Research Review™
SPEAKER SERIES
Narcolepsy and idiopathic hypersomnias

Making Education Easy 2022

About the speakers

Dr Sean Tolhurst

BSC (HONS), BMBS (HONS), RPSGT (USA), FRACP

Dr Sean Tolhurst is a Consultant Respiratory and Sleep Physician working in private practice at The Sleep and Lung Centre at Greenslopes Private Hospital. He graduated first in Science (with First Class Honours) from The University of Queensland, then completed his undergraduate medical training at The Flinders University of South Australia (again at an Honours level). He completed his basic and advanced training in Queensland and New South Wales, gaining his fellowship from the Royal Australasian College of Physicians (FRACP) in 2006 with specialist qualification in Respiratory and Sleep medicine.

Dr Tolhurst is one of Australia's most experienced Sleep Physicians with an extensive Sleep Medicine practice. He was the Head of Department of Respiratory and Sleep medicine at Greenslopes Private Hospital, and was previously the lead Clinician in Australia's largest diagnostic sleep service provider. He is an examiner for the Royal Australasian College of Physicians, and was previously the director of clinical training at Greenslopes Private hospital. He was one of the co-authors of the Australasian Sleep Association's previous guidelines on the performance of Sleep Studies in adults.

Dr Tolhurst is one of only four Australian Sleep Physicians that also hold the RPSGT sleep technologist qualification. He regularly provides expert medico-legal opinion in cases involving Sleep Medicine and is a member of the Medico-legal Society of Queensland.

Dr Claire Ellender

BSC, MBBS, FRACP

Dr Claire Ellender is a Respiratory and Sleep Physician at the Princess Alexandra Hospital as well as a conjoint appointed academic in the Faculty of Medicine at the University of Queensland.

To view the full webinar on Narcolepsy and Hypersomnias Please Click here

This review summarises highlights from the second webinar on narcolepsy and hypersomnia held on the 25th August, 2021 and sponsored by Teva Pharma Australia Pty Ltd. The seminar featured presentations from Dr Sean Tolhurst (Sleep and Lung Centre Brisbane), who discussed medicolegal aspects of parasomnias – with a specific focus on 'sexomnia' – and Dr Claire Ellender (Princess Alexandra Hospital and University of Queensland), who discussed cerebrospinal fluid (CSF) orexin testing and its utility in an Australian practice.

Australian sleep stories – medicolegal aspects of sexsomnia

Dr Sean Tolhurst
Sleep and Lung Centre, Brisbane

The classification of NREM parasomnias and sexsomnia

Dr Tolhurst started by reviewing the broad categories for parasomnias: non-rapid eye movement (NREM) parasomnias, which include sleep-related abnormal sexual behaviours ('sexsomnia') – and REM parasomnias.

Sexsomnia is primarily a combination of confusional arousal with occasional ambulation (sleepwalking).[1] The ICSD-Third Edition (ICSD-3) provide the general criteria for NREM parasomnias, which are shown in **Table 1**.[2]

Table 1. **ICSD-3 criteria for NREM-related parasomnias**[2]

1. Recurrent episodes of incomplete awakening
2. Absent or inappropriate responsiveness
3. Limited or no cognition or dream report
4. Partial or complete amnesia for the episode
5. The disturbance is **not better explained** (e.g. by another sleep disorder, mental disorder, medical condition, medication or substance abuse)

Dr Tolhurst highlights that criterion 5. is the most important – especially from a forensic perspective. There are various non-sleep conditions that need to be considered – for example underlying medical conditions (e.g. seizure disorders which can have a sexual component) or medications, malingering/voluntary/conscious bad behaviour, and drugs or alcohol; in a patient who has consumed significant amounts of alcohol, an incident at night is more likely to be caused by alcohol than an underlying sleep condition.

Parasomnias from a medicolegal perspective

A doctor's role in providing a medicolegal opinion is to educate the court, both the Judge and the jury, and to be free from bias. Dr Tolhurst discussed a major limitation with NREM parasomnias being the evidence base: although opinions must be evidence based where possible, there are very few cases of sexsomnia with polysomnography and documented sexual activity while asleep; often the involved parties are unwilling to undergo video polysomnogram, and if they do, capturing an episode of sexsomnia on the night of a sleep study is uncommon.[3]

It can be helpful in a case to clearly identify the features that are consistent/typical, atypical or not at all consistent with a parasomnia. Although the spectrum of sexual behaviour that can occur with a parasomnia is quite broad, Dr Tolhurst stated that one must keep an open mind, but also be cognisant of any confounding factors, such as alcohol or drug use. He strongly recommends seeking the opinions of additional specialties when indicated, for example forensic psychiatry or clinical toxicology.

In Dr Tolhurst's experience, defence teams or defendants may offer sexsomnia as an explanation for incident(s), sometimes after exploring other lines of defence, and usually the incident is not best explained by a sleep disorder, rather by alcohol- or drug-related behaviour, or voluntary/intentional behaviour. Clinical opinion is often the most powerful tool available in medicolegal cases; video polysomnograms while considered the gold standard in the clinical setting have a controversial role in medicolegal/forensic cases of sexsomnia and are rarely used.[4] There are often other inherent challenges related to accurate histories: there are often significant delays (months/years) before sleep-specific histories are obtained, and sleep histories are often inadequately captured at the initial police interviews. Histories from eyewitnesses and/or complainants are crucial, as it can help to identify or exclude clinical features of NREM parasomnias. Although many medicolegal cases involve alcohol intoxication in frequent heavy drinkers, there is no robust evidence that alcohol triggers parasomnias nor impacts duration or percentage of slow-wave sleep. Additionally, neither the ICSD-3 nor the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) list alcohol as a trigger for NREM sleep arousal disorders/sleepwalking.[2]

What are the features of sexsomnia?

Sexsomnia describes sleep-related abnormal sexual behaviours, that are both undesirable and involuntary, and it is primarily classified as a disorder of confusional arousal.[2] There are very few cases of video polysomnography-proven sexsomnia.[2] Unsurprisingly, this disorder can have significant personal, family, clinical and forensic consequences.

Sexsomnia:

- usually presents late in the course of a well-established NREM parasomnia. Dr Tolhurst advised that clinicians should be very wary of a first incidence of parasomnia being sexomnia with forensic consequences
- can be precipitated by obstructive sleep apnoea (OSA), and there are case reports of the parasomnia resolving upon management of the OSA
- is usually confined to the bed, but can occur in combination with sleepwalking
- is usually in the first third of the night, coinciding with the usual predominance of slow-wave sleep at that time[5]
- is usually amnestic,[2] but there are reports of partial recall in some cases[6]
- very rarely occurs during the day
- is usually in a male patient or defendant
- people involved are difficult to wake, confused, considered 'not there' or 'glassed over'.[2]

Reports of sexsomnia cover a wide range of sexual acts from kissing to sexual moaning through to penetrative intercourse. Dr Tolhurst advised that anyone suffering from sexsomnia must be extensively counselled to acknowledge full responsibility for their actions should a repeat event occur in preventable or predictable circumstances.

Concluding with case studies

Dr Tolhurst then presented two cases which highlighted the spectrum of sexsomnia that can be seen both clinically and medicolegally/forensically. To watch these cases, please view the full webinar by clicking here.

CSF orexin testing – utility in an Australian practice

Dr Claire Ellender
Princess Alexandra Hospital, Brisbane
Conjoint academic appointment, University of Queensland

A little bit of history

Dr Ellender began her presentation with some background of the discovery of the novel neuropeptides, named orexins by the Japanese group[7] and hypocretins by the US group.[8] Orexin was named after the Greek word orexis, meaning appetite.[7] Orexin A and B were found to bind to G-protein coupled receptors found in the lateral and posterior hypothalamus, and later in a knock-out mouse model, was found to be associated with cataplexy where the putative link to narcolepsy was made.[9] Groups have also investigated orexin transcript staining in autopsy samples from the brains of patients with narcolepsy, and found that, compared with healthy controls, there is a relative lack of orexin.[10]

The role of orexin in the neurophysiology of sleep

Dr Ellender referred to two publications that describe the topic in detail: Neurophysiology of sleep and wakefulness: *Basic science and clinical applications*, by Schwartz and Roth,[11] and *Sleep state switching* by Saper et al.[12] Dr Ellender then explained the "flip-flop" switch in more detail, which describes the reciprocal inhibitory exchange (feedback loop) between the major ascending monoaminergic arousal groups and the sleep-inducing ventrolateral preoptic nuclei (VLPO); when monoamine nuclei discharge intensively during wakefulness, they inhibit the VLPO, and when VLPO fire rapidly during sleep, block the discharge of the monoamine cell groups. As part of this feedback loop, orexin functions as the stabiliser between wake and sleep.[11]

In short, waking is due to the co-ordinated action of neurons producing amines, acetylcholine and orexin. Pontine pathways regulate REM sleep, and preoptic nuclei promote non-REM sleep. Orexin may promote many aspects of arousal, and deficiency produces narcolepsy.[11, 12] Polysomnography studies have shown that in patients with untreated narcolepsy, there is repeated premature and abrupt entry into REM periods, which Dr Ellender explains that we now know to be due to loss of inhibition (of wake/sleep) due to orexin deficiency.

The spectrum of hypersomnolence disorders

Dr Ellender shared a summary of the spectrum of hypersomnia of central origin, adapted from Christelle Peyron, that she finds useful in her practice (**Table 2**).

Table 2. **Summary of hypersomnias of central origin**

Type	Narcolepsy T1	Narcolepsy T2	Idiopathic hypersomnia
History	EDS with sleep attacks	EDS with sleep attacks	EDS (not sleep attacks)
	Disturbed night sleep	Disturbed night sleep	Prolonged and undisturbed nights
	Refreshing naps		Unrefreshing naps
	Sleep paralysis	Sleep paralysis	Sleep inertia
	Hypnagogic hallucinations (50-60%)	Hypnagogic hallucinations (30-40%)	Cognitive fatigability
Cataplexy	Clear cut	–	–
MSLT	<8min on MSLT >2 SOREM	SL <8min >2 SOREM	MSLT <8min Or 660min sleep/24hrs
Biomarker	CSF hypocretin-1 <110pg/mL HLA DQB1*0602	CSF HRCT-1 intermediate or normal (>110pg/mL) HLA less frequent	No biomarkers

CSF = cerebrospinal fluid; **CSF HRCT-1** = hyprocretin-1 in the cerebrospinal fluid (orexin); **EDS** = excessive daytime sleepiness; **HLA** = human leukocyte antigen; **MSLT** = multiple sleep latency test; **SOREM** = sleep onset rapid eye movement; **T1** = type 1; **T2** = type 2.

Dr Ellender also referred to the large series of data from the Stanford group that can be helpful to interpret orexin levels in clinical practice.[10] In this study, which included 274 patients with sleep disorders and 296 controls, typical cataplexy was commonly associated with CSF orexin levels <100pg/mL. Almost all patients with type 1 narcolepsy had low CSF orexin levels, and almost all were positive for the HLA DQB1*0602 gene, and >85% had positive mean sleep latency test (MSLT) and history of hypnagogic hallucinations. From these data, the authors have concluded that 110pg/mL can be considered the cutoff value for type 1 narcolepsy, with 87% sensitivity and 99% specificity.[13]

When to consider measuring CSF orexin

The following clinical scenarios are proposed by Dr Ellender where there is likely to be clinical utility in measuring CSF orexin; these are based on both her discussions with other clinicians, and reviewing the relevant literature.

- Prognostication, which is particularly important to patients
- To confirm a diagnosis when MSLT cannot be performed or cannot cease contaminating or concomitant medications
- To rule in type 1 narcolepsy with a normal mean sleep latency (MSL)
- To rule out type 1 narcolepsy with an abnormal MSL but atypical cataplexy (a challenging clinical case).

Case studies and practicalities of orexin testing in Australia

Dr Ellender presented two cases which highlighted the clinical utility of CFS orexin testing. To watch these cases, please view the full webinar by clicking here.

She also shared her experience with accessing orexin testing from Australia, which is not available locally. Dr Ellender is aware of testing being available through Oxford University, the Mayo Group, and RCH Melbourne via the Stanford Group; currently, her centre works with the Immunology department at Oxford. They require at least 2mL of CSF, and the test costs ~AUD550; the sample can be delivered at ambient temperature if delivered within 72 hours, otherwise it is recommended that refrigerated transport is considered. Freezing is not a requirement, however, they recommend that a frozen sample is retained at the source. For full details of the practicalities discussed during Dr Ellender's presentation, please view the full webinar by clicking here.

Expert Q&A and discussion

To conclude the second webinar on narcolepsy and hypersomnia, Dr Tolhurst and Dr Ellender responded to questions on their respective presentations and topics. To watch this expert Q&A and discussion, please view the full webinar by clicking here.

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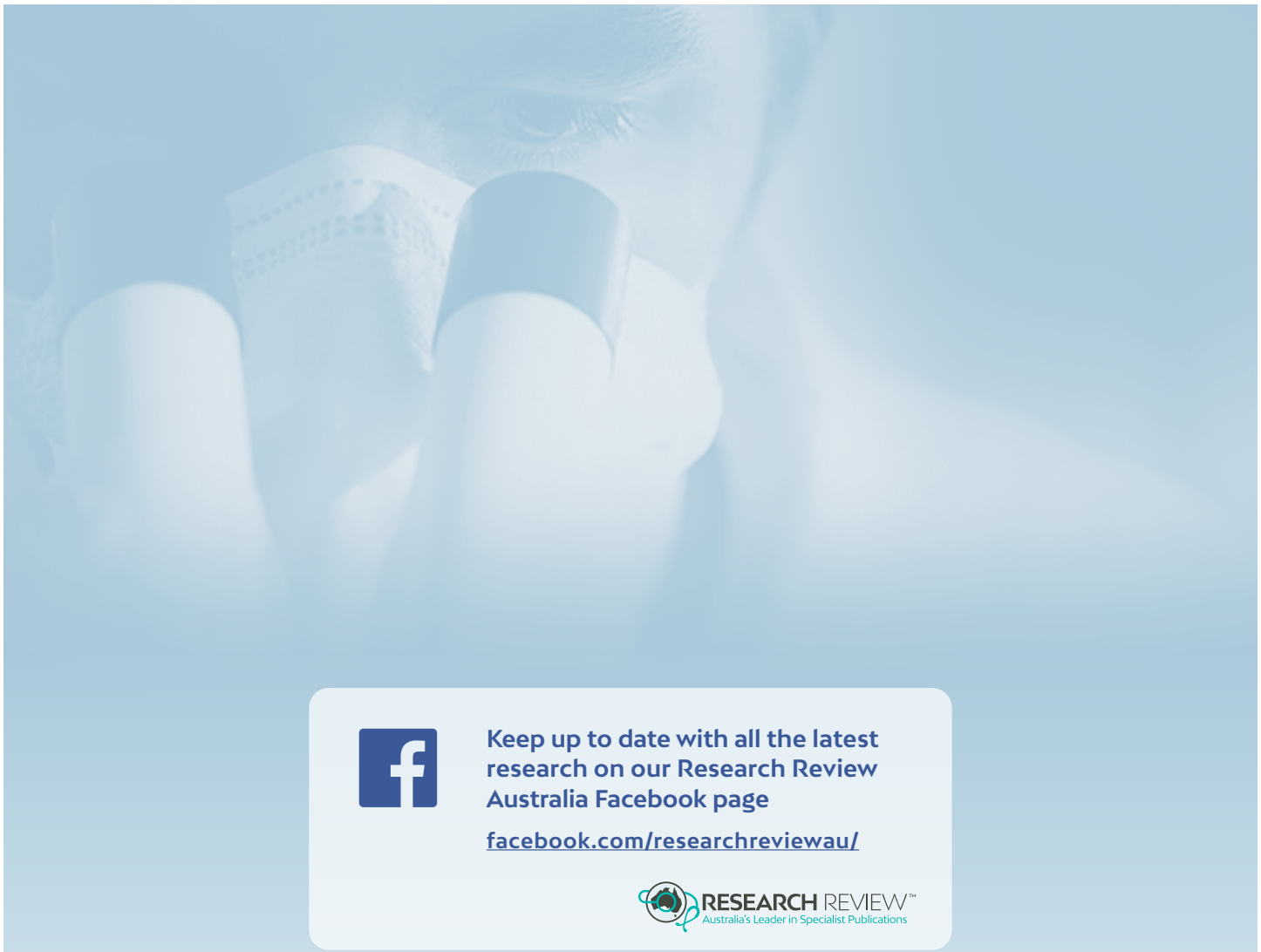

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