melatonin was observed	Small double-blind, placebo-controlled crossover trial. Details of seizure frequency in melatonin and placebo phases was not provided

AEDs anti-epileptic drugs, *MEG* magnetoencephalography, *pt(s)* patient(s)

partial seizures, and a control group of ten subjects. The patients were divided into two groups of ten patients each. Group 1 consisted of patients with nocturnal complex epilepsy and group 2 consisted of patients with diurnal complex epilepsy. The control group consisted of ten healthy volunteers (group 3). The patients in groups 1 and 2 were taking only carbamazepine as therapy, and the seizures were not completely controlled. Melatonin levels were low in both the diurnal and the nocturnal epilepsy groups, compared with the control group at 10:00, 22:00, 01:00 and 05:00 h but the difference was statistically significant only at 10:00 h. There were no differences in melatonin levels between patients with diurnal and those with nocturnal complex partial epilepsy, although the presence of exclusively nocturnal or diurnal seizures in the patients was determined on the basis of history: the authors did not demonstrate their presence with prolonged video monitoring.

Molina-Carballo et al. [19] measured melatonin serum levels in 54 children with seizures, aged 2 months–14 years. The patients were divided into two subgroups: the Day group comprising 34 patients with the convulsive episode occurring during the daytime (13 febrile convulsions, 21 episodes of other convulsions) and the Night group comprising 20 patients with the convulsive episodes occurring during the night (8 febrile convulsions and 12 with other convulsions). The untreated patients and those given AEDs were randomly and uniformly distributed among the Day and Night groups. The melatonin levels increased during either febrile or afebrile seizures. The authors suggested that this might reflect an anticonvulsant effect of the melatonin. A later assay, at 1 h after the seizure, showed a statistically significant fall to normal melatonin levels in the Day and Night groups; the level was still normal 24 h later.

Bazil et al. [20] measured melatonin levels in 11 patients with temporal lobe epilepsy (age range: 26–55 years) and six control patients (age range: 33–46 years). Patients and controls had saliva collected at 3-hourly intervals (2, 5, 8, 11, 14, 17, 20 and 23 h). Baseline measurements began following an interval of at least 24 h of seizure freedom and also during a 24-h period with no seizures. Seizure measurement began following a documented seizure and continued for 24 h. Patients with uncontrolled seizures had low baseline melatonin levels that increased dramatically following seizures.

Schapel et al. [21] measured urinary excretion of 6-sulfatoxymelatonin for three consecutive 8-h intervals, beginning at 0600 h, in 30 patients (age range: 3–53 years) with untreated active epilepsy and in 19 healthy subjects. They found increased melatonin production in patients with untreated epilepsy as compared with healthy control subjects ($p < 0.05$). They suggested

Table 2 Melatonin blood levels and seizures

Author	Study details	Results	Comments
Yalyn et al. [18]	Comparison of melatonin levels in 20 pts with diurnal complex partial seizures and nocturnal complex partial seizures, aged 18–50, with a control group of ten healthy subjects	Melatonin levels were low in both diurnal and nocturnal epilepsy groups compared with the control group. No differences in levels between pts with diurnal and nocturnal complex epilepsy	Presence of nocturnal and diurnal seizures was determined by history not video monitoring
Molina-Carballo et al. [19]	Melatonin serum levels in 54 children with seizures, aged 2 months–14 years. 34 pts had daytime and 20 pts had night-time seizures	Melatonin levels were increased after seizures in both groups	Both epilepsy and febrile seizures
Bazil et al. [20]	Melatonin levels in 11 pts aged 26–55 years with temporal lobe epilepsy and six control pts	Pts with uncontrolled epilepsy had low baseline melatonin levels that increased markedly following seizures	Only temporal lobe epilepsy pts
Schapel et al. [21]	Measured urinary excretion of 6-sulfatoxymelatonin in 30 pts aged 3–53 years with untreated epilepsy and 19 healthy subjects	Significantly increased melatonin production in pts with untreated epilepsy	Details of untreated epilepsy not provided

pt(s) patient(s)

that this observation was a reflection of an anticonvulsant effect of melatonin.

The studies reporting the apparent effects of seizures on melatonin levels, discussed above, are summarised in Table 2.

4 Discussion

Melatonin is frequently prescribed for sleep disorders in patients with a range of developmental disorders and neurodisabilities, who also frequently have epilepsy [22]. It has been shown to improve insomnia in children with autism spectrum disorders, many of whom also have epilepsy [10]. It tends to reduce time to onset of sleep but not necessarily sleep duration.

The role of melatonin as an anticonvulsant hormone is thought to be due to its effect on increasing brain GABA concentration and affinity [23]. The baseline levels of melatonin in children with nocturnal and diurnal complex epilepsy have been reported as being low compared with healthy individuals [18]. Melatonin levels were observed to increase following convulsive seizures [19]. These observations might be interpreted as supporting the hypothesis that low levels of melatonin could precipitate seizures in such patients and increased production of melatonin by the seizures might represent the response of the individual against the seizures. However, this is not the only possible interpretation of these results. Associations do not prove causality. It is possible that the observations relate more to an effect of seizures on melatonin than of melatonin on seizures. Gupta et al. [24] proposed that melatonin might exert a neuroprotective effect in epilepsy through antioxidant, antiexcitotoxic and free radical scavenging properties within the central nervous system. Goldberg-Stern et al. [17] have provided a summary of the mechanisms that might be responsible for an antiepileptic effect of melatonin. The neurochemistry of these mechanisms is discussed in more detail by Muñoz-Hoyos et al. [25]. It is interesting to note that, although animal data are not necessarily relevant to humans, the extensive work in animals indicates that melatonin appears to have antiepileptic properties [26, 27].

The data supporting a proconvulsant role of melatonin are limited. No conclusions can be drawn from the single open case report by Sandyk et al. [2]; the change in MEG activity and the fact that the patient had four brief seizures after 3 mg of melatonin might have been the result of factors unrelated to the melatonin. For example, the excitement/stress of the investigation may have been responsible for these results. Both seizure worsening and seizure improvement were observed in a small group of children with epilepsy when melatonin was prescribed [5].

Melatonin was also reported as having been associated with seizure worsening or the incidence of new seizures in a small group of children who had multiple neurological deficits [1]. It has also been suggested that melatonin could contribute to occurrence of seizures in children in whom seizures are more frequent during the night or periods of sleep, when melatonin levels are significantly higher than daytime levels [28]. An effect of melatonin on dopamine function has been proposed as an underlying mechanism for the epileptogenic role of endogenous melatonin [28], although there appears to be little or no evidence to support such a hypothesis. A much more obvious explanation for seizure worsening in association with sleep is the dramatic change in brain activity occurring in the transitions between wakefulness and sleep, clearly shown on the EEG.

The report by Saracz and Rosdy [13] that the seizures appeared to decrease in frequency when the melatonin was administered and, in both cases, increased again after the melatonin was stopped, suggests that the melatonin may have had a beneficial effect on seizure control, but no firm conclusions can be drawn from open case reports. The finding by Peled et al. [14] that five out of six children with severe disability and epilepsy had a reduction in seizures, and that the overall seizure decrease of the group was statistically significant, again refers to a small open study, which is a major limitation. Similar comments apply to the eight of ten children in the study by Fauteck et al. [12] who appeared to have a marked reduction of seizures with melatonin. A recent small, double-blind, placebo-controlled trial [17] showed a statistically significant reduction in seizures in ten subjects with refractory epilepsy when treated with 10 mg of melatonin. It should be noted that the age range was very wide (13–32 years); consequently the dose in mg/kg might have been relatively high for some of the subjects and relatively low for others. The absence of this information, and the fact that no details of the seizure control in the individuals were provided, implied that the relevance of the melatonin dose in mg/kg could not be explored with the available data. In perhaps the most convincing case report of seizure control with melatonin, very high doses were used: 20 mg in the morning and 80 mg in the evening [15], but this is an order of magnitude higher than the typical doses used for sleep problems.

With regard to basic science and animal work [26, 27], the data would appear to support an anti-seizure effect of melatonin. For example, Fauteck et al. [29] carried out experiments on human temporal neocortical slices cut from tissue resected for surgical treatment of epilepsy. Autoradiographic studies showed that the frequency of occurrence of epileptiform field potentials was reduced to 0.5 of the initial value with application of melatonin (10 and 100 nmol/l). The findings favoured the hypothesis that melatonin depresses epileptiform activity through specific neocortical receptors.

Perhaps the appropriate question to ask is not whether melatonin improves or worsens seizure control but in what circumstances melatonin might be expected to improve or worsen seizure control. Even antiepileptic medication can sometimes result in a deterioration in seizure control rather than an improvement. It would be very helpful for clinicians to know what factors might be associated with an improvement or deterioration in seizure control with melatonin. Past arguments have been in terms of changes in neurotransmitters such as GABA or glutamate. These might well be relevant, but the relationship between seizures and sleep in particular individuals or in specific epilepsy syndromes should also be examined, in view of the fact that sleep can have a profound effect on seizures. The current very limited data seem to suggest that, in the majority of cases, melatonin will not exacerbate seizures and might even improve seizure control but, in some cases, deterioration of seizure control has been reported. Although there is a need for large, double-blind, placebo-controlled trials on the effect of melatonin on seizures, these might not give the complete answer unless individual factors such as seizure syndrome or relationship between seizure control and sleep are also examined.

5 Conclusions

The striking finding of this review is the paucity of relevant data from the remarkably small number of studies. Furthermore, all the studies involved relatively small numbers of patients and most were neither blinded nor placebo controlled. Some suggested worsening of seizures and others indicated improvement in seizure control with melatonin. These results allow no firm conclusions to be drawn, although it would seem reasonable to observe that there was no marked overall effect on seizures, neither improvement nor worsening. There is clearly a need for large randomised, double-blind, placebo-controlled trials to establish the role of melatonin in either predisposing to or decreasing the likelihood of seizures. However, the limited human data and the considerable animal work suggest that melatonin is unlikely to cause significant seizure exacerbations and, perhaps in higher doses, might have antiepileptic properties.

Conflict of interest Neither author has any conflict of interests relating to the subject matter of this paper.

Sources of funding No funding was received for the preparation or writing of this review.

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