Light therapy as a treatment for epilepsy

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A B S T R A C T

From a neurobiological level to epidemiological studies, there are four strands of evidence in the scientific literature that indicate that light therapy could be an effective treatment for some people with epilepsy. (1) Sunlight is important in the endogenous production and regulation of melatonin and vitamin D, both of which influence seizure thresholds. Although melatonin influences seizure thresholds, the relationship is complex. General down-regulating effects may have different effects on seizure thresholds for people with generalised and partial epilepsy syndromes. Specific actions within the hippocampus may mean that patients with temporal lobe epilepsy are particularly susceptible to the endogenous expression of melatonin via inhibitory actions on dopaminergic activity reducing seizure thresholds. (2) If suppression of melatonin results in fewer seizures this should be evident in seasonal variations in seizure frequencies. Seizure frequencies increase in the winter and on dull overcast days. Within this larger circannual rhythm, local light conditions are also associated with variations in seizure frequencies. Controlling for seasonal patterns, complex partial seizures are significantly less likely to occur on bright sunny days, than on dull days with fewer hours of sunshine, regardless of the time of year. (3) On a wider scale, some epidemiological studies also suggest a lower prevalence of epilepsy in southern Europe compared to Scandinavia and Northern Europe. (4) Light therapy is an established medical treatment for depression. Recent research suggests that some forms of epilepsy and depression are bi-directional conditions. The mechanism of action underlying light therapy for affective disorders remains the subject of much research but is thought to involve the enhancement of the monoaminergic systems targeted by antidepressant drugs (serotonin, dopamine, and norepinephrine); systems also implicated in a number of epilepsy syndromes.

In this paper, we propose the hypothesis that exposure to high intensity light may be an effective, non-invasive add-on treatment for people with temporal lobe epilepsy. Although it is more likely to be palliative than curative, it may help smooth out some of the seasonal peaks in seizure frequencies, a pattern that increases the risk of serious manifestations of the condition such as status epilepticus and sudden unexpected death in epilepsy.

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I N T R O D U C T I O N

Approximately 456,000 people in the UK have epilepsy, equivalent to 1 in 131 people. Fortunately seizures can be well controlled by medication in the majority of cases, with 70% rendered seizure free with optimal antiepileptic drug (AED) treatment. However many AED’s have side effects such as cognitive slowing and drowsiness, which are poorly tolerated by some people who therefore cannot adhere to an optimal AED regime. These people, together with the remaining 30% for whom even multiple AED’s at maximum dose are ineffective, continue to have uncontrolled seizures. Other treatment options are limited. Neurosurgery may be an option for a minority, but remains an invasive, irreversible treatment option of last resort. Implantation with a vagal nerve stimulator (VNS) has yielded some positive results in some patients, but is only currently available in specialist centres and its long term efficacy is unproven [1]. In this paper, we propose the hypothesis that exposure to high intensity light may be an effective, non-invasive add-on treatment for people whose seizures are poorly controlled with AEDs.

Hypothesis and reasoning

Light therapy: theory

Early morning exposure to high intensity light was first proposed as a treatment for seasonal mood disorder in 1982 [2], following the report 2 years previously that exposure to bright artificial lights suppressed melatonin secretion in humans [3].
Light therapy (also known as sunlight replacement therapy or phototherapy) is now recognised as an effective treatment for seasonal affective disorder (SAD) and bipolar depression and also appears to be a promising treatment for non-seasonal depression [4–6]. Light therapy is increasingly being tested and applied in a variety of other conditions including circadian rhythm sleep disorders, dementia and insulin regulation in diabetes mellitus [7,8].

From a neurobiological level to international epidemiological studies, there are four strands of evidence in the scientific literature that indicate that light therapy could also be an effective treatment for some people with epilepsy.

1. Neurobiological changes associated with exposure to sunlight

Sunlight is important in the endogenous production and regulation of melatonin but the relationship is not straightforward and it has been as proposed as both an endogenous anticonvulsant and proconvulsant.

Some evidence for its anticonvulsant properties comes from animal studies [9]. The threshold for seizures is increased following an introduction of melatonin in seizure bred rats [10,11]. Daily injections of melatonin also significantly delay the onset of the first convulsion in pilocarpine-induced seizure rats [12]. In people melatonin has been trialed as an add-on anticonvulsant in paediatric populations resulting in reduced seizure frequencies and improved behaviour although the specific effects on the target criteria are difficult to disentangle from generally positive effects that result from improved sleep patterns in the children [13–20].

Baseline levels of melatonin in people with epilepsy may depend on their treatment and seizure history. Elevated melatonin levels have been reported in untreated patients with active epilepsy together with alterations in the normal circadian rhythm of expression [21]. However patients taking anticonvulsants have been reported to have lower baseline levels of melatonin compared to healthy controls [22] and normal circadian rhythms of expression [23]. It is unclear whether this is due to specific actions of the antiepileptic medication the fact that treated patients have fewer seizures. Levels of melatonin in people with epilepsy are raised after a seizure, compared to baseline rates, leading some to suggest that increased melatonin may be an endogenous anticonvulsant mechanism [22,24].

 Whilst the general down regulating effects of melatonin may make it an effective anticonvulsant for generalised epilepsy, inhibitory actions on dopaminergic activity may lower seizure thresholds in patients with partial epilepsy with hippocampal involvement. In such cases melatonin may act as a proconvulsant [25–27]. In rats, the nocturnal activation of hippocampal melatonin receptors depresses GABA(A) receptor function in the hippocampus, enhancing seizure susceptibility [27].

Thus, although melatonin influences seizure thresholds, the relationship is complex and may depend on both the integrity of the circadian rhythm of expression and absolute levels at a specific point in time. General down-regulating effects associated with melatonin may have different effects on seizure thresholds for people with generalised and partial epilepsy syndromes. Specific actions within the hippocampus may mean that patients with temporal lobe epilepsy are particularly susceptible to the endogenous expression of melatonin via inhibitory actions on dopaminergic activity [27].

Chronic deficiencies in vitamin D lead to seizures in animals and humans. Vitamin D deficiencies in people with epilepsy have been associated with some antiepileptic medications [20,28,29]. Modern day living with less time spent outside and increasing use of sunscreen mean that increasing numbers of people in more northerly latitudes are not exposed to enough sunlight and have vitamin D levels in the deficient range. However just a short regular exposure to sunlight or prophylactic vitamin D therapy (where climate or lifestyle does not allow an adequate exposure to sunlight) is sufficient to avoid symptomatic indicators of deficiency, including seizures [30,31].

2. Seasonal variations in epileptic phenomena

Seizure frequencies increase in the winter and on dull overcast days

The influence of seasonal factors on epileptic phenomena is well established. A peak in winter births for people with epilepsy has been documented in both the northern and southern hemispheres [32,33]. Whilst the winter months are often associated with generally increased morbidity and mortality, a meta review of seasonal birth patterns associated with neurological conditions including Alzheimer’s disease, Parkinson’s disease, epilepsy, MS and non-specific mental retardation found that it was epilepsy that had the most consistent pattern of winter births [34].

In paediatric populations the incidence of first febrile convulsions peaks in January [35] whilst the onset frequency of infantile spasms more than doubles in the winter months compared to rates in April and May [36]. In patients with established epilepsy, increases in both seizure frequency and severity have been reported with a higher incidences of sudden unexpected death in epilepsy (SUDEP) in the winter months [37].

Circannual rhythms have also been reported in the efficacy and potency of anticonvulsant medications in animal studies, with a loss of anticonvulsant efficacy in late winter and early spring [38].

Within this larger circannual rhythm, local light conditions are also associated with variations in seizure frequencies. Controlling for seasonal patterns, complex partial seizures are significantly less likely to occur on bright sunny days, than on dull days with fewer hours of sunshine, regardless of the time of year [39].

3. Global epidemiology

Some epidemiological studies suggest a lower prevalence of epilepsy in southern Europe compared to Scandinavia and Northern Europe.

Wide methodological differences in epidemiology studies make it difficult to compare the incidence and prevalence rates of epilepsy between countries [40,41]. The prevalence of epilepsy within the developing world is much higher than in the USA and Europe, partly due to local endemic and epidemic diseases and the limited availability of effective treatments [42]. Even within Europe, different methods of reporting prevalence (treated vs. untreated populations; overall population vs. paediatric/adult/elderly samples) make it difficult to make direct comparisons [40]. However there is some evidence that the prevalence of epilepsy in counties in southern Europe such as Spain (4.1 cases per 1000) [43] and Italy (3.3 cases per 1000) [44] are lower than the levels reported in more northern countries such as Finland (6.3 cases per 1000) [45] and Denmark (7.6 cases per 1000) [46].

4. Depression and epilepsy: bidirectional conditions

Light therapy is an established medical treatment for depression. The monoaminergic systems involved in depression, and altered by light therapy are also implicated in a number of epilepsy syndromes.

Light plays a critical role in regulating circadian and circannual rhythms in mammals and can be used to phase-shift and reset these patterns in variety of conditions ranging from jet lag to seasonal affective disorder (SAD) and bipolar depression and also appears to be a promising treatment for non-seasonal depression [4–6]. Light therapy is increasingly being tested and applied in a variety of other conditions including circadian rhythm sleep disorders, dementia and insulin regulation in diabetes mellitus [7,8].

From a neurobiological level to international epidemiological studies, there are four strands of evidence in the scientific literature that indicate that light therapy could also be an effective treatment for some people with epilepsy.
severe mood disorders. Light therapy is an effective treatment for seasonal affective disorder (SAD) and bipolar depression, with efficacy levels comparable to antidepressant medication in some trials [47]. It is beginning to gain ground as a treatment option for other affective disorders [4,48]. Any beneficial effects of phase shifts in desynchronised circadian rhythms may be independent of the direct effects of light therapy on serotonin, dopamine, noradrenalin [49]; important in a number of epilepsy syndromes [50,51] as discussed earlier. Depression is a common comorbidity of epilepsy but recent research suggests that depression may be a risk factor for developing seizures and that they may be bidirectional disease entities [52–55]. Interestingly trials are currently underway to establish the potential role of VNS as an adjunctive treatment for severe depression [56], following its original development as a treatment for seizures.

Hypotheses

Taken together, these four strands of clinical and experimental evidence suggest that light therapy may be an effective treatment for some people with medically intractable epilepsy. We hypothesise that:

1. Light therapy may have palliative effects on the frequency of complex partial seizures.
2. These effects will be most apparent in patients with temporal lobe epilepsy.
3. Winter treatment with light therapy will reduce the winter spike in the frequency of partial seizures in this group.

Testing the hypothesis

This hypothesis could be easily tested with a randomised controlled trial of light therapy in different groups of people with epilepsy (temporal lobe epilepsy vs. frontal lobe epilepsy vs. idiopathic generalised epilepsy). Following a baseline period participants would be randomised to receive either therapeutic or placebo doses of light therapy from an identical device during the treatment phase of the study. Participants in the light therapy condition would receive light therapy at 10,000 lux. This appears to be the most effective therapeutic dose in the treatment of affective disorders. Patients in the placebo condition would receive light exposure at 100 lux per day (a sub therapeutic dose).

The trial should be conducted over the winter months with hours of daylight in the baseline and trial conditions matched, i.e. September 21st–December 20th/December 21st–March 21st.

Potential clinical implications

If our hypothesis were proved correct we would be able to add light therapy as new, adjunctive treatment for some forms of medically intractable epilepsy. Although it is more likely to be palliative than curative, it may help smooth out some of the seasonal peaks in seizure frequencies, a pattern that increases the risk of serious manifestations of the condition such as status epilepticus and SUDEP. This would represent a novel, non-invasive treatment option for patients in whom all other treatment options have been tried and failed.

Conflicts of interest statement

Action Medical Research are currently funding a randomised, placebo controlled trial of light therapy for partial epilepsy at the National Hospital for Neurology and Neurosurgery. The trial will complete in March 2011.

References