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SPEAKER SERIES
Narcolepsy and idiopathic hypersomnias

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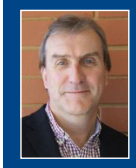
About the speakers

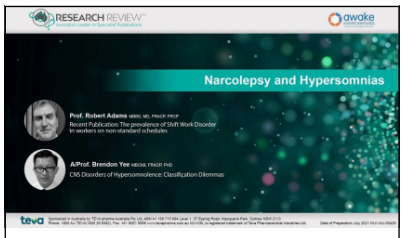


Professor Robert Adams
MBBS, FRACP, FRCP (London)

Prof. Adams has extensive experience with large population-based cohort studies. He is Principal Investigator of The North West Adelaide Health Study (NWAHS) and co-led the process of harmonisation with the Florey Adelaide Male Ageing Study (FAMAS), such that there are now over 2000 men aged over 35 years being followed in the Male Androgen, Inflammation, Lifestyle, Environment and Stress (MAILES) cohort. He was responsible for the conduct of sleep studies in almost 850 men in the MAILES cohort, one of the largest longitudinal cohort studies worldwide of sleep health in the community. He is Chief Investigator on the NHMRC Centre of Research Excellence National Centre for Sleep Health Services Research.

Professor Brendon Yee
MBChB FRACP PhD

Professor Brendon Yee is a Senior Staff Specialist at Royal Prince Alfred Hospital (RPA). He is a Clinical Professor at Sydney University and Senior research/clinician fellow at the Woolcock Institute of Medical Research.



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This review summarises highlights from the webinar on narcolepsy and hypersomnia held on the 21st July, 2021 and sponsored by Teva Pharma Australia Pty Ltd. The seminar featured presentations from Professor Robert Adams (Flinders University, Adelaide), who discussed the non-standard schedules, sleep, and shift-work disorders; and from Professor Brendon Yee (Royal Prince Alfred Hospital, Sydney, New South Wales), who discussed central nervous system disorders of hypersomnolence and the challenges for healthcare professionals related to the classification and management of these disorders.

Non-standard schedules, sleep, and shift work disorder

Professor Robert Adams
Flinders University, Adelaide

Prevalence of shift work disorders in Australian workers

Professor Adams initially discussed the impact of sleepiness or sleep problems on work absenteeism and errors at work. He presented data from a general population survey conducted in Australia for the Sleep Health Foundation (2016) which found that absenteeism from work due to sleepiness or sleep problems was common especially in younger adults.[1] In young adults, 27% of individuals aged 18-24 years and 30% of individuals aged 24-35 years reported that they had taken 1-2 days in the past month off work due to sleepiness or a sleep problem. Errors at work from sleepiness or sleep problems were also common, with approximately 30% of individuals reporting errors on more than one day in the past 3 months.[1]

The 2016 Sleep Health Foundation national survey of 551 working adults aged ≥18 years from across Australia found that sickness absenteeism (≥1 day in the past month) was reported in 27% of individuals and was more frequent in younger participants, university graduates, and those experiencing financial stress and was strongly associated with depression.[2] Individuals with diagnosed sleep disorders, such as obstructive sleep apnoea (odds ratio [OR] 9.8, 95% CI 4.7, 20.7; p<0.001) or insomnia (OR 2.5, 95% CI 1.5, 4.0; p<0.001), were significantly more likely to have days off work.[2] Sickness absenteeism was also common among people who were using sleep aids, sleeping tablets, and those reporting daytime sleepiness.[2] Among individuals without any diagnosis of insomnia or obstructive sleep apnoea, those using sleep medications, or having some sort of daytime sleep symptoms related to their sleepiness were also two to three times more likely to have days off work.[2]

The North-West Adelaide Health Study (NWAHS) population-based cohort study found that work-life balance and depressed mood was significantly related to the length of time people slept, with the effect of work-life interference on depressed mood being much stronger among people with shorter sleep.[3]

Health and safety outcomes of non-standard work schedules

Non-standard work schedules have significant impacts on health, particularly mental health. To illustrate how common this was in Australia, Professor Adams presented data from a population study conducted for the Sleep Health foundation in which non-standard work schedules were defined as inconsistent work arrangements which fell outside "standard" predictable, daytime work schedules (typically between 0900 and 1800).[4] Around 16% of the Australian workforce habitually have inconsistent work arrangements,[5] with 37% of the workforce working hours that vary from week to week, or being on call/standby. More than half a million Australians hold multiple jobs; a substantial proportion of whom (38%) work 6 or 7 days/week.[5]

Shift work disorder (SWD) is a clinical sleep disorder associated with non-standard work schedules that overlap with the usual time for sleep, and includes night shifts, as well as schedules that overlap with the usual time of sleep (e.g. early mornings, and afternoon shifts). The diagnostic criteria for shift work disorder (according to the International Classification of Sleep Disorders ICSD-3) are shown in **Table 1**.[6,7]

Table 1. **Diagnostic criteria for shift work disorder (International Classification of Sleep Disorders 3rd edition)**[6,7]

There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps with the usual time for sleep
The symptoms have been present and associated with the shift work schedule for at least three months
Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent measurement of light exposure) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern
The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder

The prevalence of SWD is poorly understood at a population level, as prevalence studies have typically been reported in specific worker subgroups (e.g. airline personnel, healthcare workers).[8] In order to establish the prevalence of SWD using current ICSD-3 diagnostic criteria across the Australian population, a cross-sectional survey of 2044 Australian adults from an online panel was conducted.[9] The final sample was matched to the Australian Bureau of Statistics (ABS) estimates for age, sex, location, and education of the population.[9] The survey found that around half of the sample was working (51.7%), with 60% of participants aged less than 64 years in work. Approximately half the participants worked a nonstandard work schedule (early starts [21%], later afternoon shifts [8%], evening shifts [6%], or rotating shifts [12%]).[9] The study did not find any association between demographics or occupational features and SWD. The prevalence of SWD depended on the definition used. SWD 1, which was defined as people working shift work and having either difficulty getting off to sleep or maintaining sleep (DIMS), or having some form of significant daytime dysfunction (DD), was identified in 39.5% of workers. SWD 2 which required people working shift work to have DIDM + DD and a ≥60 minutes decrease in habitual total sleep time (TST) occurred in 15% of the workers. SWD 3 required people working shift work to have DIDM + DD plus disturbed sleep/wake patterns and occurred in 10.5% of the population.[9] On workdays, people with SWD slept considerably less than people who do not have SWD. On non-work days, people with SWD slept significantly more than on non-work days to try and catch up with sleep. The study also found that workers who met the criteria for SWD were 1.8 times more likely to report both depression/bipolar disorder and anxiety/panic disorder, and 1.7 times more likely to report work errors due to a sleep problem.[9] In summary, this study indicated that a substantial portion of the population were working in non-standard work hours, and that these individuals often have problems with sleep, and were more likely to have depression, anxiety, and to make errors at work.

Recognising and managing sleep problems in shift workers

In conclusion, Professor Robert Adams noted that absenteeism and worker errors due to sleep issues are very common. Non-standard work schedules are also very common, and this is having a significant impact on sleep opportunities and the quality of workers' sleep. Shift work is commonly associated with sleep problems and daytime impairment and associated mental health and safety consequences.

From a clinical perspective, since many of the non-standard work schedules are unavoidable, the impact of these work patterns needs to be effectively managed. Clinicians need to identify if there is a problem and ask patients if work is impacting the duration and quality of sleep. In addition, there is substantial individual variability in how people respond to changes in their sleep opportunity and changes in their sleep time; the sleep timing/sleep opportunity that may be adequate for many people will probably be inadequate for others. As a result, the impact of poor sleep on functioning and the ability to sleep out of synchronisation with the biological night can impact people in various ways.

CNS disorders of hypersomnolence: classification challenges

Professor Brendon Yee
Royal Prince Alfred Hospital, Sydney

Past, current, and future classifications

The diagnostic criteria for central nervous system (CNS) disorders of hypersomnolence has changed over the last decades, with the current third edition of the International Classification of Sleep Disorders (ICSD-3) published in 2014 (**Table 2**) identifying three central disorders of hypersomnolence: narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH).[7, 10] All three diagnoses require at least 3 months of daily sleepiness, defined as either daytime sleep episodes or an "irrepressible" need to sleep. Further diagnostic criteria for these disorders are shown in **Table 2**.

Table 2. **International Classification of Sleep Disorders 3rd edition classification of CNS disorders of hypersomnolence; diagnostic criteria**[7, 10]

Narcolepsy Type 1 Criteria A and B	Narcolepsy Type 2 All Criteria A-E	Idiopathic Hypersomnia All Criteria A-F
A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months	A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months	A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months
B. Either 1 or 2 or both	B. Mean sleep latency ≤8 min and two or more SOREMPs on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs	B. Fewer than two SOREMPs on MSLT (or fewer than one if nocturnal REM latency was ≤15 min)
1. Cataplexy and mean sleep latency ≤8 min and two or more SOREMPs on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs	C. No cataplexy	C. No cataplexy
2. Low CSF hypocretin-1 concentration (<110 pg/mL or less than one-third of control values)	D. CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration is ≥110 pg/mL or greater than one-third of control values	D. Either 1 or 2 or both
	E. The hypersomnolence and/or MSLT findings are not better explained by other causes	1. Mean sleep latency ≤8 min on MSLT
		2. Total 24-h sleep time ≥660 min on 24-h polysomnographic monitoring or wrist actigraphy (averaged over ≥7 day)
		E. Insufficient sleep syndrome is ruled out
		F. The hypersomnolence and/or MSLT findings are not better explained by other causes

CSF = cerebral spinal fluid; **MSLT** = multiple sleep latency test; **REM** = rapid eye movement; **SOREMP** = sleep-onset rapid eye movement period.

More recently, a new classification has been proposed, which combines patients with NT2 and patients with IH without a long sleep time into a single, new diagnosis called "narcolepsy spectrum disorder" (**Figure 2**).[11]

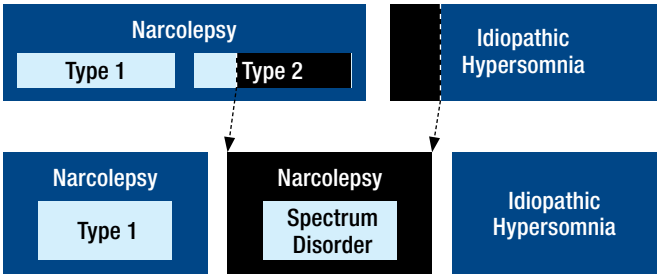

Figure 2. Proposed reclassification of central disorders of hypersomnolence. The ICSD-3 lists eight central disorders of hypersomnolence, including narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia (top row). The proposed new classification is shown on the bottom row.[11]

Current classification: The International Classification of Sleep Disorders, Third Edition

NT1: NT1 is a distinct disorder with immune-regulated involvement (HLA subtypes, particularly DQB1*0602).[11] It is associated with cerebrospinal fluid (CSF) hypocretin deficiency, which is probably the result of a destruction or autoimmune attack on the hypocretin neurons in the lateral hypothalamus in genetically susceptible patients.[11] The identification of CD4 autoreactive T cells against hypocretin cells points to the autoimmune nature of this disorder.[11] Surrogate markers such as polysomnography (PSG)/multiple sleep latency test (MSLT) protocol plus cataplexy is usually sufficient for the diagnosis and, importantly, the retest reliability of these diagnostic tools is high (78-81%).

NT2: NT2 involves a more heterogenous group of patients. It is not characterised by hypocretin deficiency, but patients have excessive daytime sleepiness (EDS) and at least two sleep onset rapid eye movement periods (SOREMs). Patients traditionally lack symptoms of sleep inertia and habitual long sleep time, but they have chronic daytime sleepiness, refreshing brief naps, and may have REM intrusion symptoms. There is a considerable amount of overlap between NT2 and IH. There is also considerable variability with NT2 and that may reflect the fact that these patients may develop cataplexy (with low/normal CSF hypocretin), or they may have low levels of hypocretin, but no cataplexy.

IH: IH also involves a heterogeneous group of patients. Classically, it is characterised by long and unrefreshing naps, prolonged and undisturbed nocturnal sleep, impaired daytime alertness, and focus and sleep inertia (plus EDS). Patients may describe being "never fully awake", "foggy" and "lacking clear alertness" with rare daytime sleep attacks. The diagnosis of IH relies heavily on MSLT, but a positive MSLT test is seen in only half the IH patients diagnosed according to expert clinical judgment. So, there is a need for other diagnostic measures other than MSLT to capture IH characteristics e.g. PSG, 7 days of actigraphy, or *ad lib* protocols for capturing excessive sleep duration, with differing cut-offs have also been used in research studies. There is also a potential role for home sleep studies or home monitoring to diagnose IH. The clinical phenotype of IH without long sleep time may be more difficult to capture because it relies only on MSLT. IH with long sleep time is associated with the classic symptoms of sleep inertia and decreased alertness.

The Montpellier protocol has been used in research to diagnose IH.[12] In this protocol, patients undergo a sleep study with a MSLT, then patients may be referred for a second procedure lasting 58 hours.[12] It starts with a night-time PSG, followed by a modified MSLT in which patients are interrupted after 1 minute of sleep, in order to reduce their reduction in homeostatic sleep drive. Sleep is then monitored during a 32-hour bedrest procedure in a quiet dark room, with participants invited to sleep as long as possible, *ad libitum*. If participants slept for more than 19 hours over the 32-hour period that is diagnostic with high specificity and sensitivity for IH. Over the first 24 hours of the 32-hour bedrest period, a cut-off of 12 hours also had highest sensitivity (100%) and specificity (86%) for IH.[12]

Evidence for combining IH with NT2

Phenotype overlap: There is a great deal of overlap between the clinical phenotype of NT2 and IH patients. Many features, such as sleep paralysis, sleep-related hallucinations, fragmented nocturnal sleep, REM sleep behaviour disorders, sleep drunkenness, and even long nocturnal sleep times can occur in either NT2 or IH patients.

Poor test/retest reliability: Another reason for combining NT2 and IH without long sleep time is the poor retest reliability of MSLT for an IH or NT2 diagnosis. Patients initially diagnosed with these disorders who were retested with a MSLT often have a change in diagnosis due to a change in SOREM and/or sleep latency. This may be due to the differing MSLT protocols, the instability of the symptom characteristics, or that the MSLT diagnosis of IH/NT2 is also not stable for these disorders. To this end, longitudinal studies have shown clinical remission occurs after 5 years in 30-40% of patients with NT2 or IH.[13-15] In comparison, NT1 is unlikely to go into remission.[14] One of these studies examined the test/retest reliability of the MSLT in patients with CNS disorders of hypersomnia.[13] Patients with NT1 and patients with other non-cataplectic central disorders of hypersomnolence (including NT2, IH, and unspecified hypersomnolence) underwent PSG-MSLT twice in drug-free conditions (an average 1.9 years apart). The test/retest of MSLT was reliable for patients with NT1, but there was a lack of stability of the PSG-MSLT-based classification in the other patients, with frequent diagnostic changes in the NT2 and IH groups. Professor Yee noted that although MSLT is the gold standard for diagnosing these conditions, the lack of repeatability of these diagnostic tools is concerning and reflects the fact that these conditions are quite changeable in terms of the diagnostic criteria.

Data driven cluster analysis: A hierarchical cluster analysis based on MSLT findings and clinical features (cataplexy, sleep times, and nap characteristics) identified three well-differentiated clusters of central hypersomnia: NT with cataplexy (NT1), IH with long sleep time, and a combined group of NT without cataplexy (NT2), and IH without long sleep time.[16]

Where to from here?

In the final part of his talk, Professor Yee outlined various potential ways forward for the improved classification of these disorders. He noted that there is a need to further refine the definition of the disease in larger validation cohorts. Novel biomarkers may also be required to differentiate between these disorders of CNS hypersomnolence. Researchers might look at sleep disruption, which is very common in NT1 and comparing the outcomes with IH (in which there is higher sleep efficacy and stability) to see if there are markers that can be used. Better markers for measuring sleep inertia, sleep drunkenness, or morning cognitive performance may be helpful. Many patients have wearable monitors (EEGs) which may be a valuable tool to diagnose IH or narcolepsy. Functional imaging, or even fluid biomarkers (blood or CSF) may help to differentiate these conditions.

Professor Yee also noted that is important to clearly phenotype patients with CNS disorders of hypersomnolence, including their treatment history and treatment decisions. Patients diagnosed with these disorders may potentially have a diagnosis that remains with them for the rest of their life. Importantly, those with NT1 need to be established on life-long treatment. However, NT2 or IH is a phenotype that is not so stable, and patients may spontaneously remit and not require medication. Being labelled as having narcolepsy also has implications for the rest of the patient's life in terms of work, study, driving, and their occupation. Secondary causes of the phenotype need to be excluded (such as mood disorder, circadian misalignment, and chronic sleep deprivation). It is important clinicians focus not just on excessive daytime sleepiness, but also the quality of wakefulness daytime performance.

In summary, Professor Yee highlighted that the future should have better tools for diagnosing CNS disorders of hypersomnolence, as the correct diagnosis has clinical implications for the management of these patients who present in their teens and or early twenties.

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