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► To cite this version:

Rhys H Thomas, Will H King, Ann Johnston, Philip Em Smith. Awake seizures after pure sleep-related epilepsy: a systematic review and implications for driving law. *Journal of Neurology, Neurosurgery and Psychiatry*, 2010, 81 (2), pp.130. 10.1136/jnnp.2009.181438 . hal-00552789

HAL Id: hal-00552789

<https://hal.science/hal-00552789>

Submitted on 6 Jan 2011

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Awake seizures after pure sleep-related epilepsy: a systematic review and implications for driving law

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Keywords: Sleep; epilepsy; driving; awake; nocturnal

Word count: Abstract 245; Article 3564; Combined 3809

ABSTRACT

Who with sleep seizures is safe to drive? Driving law is controversial; ineligibility varies between individual US states and EU countries. Current UK driving law is strongly influenced by a single-centre study from 1974 where most participants were not taking antiepileptic drugs (AEDs). However, pure sleep-related epilepsy is often fully controlled on medication, and its withdrawal can provoke awake seizures.

This systematic review asked, 'What is the risk of awake seizures in pure sleep-related epilepsy?' 9885 titles were identified; 2312 were excluded (not human or adult); 40 full texts were reviewed; six papers met our inclusion criteria; each of these six studies had a different pure sleep-related epilepsy definition.

Using the largest prospective study (D'Alessandro 2004), we could calculate next year's awake seizure chance (treated with antiepileptic medication). This was maximal in the second year: 5.7% 95% CI (3.0 to 10.4%). European licensing bodies including the UK's Driver and Vehicle Licensing Agency broadly accept a risk of less than 20% for Group 1 licensing. However this study excluded patients with frontal lobe epilepsies. Furthermore, follow-up (n=160) varied from 2–6 years, yet new awake seizures may occur even after 10–20 years of pure sleep-related epilepsy

A paucity of evidence underpins present licensing law; current rulings would be difficult to defend if legally challenged. The law may be both penalising people with pure sleep-related epilepsy without increased risk of awake seizures, whilst failing to identify subgroups at unacceptable risk of an awake seizure at the wheel.

Awake seizures after pure sleep-related epilepsy: a systematic review and implications for driving law

“I have known many persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason until they awaken, and afterward becoming well and rational as before, although they be pale and weak; and this will happen not once but frequently” Hippocrates, On the Sacred Disease, circa 400 BCE [1]

INTRODUCTION

Sleep-Related Epilepsy

The relationship between sleep and epilepsy is both intricate and complex. Seizures from sleep have been recognised for as long as we had an appreciation of epilepsy itself. The International League Against Epilepsy (ILAE) defines sleep seizures as “seizures occurring exclusively or predominantly (more than 90%) from sleep.” Depending on the method of case ascertainment this estimate has varied from 7.5 to 45% of people with epilepsy,[2,3,4,5] with some estimates clustering around 12%. We define pure sleep-related epilepsy as seizures occurring exclusively from sleep; including seizures that begin in sleep and continue with the patient awake.

Sleep seizures may be relatively benign, for example the childhood partial epilepsy syndromes: benign Rolandic epilepsy (three-quarters occur from non-REM sleep, mainly at sleep onset or just before awakening) or Panayiotopoulos syndrome (two thirds arise from sleep).[6] In contrast, some seizures in nocturnal frontal lobe epilepsy (NFLE) are not only recurrent but are challenging to diagnose, frequently mimicking parasomnias and having a high seizure reoccurrence rate after discontinuing AEDs.[7] Pure sleep-related epilepsy may be more likely to respond to antiepileptic medication[8] but equally some people with infrequent sleep-only seizures not interfering with lifestyle do not necessarily require AEDs. However, the risk of sudden death in epilepsy is greater for those with recurrent un-medicated

seizures, particularly if they sleep without a bed partner and there are published reports of people with epilepsy dying alone in their sleep.[9]

Driving

Driving is a privilege enjoyed by 63 per cent of women and 81 per cent of men in Great Britain (2006).[10] An inability or ineligibility to drive can negatively affect self esteem, reduce self sufficiency and dent employment prospects. Despite this, most countries legislate against those drivers at greatest risk of an accident when driving. Certainly any epileptic seizure could have a deleterious impact on attention, cognition and reflex response times. Uncontrolled awake seizures ensure that a driver is both unable and ineligible to drive in the UK. However there are an unknown number of drivers with ongoing generalised seizures who are legally able to drive: they have pure sleep-related epilepsy.

The governmental body in the UK responsible for vehicle licensing is the Driver and Vehicle Licensing Agency (DVLA). They are also charged with deciding if a patient is legally able to drive. In many cases the answer may be apparent to their clinician after consulting the DVLA guide to medical rules, named 'At a Glance'. [11] Although on-road testing can assess fixed disabilities, paroxysmal disorders, such as seizures, are less well suited; the proscriptive DVLA regulations are therefore of greater importance for epilepsy.[12] Medical advisory panels meet at intervals to discuss these regulations and it is in support of this process that we have undertaken a systematic review of the literature.

Accident risk

There are a number of *legal* driving situations where individuals are at a higher than average risk of a vehicle accident. In particular, male drivers under the age of 25 years are perhaps at five to seven times greater risk than the mean. Schmedding [13] has suggested that a relative risk of two (a risk equivalent to legal driving after 17 to 19 hours without sleep) may be an acceptable risk for people prone to unpredictable paroxysmal events. A relative risk of 2.1 equates to a risk of a seizure (at any time) of 20% a year, (RR of 1.5 to 10% and RR1.1 to 5%).

In the UK, people with seizures occurring only from sleep for three years or more are eligible to drive; providing that they have had two sleep-related seizures in the past ten years.[11] Surprisingly, there is marked diversity throughout Europe in the eligibility criteria for legal driving following sleep-related epilepsy.[14] Indeed, a 2004 report from the second EU working group on epilepsy and driving noted that eleven European countries had no epilepsy driving regulations at all.[15] Harmonisation of EU driving regulations is underway at present; however, nations retain the ability to interpret the rulings more cautiously.[16]

World view

In Japan in 2002 for the first time people with epilepsy could apply for a licence if they were seizure-free for two years: this included people with pure sleep-related epilepsy for two years' duration.[17] US licensing legislation varies between states. Krauss (2001) noted that Utah permitted driving after 3 years of pure sleep-related epilepsy and fifteen states considered "nocturnal" seizures as a mitigating factor when considering ineligibility.[18] It is presumed (but difficult to ascertain) that here the word 'nocturnal' is being clumsily used to be synonymous with sleep-related seizures. In Australia, the twelve month ineligibility for people with sleep related seizures was scrutinised in the courts.[19] Beran's discussion of a case where someone with pure sleep-related epilepsy failed to disclose that he had epilepsy to the licensing authorities also includes a detailed description of a vehicle accident occurring following a generalised seizure at the wheel, ten years after his last reported awake seizure.

The UK requires a thirty-six month period of pure sleep-related epilepsy before driving can resume. In contrast the observation period is twenty-four months in Belgium and Republic of Ireland, but sixty months in some cases in Sweden.[15] Belgian law[13] in 2002 recommended day-time driving only. Perhaps this represents a semantic error, confusing nocturnal and sleep-related seizures. Attempts at reducing the risk of an accident for higher risk groups (driving fewer miles, avoiding

motorway journeys or not attempting right turns across traffic) have thus far been avoided by legislators. In 2004 after a review of the available published evidence the working group recommended that a period of pure sleep-related epilepsy of twelve months may be sufficient before driving resumes. Since 2004 there have been a number of valuable papers published: we aim to update this recommendation by systematically reviewing the data.

Objectives and question

We set out to identify the risk of awake seizures in patients with a diagnosis of pure sleep-related seizures. We identified and considered two subcategories: seizures treated with AEDs and seizures with onset that was generalised, focal or undetermined. We endeavoured to ascertain if the risk were static or whether it reduced for each year after diagnosis. We then wanted to compare the actual risk to that accepted by the DVLA to determine the implications for driving regulations.

METHODS

Two reviewers (RHT and JAJ) independently searched MEDLINE (1950 to February 2009), EMBASE and PsychINFO (1806 to February 2009), Web of Science and PUBMED using a comprehensive search strategy. No language restrictions were imposed. We identified pertinent studies by searching under the terms sleep epilep*, pure sleep epilep*, wake seizure*, diurnal epilep*, driving epilep*, nocturnal epilep*, nocturnal seizure*, sleep seizure*, transform* and sleep epilep*, driv* and sleep epilep*. Studies included in the review were randomised controlled trials, case control and observational cohorts. Studies focussing only on children or animals were excluded.

Table 1	Retrieved	Excluded animals or under 18	Excluded at abstract	Full text Retrieved	Duplicates	Excluded after full text	Included
PUBMED	4126	1378	1368	10	0	6	4

Web of Science	5403	902	883	19	10	7	2
EMBASE	117	32	27	5	4	1	0
PsychINFO	239	37	35	2	1	1	0
MEDLINE	247	100	96	4	3	1	0
TOTAL	9885	2312	2278	40	18	16	6

RHT and JAJ independently read all the abstracts from the citations yielded by the combined search strategy. Any disagreements were resolved by mutual discussion. We cross referenced the identified publications by hand searching and with SCOPUS we identified articles which cited the original retrieved studies. We also contacted authors of these key papers for any ongoing or previously unpublished data (seven contacted; five replied).[3,7,20,21,22]

For each of the identified studies, RHT and WHK assessed the methodological quality of each study, the numbers of participants excluded from the reported analyses or lost to follow-up, the duration of the study and the follow-up period. Particular care was made to understand the case selection and entry criteria. Participant demographic characteristics were recorded such as age and sex and the numbers allocated to each study group. Definitions of pure sleep-related epilepsy and how such a diagnosis was confirmed, seizure types, the underlying aetiology of the seizure disorder and the presence of any co-morbidities such as learning disability were noted.

Search strategy: **Illustration 1** (left) demonstrates the process of identifying articles from PubMed. A similar process was undertaken for each of the other medical databases.

Outcomes

Having identified the methodological quality of each study, data relevant to determining the annual risk of conversion to awake seizures were extracted from each study. This included information on the total numbers of patients studied, the number of patients censored and the number of patients converting to awake seizures. Where this information is not clearly available from the study, the authors were contacted and the relevant information was requested. In studies where it was possible to obtain this information, annual risks of conversion to awake seizures were calculated, with censoring corrected for using the actuarial method.[23] Confidence intervals for these risks were calculated using the method of Wilson.[24] The study design of two key papers[7,22] prevented us from calculating these rates. We also identified: whether the patients had a diagnosis of a generalised or focal seizure disorder (and how this was ascertained); whether patients were taking AEDs at entry to the study and during the observation period; the response to medication; the people with epilepsy excluded from the study.

RESULTS

	Study size and period	Minimum sleep seizures	Location and design	Antiepileptic therapy	Excluded
Gibberd [3]	6 year retrospective. Follow up of one to 42 years. Sample size – 645; 76 with sleep seizures.	One seizure, clinical epilepsy diagnosis and an EEG. Pure sleep epilepsy for six months following first seizure. Motor seizures only.	Retrospective cohort of outpatients. Single UK centre	Unclear. Most probably untreated.	17% of case notes were unavailable.
D’Alessandro 1983 [20]	Unclear	2 or more	Retrospective cohort of outpatients. Tertiary		Focal onset and unclassified

			referrals Italy		
Park [21]	4 year retrospective. Sample size – 63 with sleep seizures.	2 or more, unprovoked. All had sleep-provoked EEG.	Retrospective cohort of outpatients. Single centre South Korea	35% untreated at entry All patients received AEDs	Syndromic epilepsy e.g. Juvenile myoclonic epilepsy
D’Alessandro 2004 [22]	Consecutive patients over 4 years. Sample size – 161.	2 or more within two years. Must have witness	Prospective cohort. Multi-centre in North East Italy	46% at enrolment, 93% at end of follow-up	Frontal lobe epilepsy
Fernandez [7]	Retrospective 10 years. Sample size – 55 with sleep seizures.	3 or more seizures. No awake seizures for ten years.	Retrospective cohort of outpatients. Single University Hospital centre, Spain	2 untreated 64% monotherapy, 31% dual therapy 1 on three AEDs	Under 18s. Absences and myoclonus

Included studies

The search strategy yielded 9885 papers, many of which were duplicates. Five key papers were identified for systematic review; the sixth was Provini’s [25] paper which did not meet our criteria but provided useful information on the topic. Table 2 summarises the characteristics of the papers.

Description of included papers

Gibberd’s [3] retrospective study of patients at a single UK centre identified 76 people with pure sleep-related epilepsy of whom 23 developed new awake seizures over a remarkably variable study period of one to 42 years. D’Alessandro’s [20] paper from 1983 was more a description of outcomes from their practice than a robust study and was not considered further. Park’s [21] retrospective single centre study identified 63 people with pure sleep-related epilepsy and 12 of whom developed awake seizures within the two years of study. Provini’s [25] retrospective review of nocturnal frontal lobe epilepsy was performed at a tertiary centre in Italy solely including people referred for polysomnography. Between 1972 and 1995 100

manifested nocturnal attacks during the recordings which were performed after medication had been withdrawn. They reported that 34% of patients had 'occasional' awake seizures, 8% (8/34) developing new awake seizures after first developing pure sleep-related epilepsy.

D'Alessandro [22] published a multicentre study of 161 consecutive people with a new diagnosis of epilepsy and sleep-only seizures. Treatment was pragmatic with each centre allowed to treat as usual practice: 93% were given AEDs and 78% achieved total seizure freedom at two years. Fernandez's[7] ten year retrospective study of 55 people with pure sleep-related epilepsy, 17 of which developed awake seizures, is the most recently published. For inclusion the patients needed to have had at least three sleep-related seizures over a period of ten years or more. The mean age of seizure onset was 25.2 years; the average age of participants was 52.6 years.

Estimates of awake seizure rate

We were able to calculate the year-on-year risk of an awake seizure from two papers. The maximum estimated chance of seizure in the next year in Gibberd's [3] paper was 15% (95%CI(8.2 to 26.5%)) and for D'Alessandro's study 2004,[22] 5.7% 95%CI(3.0 to 10.4%).

Focal versus generalised epilepsies

Each study attempted to distinguish between focal and generalised epilepsies using EEG criteria and sometimes an eye witness. However there was shared speculation that focal onset seizures would be poorly described by a bed partner. Park's [21] paper identified a discrepancy between focal and generalised epilepsies. 11/42 (26%) developed awake seizures in the partial-onset group, and the single individual in the generalised-onset epilepsy (1/21, 5%) experienced a likely focal event. It is important to state that the people with pure sleep-related epilepsy were not newly diagnosed and indeed had epilepsy for an average of 8 years before inclusion into the study. This lag-time between diagnosis and inclusion exhibited great variability

and therefore it is difficult to draw conclusions about time to awake seizures following diagnosis with pure sleep-related epilepsy.

Illustration 3: Probability of new awake seizures from D'Alessandro 2004. Risk of transformation much below the 0.2 level (20% chance of seizure in the next year) mark. Study excluded NFLE however.

Multivariate analysis of D'Alessandro's data [22] suggested that high initial seizure frequency and sudden AED withdrawal were associated with increased risk of awake seizures. Although intuitively correct, we must be cautious in relying on *post hoc* analysis of such small samples, e.g. only two people had both risk factors. There is a striking predominance of generalised-onset seizures in both the sample group as a whole (85%) and in the proportion that developed awake seizures (n=18, 83%). If real, this distribution may have resulted from the decision to exclude frontal lobe epilepsies. However the decision to differentiate between focal and generalised epilepsies using primarily EEG criteria may have skewed the data: 47/161 had diagnostic EEGs, 31 showing a focal abnormality. This low pick-up can be partially explained by the high prevalence of participants on AEDs at entry to the study.

Response to treatment

The year-by-year risk of developing awake seizures (after the second year peak) for Gibberd's paper [3] (Figure 1) seems to support the UK 3-year rule (implemented 3 years earlier), However the pharmacological options available to a twenty-first century epileptologist are greater and it is now much more common for people with pure sleep-related epilepsy to receive antiepileptic therapy. It is unclear as to how many patients were treated but the last paragraph suggests it was not many "... *a few sleep attacks do not themselves justify therapy. Until a proper trial is published the physician must be alive to the possibility of worsening the patient's seizures with his medication*" This may explain why so few of the study group attained seizure freedom (23/73 within fifteen years and 15 at three years) in stark contrast with later studies. Yaqub's [8] consecutive cases of sleep-related epilepsy in Saudi patients achieved 94% seizure freedom at 2 years. Park's study[21] also confirmed a favourable response to treatment: a third were AED-naïve at entry to the study, all

went on to receive medication and 57% were seizure free at two years. Provini's [25] study was likely to include a skewed sample from the ascertainment method, who were untreated for the period of testing and certainly not treated with modern AEDs due to the length of recruitment.

DISCUSSION

Context

Early observers who have attempted to categorise seizure semiologies identified the importance of sleep on epilepsy. Gowers recognised that some people with epilepsy had their own rhythm or pattern, some having predominantly seizures from sleep.[26] His study of 840 people with epilepsy stated that 21% had seizures 'only or almost only at night'. On discussing the periodicity of attacks he said "*Frequently fits which have recurred for a time in one condition, during sleep, waking or both, change their time*" recognising that some sleep-related epilepsy could transform into awake seizures. Studies by both Langdon-Down and Brain [27] (66 institutionalised patients) and Hopkins [2] (302 people with epilepsy, including first seizures and people of normal IQ) identified that people with sleep-related epilepsy were at risk of later developing awake seizures.

Illustration 2: Probability of new awake seizures from Gibberd 1974. High transformation rates relate to low likelihood of treatment with AEDs and also patients were removed from study if they became seizure-free.

Late risk of transformation

In Fernandez's [7] paper the 17 who developed new awake seizures were not excluded from later analysis and therefore we know that three had greater than 10 awake seizures in 10 years and 4 only had single seizures whilst awake. Of note the majority of these were focal (skewed perhaps by the over representation of partial onset seizures. Most people who had awake seizures were also on two or more AEDs: the authors suggested that this may represent a more drug-resistant epilepsy. As 10/17 of the awake seizures occurred during drug withdrawal, then non-concordance with prescribed medication also must be considered.

Only 3% of their study group had generalised seizures (38% undetermined). Did very few people with generalised-onset pure sleep-related epilepsy manage the ten years without awake seizures, to enable them to be included in the paper? Or perhaps people with generalised-onset seizures achieved total seizure freedom and the partial-onset group represent a subset with relative AED resistance who continued to have sleep seizures.

Accident risk

It is possible to understand why the present UK rule recommending a three year observation period before granting a three year licence on review was unchanged after looking at the two year risk from Gibberd's paper[3] of 15% (95%CI(8.2 to 26.5%)) (illustration 2). However as stated above the management of pure sleep-related epilepsy has changed in the thirty years following the landmark paper, particularly with regards to treatment. D'Alessandro's study 2004,[22] (Figure 2) has a maximum estimated chance of seizure whilst driving in the next year of 5.7% 95%CI(3.0 to 10.4%). This is comparable to the difference in accident rate attributable to the day of the week (Sunday vs. Tuesday) or the month (July vs. April). It is important to recognise a weakness when comparing these calculated risks: some papers enrolled patients with a new diagnosis (time to new awake seizure represents time in the study not necessarily time from first seizure or first diagnosis);[22] some papers recruited patients with the diagnosis regardless of time from first seizure, in some cases this was many years.[3,7,21]

An individual's relative risk of a fatal accident will vary depending on the number of hours spent behind the wheel and the chance of any accident being a fatal one. A cautious, low speed driver of a modern vehicle in a rural area will be at a lower risk than a speeding, truck driver, without a seat-belt, driving through a heavily built up area. Reflecting this scenario, presently a risk of a seizure at the wheel in the next year of 2% is recommended for Group 2 licences. Group 2 drivers (e.g. lorry drivers) may spend five times longer behind the wheel and accidents may be three times more likely to be fatal, equating to a fifteen-fold increase in risk. However it is predicted therefore that the acceptable risk would vary between and within countries.

Variation in the definition of pure sleep-related epilepsy

The ambiguity inherent in the ILAE definition of 'sleep epilepsy' has led authors to coin the term 'pure sleep epilepsy'; whether a driver with greater than 90% of their seizures during sleep would be safe to drive depends entirely on seizure frequency. However it is clear that there is little agreement as to the optimum definition of pure sleep-related epilepsy for use in the studies included in our analysis, nor to assist driving regulations. This is of importance for two main reasons. Firstly overly rigid operational criteria mean that a great deal of probable sleep-related epilepsy has been excluded from all the studies. If sleep-related epilepsy possibly affects 12% of the epilepsy population why did Park *et al*[21]. and D'Alessandro[22] need four years each to recruit their cohorts? Secondly it is important to know whether there are two identifiable groups; pure sleep-related epilepsy (never had an awake event) and sleep-related epilepsy (infrequent awake events) because they may need separate rulings when interpreting driving law.

We recommend the use of sleep-related seizures/epilepsy, as of course without overnight monitoring it would be impossible to ascertain whether all events occurred from sleep. We prefer the term awake seizures to the previously used wake seizures (to differentiate from seizures on wakening). We also would refrain from diagnosing *pure* sleep-related epilepsy lightly, knowing that new awake seizures can occur even after ten to twenty years.[7]

Recommendations

There is a paucity of data to support driving law and in particular to guide license provision for those with pure sleep-related epilepsy. It is important that the evidence is current, particularly as antiepileptic prescription options and patterns have changed. On the basis of a single study [22] (which importantly excluded frontal lobe epilepsy) it would appear that people who have had two or more seizures only from sleep can be granted driving licences: their additional risk of a fatal accident is not greater than other legal road users. It would appear sensible for them to observe the usual seizure ineligibility period prior to returning to driving as per current UK regulations; this is presently a year but six months might well be adopted in the future.

It would be predicted that in those with pure sleep-related epilepsy who are unmedicated, withdrawing medication or being likely to self-discontinue treatment would present an unacceptable risk of an awake seizure. Additionally care should be taken when offering a licence to a patient with a high seizure frequency prior to medication, until further evidence can answer this uncertainty.

As awake seizures are relatively rare in people with hitherto pure sleep-related epilepsy, larger more comprehensive prospective studies are needed. Not only will these inform the legal aspects of driving but, equally importantly for clinicians, will enable evidence-based communication and treatment decisions. A number of treatment uncertainties remain including: whether we really need to treat pure sleep-related epilepsy; how long to treat patients with pure sleep-related epilepsy; whether it is ever reasonable to consider withdrawing medications; whether treating pure sleep-related epilepsy reduces the risk of sudden death in epilepsy; and whether the present risk model [13] correctly estimates the fatal accident risk for people with epilepsy.[28] Crucially we wait to discover whether treated focal-onset epilepsy is associated with an unacceptable risk of awake seizures.

CONCLUSION

128 years on from Gowers[26]we still do not know the natural history of sleep-related epilepsy and in particular treated sleep-related epilepsy. It is likely that its response to antiepileptic treatment is favourable and that new awake seizures are associated with medication withdrawal. However there is a dearth of comprehensive prospective data on which to base decisions regarding driving law. We may be both penalising people without increased risk of awake seizures, whilst failing to identify subgroups at unacceptable risk of an awake seizure at the wheel.

Acknowledgments

We are grateful for the views of the DVLA (Secretary of State's Panel on Driving and Disorders of the Nervous System) to whom these data were presented in March 2009. We wish to acknowledge the work of Dr Eric Schmedding who presented his risk model to the Panel in 2007 and it is on the basis of this work that many decisions across the Medical Panels are made. We are grateful to Professor Tony Marson for his detailed and constructive comments when reviewing this paper for the Journal. Many thanks to the Whitchurch Hospital Library staff for their support in sourcing papers necessary for this review. We are indebted to the authors who entered into correspondence with us and provided access to their original data where available: Dr Park and Dr Byung-In Lee; Prof D'Alessandro and Dr Leona Bassein; Dr Salas-Puig and Dr Lorena Benavente Fernandez.

Competing interests

PEMS has been a member of the Secretary of State's Panel on Driving and Disorders of the Nervous System since October 2004.

Funding

None

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