PO Box 5278
Algester Qld 4115
info@hypersomnolenceaustralia.org.au

HYPERSOMNOLENCE AUSTRALIA

ABN: 19662120036

Idiopathic Hypersomnia – A comprehensive review

Michelle Chadwick

8th September 2017

This is a comprehensive review of how we have gone from the identification of Idiopathic Hypersomnia to where we are now. Drawn from 54 references, including over 40 peer-reviewed papers and book chapters on Idiopathic Hypersomnia and Narcolepsy that span more than 6 decades as well as numerous personal conversations with the world's leading Idiopathic Hypersomnia researchers.

This review is also relevant if you are treating patients with Narcolepsy Type 2 (without cataplexy) or are a patient yourself.

Compared to the advances in narcolepsy research there has unfortunately not been a lot of meaningful progress made with idiopathic hypersomnia. This is due to several reasons. One issue is that the MSLT was considered the ‘gold standard' with regards to diagnosing idiopathic hypersomnia and narcolepsy, however, research has shown not only it's inadequacy in diagnosing idiopathic hypersomnia and narcolepsy without cataplexy (now known as narcolepsy type 2 [N2]) but also its inability to accurately distinguish N2 from idiopathic hypersomnia. [1-19] Consequently, a lot of the work that has been done has not advanced the epidemiological, etiological or pathophysiological understanding of idiopathic hypersomnia thus our knowledge has not moved on much further from what we have learnt from Bedrich Roth’s original work.

Research into narcolepsy has come a long way since Roth’s early narcolepsy epidemiology studies. With the discovery of hypocretin/orexin deficiency being unique in narcolepsy with cataplexy (now known as narcolepsy type 1 [N1]) [20,21] we now know that Roth’s very early observations were accurate in that N1 and idiopathic hypersomnia are separate clinical entities. Roth also noted that N2 was more similar to what he described as monosymptomatic hypersomnia

(referred to in the ICSD-2 as idiopathic hypersomnia without long sleep [IH w/o LST]) than it is to N1. Could Roth be right about this too?

The history of Idiopathic Hypersomnia

The identification of idiopathic hypersomnia started with the first description of sleep drunkenness by Bedrich Roth in Prague in 1956 [22] and culminating in the name idiopathic hypersomnia and the initial description of the condition with two forms, polysymptomatic and monosymptomatic by Bedrich Roth in 1976. [23] Roth's early work, dating back to the early 1950's included a number of studies where he recognised and recorded the clinical differences between narcolepsy and hypersomnia [22,24-28]. One year after the description of sleep drunkenness in his 1956 paper [22] Roth published a book entitled 'Narcolepsy and hypersomnia, from the aspect of physiology of sleep' [29]. It was during this time that Roth started to realise that patients with hypersomnia but without the classic clinical features of narcolepsy and without any other explanation for their symptoms were suffering from an independent clinical entity. In 1960, Vogel showed that narcoleptic patients fall directly into REM sleep, paving the way to a more accurate distinction between these different forms of hypersomnolence [30]. By the mid 1960's Roth's work was confirmed by other researchers including Dement et al. who, in 1966 wrote: "Subjects with excessive daytime sleepiness but no cataplexy, sleep paralysis or sleep onset REM periods do not have narcolepsy and should be relegated to another diagnostic category" [31]. Over the next 10 years, two different groups proposed the terms "essential narcolepsy" [32] and "NREM narcolepsy [33] for this category of patients while Roth continued to study them. Roth published two papers, one in 1969 with Alan Rechtschaffen, Nocturnal sleep of hypersomniacs [34] and another in 1972, with Nevsimalova and Rechtschaffen, Hypersomnia with "Sleep drunkenness" [35].

The following is an excerpt from Michel Billiard and Karel Šonka 2016 review paper, Idiopathic Hypersomnia [36];

"Finally, in a landmark article published in 1976, Roth reported 642 personally observed cases of narcolepsy and hypersomnia and coined the term "Idiopathic hypersomnia". Two forms were proposed: a polysymptomatic form characterized by excessive diurnal sleep of one to several hours duration, prolonged night sleep of a 12–18 h duration and great difficulty upon awakening in the morning, and a monosymptomatic form characterized by the most prominent and often unique manifestation of excessive diurnal sleep of one to several hours duration, however not as irresistible as in narcolepsy. In 1979, the Diagnostic classification of sleep and arousal disorders referred to "Idiopathic CNS hypersomnolence" as a disorder of excessive somnolence "characterized by recurrent daytime sleepiness, but "sleep attacks" do not occur because the sleepiness is not as irresistible as in narcolepsy"…In 1990, the ICSD referred to "Idiopathic hypersomnia" as an "intrinsic sleep disorder". It also pointed out that PSG should rule out SOREMPs; with regard to the MSLT it stated: "The MSLT usually demonstrates a sleep latency of less than 10 min"...In 1997, Bassetti and Aldrich proposed three forms of idiopathic hypersomnia: "classic", referring to patients who tended to have sleepiness that was not overwhelming, to take long non-refreshing naps up to a 4hr duration, to have prolonged night-time sleep and to have difficulty in awakening in the morning; "narcoleptic-like", referring to patients with overwhelming hypersomnolence, who took short refreshing naps and awakened without difficulties and "mixed", referring to patients with clinical features intermediate between the two other groups. In 1998, Billiard et al. suggested returning to Roth's initial distinction and proposed the terms "complete" and "incomplete" forms. Thereafter, the ICSD-2 returned to two forms of idiopathic hypersomnia, namely idiopathic hypersomnia with and without long sleep time. The form with long sleep time was clinically characterized by excessive daytime sleepiness, prolonged nocturnal sleep time (more than 10 h) and great difficulty waking up or sleep drunkenness, either in the morning or at the end of naps, and additionally polysomnographically characterized by a major sleep

> period prolonged to more than 10 h in duration, a mean sleep latency (MSL) of less than 8 min and fewer than 2 SOREMPs on the MSLT. The form without long sleep time was clinically characterized by excessive daytime sleepiness and normal nocturnal sleep (6– 10 h in duration) and polysomnographically by a major sleep period of normal duration (6–10 h) and, similarly, a MSL of less than 8 min and fewer than 2 SOREMPs on the MSLT.
>
> However, the distinction between idiopathic hypersomnia with and without long sleep time was later challenged by the absence of symptoms specific to one subgroup (e.g., great difficulty waking up or sleep drunkenness were found in both subgroups, albeit less frequently in the form without long sleep time). In addition, the validity of SOREMPs during the MSLT in diagnosing narcolepsy without cataplexy or narcolepsy (without affiliation status), was brought into question, as well as the validity of MSL during the MSLT in diagnosing idiopathic hypersomnia."

Thus, the current ICSD-3 abandoned the division between idiopathic hypersomnia with and without long sleep time and revised the polysomnographic criteria of idiopathic hypersomnia. However, considering Roth's early findings and the data from 4 papers from two separate groups [11,37-39] that showed there was a "complete" or "classic" form of idiopathic hypersomnia, did the ICSD-3 get it right this time?

In Billiard and Dauvilliers 2001 review [19] they discussed the previously mentioned four papers that revisited the concept and the borders of idiopathic hypersomnia from two sleep disorders centres, one North American (with Bassetti and Aldrich) [11,37] and one European (Billiard el at) [38,39]. The emphasis in the North American papers was on a substantial overlap in the clinical features of narcolepsy and idiopathic hypersomnia. The European papers focused on Roth's initial distinction of a well-defined "polysymptomatic" form characterized by excessive day sleep, nocturnal sleep of abnormally long duration and signs of sleep drunkenness as well as a much poorly

defined monosymptomatic form. “In conclusion, the North American group and the European group agreed on a rather well clinically delineated form of idiopathic hypersomnia, referred to as “polysymptomatic” or “classic”. This form represented less than a third of the cases of idiopathic hypersomnia for the North American group and more than half of the cases for the European group.” For the rest of the cases the North American group was in favour of separating them into two “intermediate forms” referred to as “narcoleptic-like” and “mixed” idiopathic hypersomnia, whereas the European group was in favour of a yet unspecific classified group which should be clearly separated from both N1 and classic or polysymptomatic idiopathic hypersomnia”. [19]

Since hypocretin/orexin deficiency has been found to be unique in N1 and the knowledge that there is no test that can confidently diagnosis N2 and no biomarkers that can identify it, it has been asked, is N2 actually narcolepsy, or more specifically “does N2 only exist because of the existence of the MSLT and the at-time controversial results it yields?” [8] Is N2, narcolepsy in name only? My discussions with clinician-scientists would suggest this is the case. Khan and Trotti noted that N1 and N2 have “now been recognized to be quite different entities despite their similar nomenclature”. [42] There are several research studies that have shown a biological difference [20,21] and others that have determined that various “narcolepsy markers” are less likely to occur in people with N2 than in people with N1 and that people with N2 have markers that are more similar to people with idiopathic hypersomnia than those with N1. [41,43]

So how similar is Narcolepsy Type 2 and Idiopathic Hypersomnia?

While the division of idiopathic hypersomnia into with and without long sleep may not be accurate, research suggests that there is more than one form of idiopathic hypersomnia [37-39,43] or perhaps that idiopathic hypersomnia is a spectrum disorder that encompasses N2 [1]. Following the latest classification of idiopathic hypersomnia in the ICSD-3, it was felt that idiopathic hypersomnia had been "defined negatively against narcolepsy and secondary and comorbid hypersomnias and

encompasses perhaps a variety of different diseases". [40] This led Billiard and Šonka to perform a detailed cluster analysis [43]. The analysis included subjects with idiopathic hypersomnia and narcolepsy with and without cataplexy. The analysis found that there were 3 distinct and separate clinical entities.

Cluster 1 – "Combined monosymptomatic hypersomnia/ narcolepsy type 2"

(23 cases of IH w/o LST, 19 cases of N w/o C and two cases of IH with LST)

Cluster 2 – "Polysymptomatic hypersomnia"

(24 cases of IH with LST, two cases of IH w/o LST and one case of N w/o C)

Cluster 3 – Narcolepsy type 1

(23 cases of N with C)

**IH w/o LST = idiopathic hypersomnia without long sleep time, IH with LST = idiopathic hypersomnia with long sleep time, N w/o C = narcolepsy without cataplexy, N with C = narcolepsy with cataplexy.*

The study also discussed the spectra of narcolepsy and idiopathic hypersomnia;

"The important contribution of this work lays in the confirmation that cluster narcolepsy type 1 (former N with C) and cluster polysymptomatic hypersomnia (former IH with LST) constitute independent nosological entities. On the other hand, cluster monosymptomatic hypersomnia/narcolepsy type 2 (former N w/o C and IH w/o LST) merges the two diagnostic categories into a single one. This is in line with other evidence:

a) Both conditions are characterized by a complaint of excessive daytime sleepiness occurring almost daily for at least three months.
b) The MSLT distinction between N w/o C and IH w/out LST, according to the ICSD-2, and between narcolepsy type 2 and idiopathic hypersomnia, according to the ICSD-3, is based on the number of SOREMPs on the MSLT, two or more in narcolepsy and less than two

in idiopathic hypersomnia, which is a rather arbitrary and subtle distinction. Moreover, a recent study has shown that compliance or non-compliance with the criterion of two or more SOREMPs is unstable over time.

c) A study comparing participants with N with C, N w/o C HLA-DQB1*0602 positive participants, N w/o C HLA-DQB1*0602 negative participants, and IH w/o LST participants, did not find differences between the two latter groups in terms of ESS and mean sleep latency on the MSLT before and after treatment with stimulants.

d) Finally, in a recent study on health-related quality of life in drug naïve participants with N with C, N w/o C and IH w/o LST, the magnitude of impairment of quality of life did not differ among the three disease categories." [43]

The study concluded,

> "To be totally defined, the spectra of narcolepsy and idiopathic hypersomnia still need further biological markers. However, the present study gives credit to those in favour of merging the former IH w/o LST and narcolepsy type 2 into a single condition, combining monosymptomatic hypersomnia/narcolepsy type 2, and considering polysymptomatic hypersomnia (formerly IH with LST) as a unique form of idiopathic hypersomnia. The next steps should include more in-depth clinical analysis, HLA testing, functional imaging, genetic studies and biochemical measurement in search of valuable biological markers.*"* [43]

This analysis supports the findings of other studies that have shown a subgroup of patients with "a complete form" of idiopathic hypersomnia with symptoms that are unique to this group. [37-39] It also supports the findings in other studies that show N2 and idiopathic hypersomnia without long sleep time, or 'incomplete' idiopathic hypersomnia have clinical features that are more closely related. [18,44,45] This analysis also noted the MSLT distinction between idiopathic hypersomnia and N2 relies on the absence of SOREMs and that this "is a rather arbitrary and subtle distinction". It

referred to one study that "has shown that compliance or non-compliance with the criterion of two or more SOREMPs is unstable over time". [1] There are however many other studies that also question the validity of the MSLT in diagnosing idiopathic hypersomnia and N2. [2-19]

The relevant key issues in these studies include;

a) The specificity of multiple SOREMPs is poor;

Multiple SOREMs can occur in other conditions associated with sleepiness, such as sleep apnea, Kleine-Levin syndrome, delayed sleep phase syndrome, periodic limb movement disorder, upper airway resistance syndrome and Parkinson disease. Multiple SOREMPs are also common in the general population.

b) Poor test-retest reliability of the MSLT resulting in high rates of false negative and false positive MSLT results.

c) 8-minute average sleep latency on the MSLT fails to capture up to 40% of patients who otherwise meet clinical criteria for idiopathic hypersomnia.

d) Waking the patient in the morning to perform the MSLT precludes the recording of the prolonged nighttime sleep which is a typical symptom for a subgroup of idiopathic hypersomnia patients, and the MSLT procedure itself prevents the documentation of prolonged, unrefreshing, daytime sleep episodes. The difficulty waking patients up for the MSLT and keeping them awake between naps has also been noted.

There is an overwhelming amount of research that suggests "The MSLT can no longer be considered the gold standard" [17] for diagnosing idiopathic hypersomnia and N2. Trotti et al have stated that "Collectively, these data and the absence of apparent therapeutic or biological significance to multiple SOREMs argue that the continued use of SOREMs to distinguish narcolepsy without cataplexy from idiopathic hypersomnia is not justified." [1] None of the researchers I have spoken to

disagree with this. It is therefore ironic that the ICSD3 "now pools both conditions (with and without long sleep time) into one heterogeneous condition because researchers were unable to objectively separate both forms of the disease based on the length of nocturnal sleep; patients above the cut-off of 10 hours of sleep showed no significant differences in daytime sleepiness assessed by the Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT).." [46] considering that neither the ESS or the MSLT have been found to be reliable objective tests.

The need for alternatives to the MSLT has been discussed and questions raised regarding the appropriateness of the MSLT for diagnosing idiopathic hypersomnia and N2 as early as the "Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness." were published in 1986. But is there a suitable alternative test to the MSLT?

Some researchers have suggested a prolonged (up to 24 to 32 hours) continuous ad libitum polysomnography or night polysomnography followed by MSLT and then 24hour continuous ad libitum sleep polysomnography. [2,19] Spontaneous sleep periods of up to 19 hours have been reported in idiopathic hypersomnia, despite a normal MSL (11 mins). [47] With regards to the MSLT and 24-hr continuous ad libitum sleep polysomnography Billiard said in his paper, Idiopathic Hypersomnia [39];

> "because the multiple sleep latency test (MSLT) procedure is somewhat questionable in subjects with idiopathic hypersomnia we added a 24-h continuous polysomnography. Indeed, awakening the subject early in the morning in view of the MSLT prevents the documentation of the prolonged night-time sleep and the MSLT procedure itself prevents the documentation of prolonged, unrefreshing, daytime sleep episode(s)."

Billiard concluded,

> "(an) important result of this study is the confirmation of two forms of idiopathic hypersomnia: a complete one and an incomplete one… The terms complete and incomplete

> seem more appropriate than the terms polysymptomatic and monosymptomatic as the incomplete form may include two symptoms, prolonged night sleep and excessive daytime sleepiness. Polygraphically we found a significantly longer duration of night sleep in the complete form when the subjects were allowed to sleep at will. According to the characteristic difficulty waking up, it could be that the complete form is the only genuine idiopathic hypersomnia and that the incomplete form awaits further study." [39]

Another interesting point in Billiard's study is that a marked family pattern has been evidenced by different authors and that their "results are similar and emphasize the very strong genetic component of idiopathic hypersomnia". Bassetti and Dauvilliers have stated that Idiopathic Hypersomnia can present in families, although these individuals are more likely to have long sleep time. [46] Recommendations developed by Billiard and Dauvilliers [19] were used by Vernet and Arnulf in their study, Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients. [2]

> "These recommendations specify to monitor patients after nighttime sleep monitoring followed by MSLT and to allow the patients the opportunity to develop extended uninterrupted sleep. The subjects receive the instruction of not fighting against sleep, and the technician of not interrupting sleep for whatever reason".

Following these instructions, Vernet and Arnulf documented "for the first time normative values for the duration of sleep during an ad libitum 24-h continuous monitoring in 30 healthy volunteers". Apart from the differences between normal subjects and hypersomniacs eg: when considering the amount of sleep during a 24-h period,

> "hypersomniacs had much longer total sleep time than controls", they also noted differences between those classified as having Idiopathic Hypersomnia with and without long sleep as per the ICSD-2. As was the case in Billiard's study, total sleep time during the 24-h

> monitoring was higher in the group with long sleep than without. Patients that slept longer had higher sleep efficiency during the night and had more frequent SWS episodes at the end of the night. Apart from this, there was no other difference in sleep structure. However, patients without long sleep had more sleep fragmentation arousals, periodic legs movements and apnea/hypopnea events.

Perhaps the most significant difference between the two groups is that while all the patients without long sleep had MSL <8 min, "71% of patients with long sleep time have normal MSL (MSL > 8 min) during MSLT, reinforcing the idea that the latter test is poorly sensitive for diagnosing hypersomnia". [2] In fact, more than half of the patients with long sleep time had MSL > 10 min.

> "These results support the idea that hypersomniacs would not fall asleep as quickly as narcoleptic patients (i.e., without rapid shift from wakefulness to sleep). In contrast, they would have difficulty waking spontaneously after sleep (i.e., difficulty shifting from sleep to wake), which could result in severe cases in sleep drunkenness." [2]

The study concluded, "This study highlights the MSLT limitations for the diagnosis of hypersomnia, compared to the sensitivity of 24-hour monitoring".

The advantage of 24-hr continuous ad libitum polysomnography for idiopathic hypersomnia is that it "allows for the documentation of a major sleep episode (>10 hours) and of daytime sleep episodes of more than 1 hour's duration". [46] However there is currently a lack of standardisation and normative values for 24-hour continuous ad libitum sleep polysomnography, especially regarding the level of physical and social activity allowed during the recording. [2,46] eg: "Does the patient remain in bed during the full recording or perform some physical activity, and to what degree? Do these prolonged polysomnograms need to be performed in an ambulatory or only in laboratory setting? Do age and gender modify both night and daytime quantity of sleep obtained in normal controls and in IH patients?" [46]

While adding a prolonged 24-hr continuous polysomnography to the current polysomnography/MSLT would add considerable cost to the diagnostic workup, one might argue that the current polysomnography/MSLT alone has next to no diagnostic value. It is not uncommon for patients to have several polysomnography/MSLT in the pursuit of the "right" diagnosis despite us knowing that "when the MSLT is repeated the diagnosis can change 50% of the time". [1,47] Therefore, a prolonged 24-hr continuous polysomnography, with prior 2-week actigraphy and sleep log may be more appropriate.

Ambulatory actigraphy monitoring over two weeks has been suggested as a possible alternative to the MSLT as it can be helpful in ruling out behaviorally induced insufficient sleep syndrome and circadian disorders that may lead to excessive daytime sleepiness. However, actigraphy protocols have also not been standardised or validated in idiopathic hypersomnia and determining the difference between sleep and rest while awake is difficult, especially in the context of depression. [46]

As idiopathic hypersomnia (and N2) lack biological markers and "sufficient electrophysiological diagnostic criteria." [48] the diagnosis of idiopathic hypersomnia (and N2) currently rests on the exclusion of other causes of excessive daytimes sleepiness, detailed history and careful clinical analysis. Idiopathic hypersomnia is frequently misdiagnosed therefore it is important to consider all the conditions that can be confused with idiopathic hypersomnia. [19,39,46,49]

Differential diagnosis

Narcolepsy is the most common differential diagnostic consideration. N1 can be ruled out in the presence of excessive daytime sleepiness (EDS) with clear-cut (definite) cataplexy, and low or undetectable CSF hypocretin-1 levels, however, there are no biomarkers and no reliable test that can determine the difference between N2 and idiopathic hypersomnia. Several medications can cause excessive daytime sleepiness and hypersomnia. [46,50] Breathing-related sleep disorders including

sleep apnea and upper airway resistance syndrome need to be ruled out. Other common differential diagnostic considerations are insufficient sleep, long sleepers and hypersomnia associated with psychiatric disorders (depression, bipolar disorder). [46,50] Hypersomnia associated with psychiatric disorders can be difficult to differentiate from idiopathic hypersomnia. Both can include excessive daytime sleepiness, long unrefreshing naps, long sleep times, sleep drunkenness/inertia, and depressed mood. Polysomnography findings may be very similar, although patients with hypersomnia associated with psychiatric disorders generally have higher amounts of NREM stage 1, less SWS, and lower sleep efficiency. In patients with hypersomnia associated with psychiatric disorders, the MSLT typically shows normal mean sleep latencies. [46] "Hypersomnia associated with psychiatric disorders may also, however, be accompanied by abnormal MSLT findings, and conversely, patients with idiopathic hypersomnia may exhibit normal MSLT findings. In unclear cases, formal psychiatric assessment is needed. [46] There are many other differential diagnostic considerations including but not limited to chronic fatigue syndrome, restless legs syndrome and sleep-related movement disorders, circadian disorders and hypersomnia associated with other medical disorders. "A medical condition may produce hypersomnia and mimic IH with EDS (excessive daytime sleepiness), automatic behaviours, prolonged sleep episodes, and sleep drunkenness.", including several neurological disorders. Hypersomnia and EDS are occasionally observed in diabetes and is common in hypothyroidism, also after an acute viral infection. [46]

> "In the clinical practice of sleep medicine, one of the most frustrating diagnoses to make (and for the patient to receive) is idiopathic hypersomnia. The dissatisfaction stems from diagnostic uncertainty, unclear natural history and unpredictable response to treatment". [51]

Because idiopathic hypersomnia is essentially a diagnosis of exclusion, in the absence of biomarkers and reliable testing methods "the main pitfall is not making an accurate diagnosis". [46]

> "The terms idiopathic hypersomnia and hypersomnia of unknown origin are not synonymous. Different research groups have historically used different diagnostic criteria, making comparisons across studies difficult. This is particularly true of case series that did not exclude mild forms of sleep-disordered breathing, behaviorally induced insufficient sleep syndrome, and hypersomnia associated with psychiatric disorders.
>
> The main controversies relate to (1) the clinical and neurophysiologic overlap between IH and hypersomnia associated with psychiatric disorders, mild sleep apnea, narcolepsy without cataplexy, and behaviorally induced insufficient sleep syndrome; (2) the potential for spontaneous improvement or change in diagnostic category; and (3) the currently unknown pathophysiology of IH. Further studies are required to understand the pathophysiology of IH, to determine whether there are different clinical subtypes of IH (forms with and without long sleep time), and to validate the specificity and sensitivity of biomarkers involved with diagnostic and therapeutic significance. Finally, prospective studies are needed to obtain objective evidence for the efficacy of medications in treating IH and to clarify whether mood changes in IH are consequent to difficulty adapting to the disease or indicate a primary brain dysfunction." [46]

Considering the many differential diagnostic considerations, and an unfortunate tendency to label all difficult to classify cases of excessive daytime sleepiness as idiopathic hypersomnia [19] it has been suggested that "for the patient and the general population it is much more important to know if excessive daytime sleepiness is caused by a lifestyle problem or a sleep disorder, and how to deal with it or prevent it." [8] Very little time is dedicated to sleep in general during medical training much less sleep disorders. On average, the amount of time spent on sleep education (sleep in general, not sleep disorders) is just under 2.5 hrs during an entire 4 year degree. [52,53,54,55,56] Even during specialty training, hours in non-respiratory sleep disorders are limited [53,54,55,56]. The Royal Australasian College of Physicians acknowledges the limitations in their training in the 'Sleep

Medicine Advanced Training Curriculum', "There are too few training posts in Australia and New Zealand that can provide broad exposure to and quality training in, the whole range of sleep disorders, particularly nonrespiratory sleep disorders'. [53] Similar problems are seen in other countries. [54,55,56] This contributes significantly to the misdiagnosis of hypersomnolence disorders and narcolepsy and sorely needs attention.

It is the view of some clinician-scientists that "narcolepsy is the prism that sleepiness is always viewed and therefore defines how diagnosis, treatments and outcome measures are framed however this framing is not appropriate for idiopathic hypersomnia not least of all because narcolepsy and idiopathic hypersomnia are not the same disorder". [54] An example of this is the MSLT. The 8 minute cutoff replaced a 10 minute cutoff because the authors of the ICSD-2 decided an 8 minute cutoff was best "to define sleepiness for diagnostic purposes" based on the fact that this cutoff appeared to be the best cutoff for diagnosing narcolepsy. There is an assumption that if it (diagnostic criteria, treatment etc) works well for narcolepsy then it will work well for idiopathic hypersomnia despite the authors of the ICSD-2 citing data that actually contradicts their decision. [42] In Australia access to medications and tests are set under criteria for narcolepsy. The criteria rely on that assumption if its suitable for narcolepsy then its suitable for idiopathic hypersomnia. Therefore, people with idiopathic hypersomnia need to meet criteria for narcolepsy to access medication approved for narcolepsy. The advantage of a 'narcolepsy' diagnosis in the US is huge. [54] Similar to Australia's PBS and MBS (Pharmaceutical Benefits Scheme and Medicare Benefits Scheme) US insurance companies typically cover narcolepsy, not idiopathic hypersomnia so it is not uncommon for doctors to formally 'code' patients as narcoleptic on a billing sheet or formal medical records to get medications more readily/easily approved. [54] Similar issues to those in Australia and the US are also seen in parts of Europe. [55]

Whether doctors are labelling difficult to classify cases of excessive daytime sleepiness as idiopathic hypersomnia which end up on the record as narcolepsy or genuine cases of idiopathic

hypersomnia are being ‘coded’ as narcolepsy, it creates many problems. [54,55,56] It perpetuates ignorance in relation to the "genuine" diagnosis and it also renders any epidemiological study ‘flawed’. [54] Marketing arms of pharmaceutical companies have access to prescribing patterns of individual US physicians and in Australia government authorities (including the Therapeutic Goods Administration) rely on statistics from Australia’s PBS and MBS yet these records do not reflect the true prevalence of idiopathic hypersomnia and narcolepsy. Therefore, one could get a false impression of an epidemic of "narcolepsy" when in fact if you were to isolate the true narcoleptics (N1) the number would be quite small. [54]

I have spoken to a number of clinician-scientists experienced in idiopathic hypersomnia and narcolepsy since the release of the ICSD-3 and there isn’t a lot of confidence in it. Some question whether it is sufficiently justified by data, [50,54,55] while others believe that it is a step back in the definition of idiopathic hypersomnia. [40] The consensus is that it fails to adequately define disorders of Hypersomnolence outside of N1. I was reminded of several papers that discuss a ‘complete’ form of idiopathic hypersomnia, the likelihood that N2 is more like the ‘incomplete’ form of idiopathic hypersomnia, and the inadequacy of the MSLT and the pros and cons of possible alternatives. What my discussions and these papers reveal above all else is that identification of a biomarker with diagnostic and therapeutic significance is urgently needed for N2 and idiopathic hypersomnia and that perhaps the path that should be considered when looking at disorders of hypersomnolence and N1 is that these two groups are not the same. They also reveal that considering the lack of biological markers and sufficient or perhaps, relevant electrophysiological diagnostic criteria lumping all of idiopathic hypersomnia into the one group and keeping N2 separate based solely on the presence of 2 or more SOREM is a stop-gap measure simply because an agreement couldn't be reached with regards to appropriate diagnostic criteria.

The consensus also seems to be that it is likely that an incomplete form of idiopathic hypersomnia and N2 are manifestations of the same underlying pathology and that a complete form

of idiopathic hypersomnia stands alone as a separate clinical entity or at the very least, idiopathic hypersomnia and N2 exist along a spectrum with overlapping features. There is support for merging N2 and the incomplete form of idiopathic hypersomnia into one single condition, leaving the complete form as a separate disorder. Or to combine N2 with idiopathic hypersomnia as a spectrum disorder that encompasses the two conditions. All of the clinician-scientists I spoke to agree that research is needed to investigate this line of enquiry with the aim of finding diagnostic criteria and treatments that are relevant to these conditions rather than using diagnostic criteria and treatments for a different disorder (N1).

I asked them all why they think Idiopathic Hypersomnia research is important. Professor Šonka acknowledges that people are suffering, "idiopathic hypersomnia diminishes quality of life" and that research has the potential to change lives. [55] Professor Dauvilliers summarised the consensus, "Because we understand currently so little in hypersomnia outside of narcolepsy type 1… We need to improve our knowledge on sleep duration, long vs short sleepers (genetic, biology, prognosis, stability), to better identify and recognize the idiopathic hypersomnia disease, also its evolution and response to medication. [56]

I would like to thank all the clinician-scientists that advise me in general, or who I have spoken to specifically for this piece, particularly Professors David Rye, Karel Šonka, Michel Billiard and Yves Dauvilliers. Their passion and enduring dedication to idiopathic hypersomnia research gives hope to all those that desperately need appropriate treatments, relevant diagnostic methods and ultimately biomarkers that are specific to their condition.

References:

1. Trotti LM, Staab BA, Rye DB, Test-retest reliability of the multiple sleep latency test innarcolepsy without cataplexy and idiopathic hypersomnia, J Clin Sleep Med 2013;9, pp.789–95.

2. Vernet C, Arnulf I, Idiopathic hypersomnia with and without long sleep time: a controlledseries of 75 patients, Sleep 2009 Jun; 32(6): pp.753-9.

3. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM, Idiopathic hypersomnia: astudy of 77 cases, Sleep 2007, 30, pp. 1274-1281.

4. Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, et al. Correlates of sleep-onsetREM periods during the multiple sleep latency test in community adults, Brain 2006, 129, pp.1609-1623.

5. Singh M, Drake CL, Roth T, The prevalence of multiple sleep-onset REM periods in a population-based sample Sleep 2006, 29, pp. 890-895.

6. Baumann C, Mignot E, Lammers G, Overeem S, Arnulf I, Rye D, Dauvilliers Y, Honda M,Owens J, Plazzi G, Scammell T, Challenges in Diagnosing Narcolepsy without Cataplexy: AConsensus Statement, Sleep 2014 Jun 1; 37(6): pp.1035–1042.

7. Goldbart A, Peppard P, Finn L, Ruoff C, Barnet J, Young T, Mignot E, Narcolepsy andPredictors of Positive MSLTs in the Wisconsin Sleep Cohort, Sleep 2014 Jun 1; 37(6): pp.1043–1051.

8. Mayer G, Lammers G, The MSLT: More Objections than Benefits as a Diagnostic GoldStandard?, Sleep 2014 Jun 1; 37(6): pp.1027–1028.

9. Chervin RD, Aldrich MS, Sleep onset REM periods during multiple sleep latency tests inpatients evaluated for sleep apnea. Am J Respir Crit Care Med. 2000 Feb; 161(2 Pt 1): pp.426-31.

10. Aldrich MS, Chervin RD, Malow BA, Value of the multiple sleep latency test (MSLT) forthe diagnosis of narcolepsy, Sleep 1997 Aug; 20(8): pp.620-9.

11. Aldrich MS, The clinical spectrum of narcolepsy and idiopathic hypersomnia, Neurology1996, 46, pp.393–401.

12. Rye DB, Bliwise DL, Dihenia B, Gurecki P, FAST TRACK: daytime sleepiness inParkinson's disease. J Sleep Res. 2000 Mar; 9(1): pp.63-9.

13. Dauvilliers YA, Laberge L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation, Sleep Med Rev 2012, vol. 16, pp. 539-45.

14. Andlauer O, Moore H, Jouhier L, Drake C, Peppard PE, Han F, Hong SC, Poli F, Plazzi G,O'Hara R, Haffen E, Roth T, Young T, Mignot E, Nocturnal rapid eye movement sleep latencyfor identifying patients with narcolepsy/hypocretin deficiency, JAMA Neurol. 2013 Jul; 70(7):pp.891-902.

15. Moscovitch A, Partinen M, Guilleminault C. The positive diagnosis of narcolepsy andnarcolepsy's borderland. Neurology 1993; 43: pp.55-60.

16. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiplesleep latency test and the maintenance of wakefulness test, Sleep 2005, 28: pp.113–121.

17. Johns MW, Sensitivity and specificity of the multiple sleep latency test (MSLT), themaintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a goldstandard, J Sleep Res. 2000 Mar; 9(1): pp.5-11.

18. Sasai-Sakuma T, Inoue Y. Differences in electroencephalographic findings among categoriesof narcolepsy-spectrum disorders. Sleep Med 2015 doi: 10.1016/j.sleep.2015.01.022.

19. Billiard M, Dauvilliers Y Idiopathic Hypersomnia, Sleep Medicine Reviews 2001, Vol. 5,No. 5, pp 351–360.

20. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, Nevsimalova S, AldrichM, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J,Maki R, Lammers GJ, Bouras C, Kucherlapati R, Nishino S, Mignot E, A mutation in a case ofearly onset narcolepsy and a generalized absence of hypocretin peptides in human narcolepticbrains, Nat Med, 2000 Sep;6(9): pp.991-7.

21. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Shrader H, Nishino S, The role of cerebrospinal fluid hypocretinmeasurement in the diagnosis of narcolepsy and other hypersomnias, Arch Neurol 2002 Oct;59(10): pp.1553-62.

22. Roth B, Spankova opilost a spankova obrna (Sleep drunkenness and sleep paralysis),Ceskoslovenska Neurol 1956,19, pp.48-58

23. Roth B, Narcolepsy and hypersomnia; review and classification of 642 personally observedcases, Schweiz Arch Neurol Neurochir Psychiat 1976, 119, pp.31-41.

24. Roth B, Simek J, Electroencephalographic finding in essential and symptomatic narcolepsy.Neurol Psychiatr Ceskoslov, 1952 Aug;15(3-4): pp.80-109.

25. Roth B, On the dissociation of sleep inhibition, Neurol psychiat, 1954, Ceskoslov. ;17: pp.18–26

26. Roth B, The Influence of Cardiazol and Psychoton on the EEG in narcolepsy, Physiol. 1954, bohemoslov. 3, pp.420-423.

27. Roth B, Tuhacek M, Electroencephalographic findings in organic and so-called functional hypersomnias. Neurol Psychiatr Ceskoslov. 1954 Aug;17(4): pp.235-44.

28. Roth B, Sleep activity in the EEG as a manifestation of the insufficiency of wakefulness andits diagnostic and pathophysiological importance, Psychiat. 1957, pp.163-170.

29. Roth B, 1957 Narkolepsie a Hypersomnie S. Hlediska Fysiologie Spanku (Narcolepsy and hypersomnia from the aspect of physiology of sleep) Praha : Stani Zdravonické Nakladatelstvi

30.Vogel G, Studies in the psychophysiology of dreams III. The dream of narcolepsy, Arch Gen Psychiatry, 3 (1960), pp. 421-425.

31. Dement WC, Rechtschaffen A, Gulevich G, The nature of the narcoleptic sleep attack,Neurology, 16 (1966), pp. 18-33.

32. Berti-Ceroni G, Coccagna G, Gambi D, Lugaresi E, Considerazioni clinico poligrafiche sull narcolessia essenziole a somno lento, Sist Nerv, 19 (1967), pp. 8189.

33. Passouant P, Popoviciu L, Velok G, Baldy-Moulinier M, Etude polygraphique desnarcolepsies au cours du nycthémère, Rev Neurol Paris, 118 (1968), pp. 431-441.

34. Rechtschaffen A, Roth B, Nocturnal sleep of hypersomniacs, Act Nevr Sup Praha, 11 (1969), pp. 229-233.

35. Roth B, Nevsimalova S, Rechtschaffen A, Hypersomnia with "Sleep drunkenness", Arch Gen Psy, 26 (1972), pp. 456-462.

36. Billiard M, Šonka K, Idiopathic Hypersomnia, Sleep Medicine Reviews October 2016, Volume 29, pp.23-33.

37. Bassetti C, M.S. Aldrich MS, Idiopathic hypersomnia. A series of 42 patients, Brain 1997, 120, pp.1423-1435.

38. Billiard M, Merle C, Carlander B, Ondze B, Alvarez D, Besset A, Idiopathic hypersomnia, Psychiatry and Clinical Neurosciences 1998, 52, pp.125-129.

39. Billiard M, Idiopathic hypersomnia, Neurologic Clinics, 1996; 14: pp.573–582.

40. Šonka, K, Interview with Prof. Karel Sonka for the 6th European Narcolepsy Day,Neurologia, 13 March 2015.

41. Hypersomnia Foundation, It's a Fine Line Between Type 2 Narcolepsy and IdiopathicHypersomnia… and it's Getting even Finer, June 23, 2015, review of Sasai-Sakuma T, Inoue Y.Differences in electroencephalographic findings among categories of narcolepsy-spectrumdisorders. Sleep Med 2015 doi: 10.1016/j.sleep.2015.01.022.

42. Trotti, LM, Answers Questions on Diagnostics Relating to Hypersomnia, HypersomniaFoundation, June 20, 2017

43. Šonka K, Susta M, Billiard M, Narcolepsy with and without cataplexy, idiopathichypersomnia with and without long sleep time: a cluster analysis. Sleep Medicine February 2015;16 (2), pp.225–231.

44. Sasai T, Inoue K, Komada Y, Sugiura T, Matsushima E, Comparison of clinicalcharacteristics among narcolepsy with and without cataplexy and idiopathic hypersomniawithout long sleep time. J Clin Sleep Med. 2008; 5: pp.572–578.

45. Ozaki A, Inoue Y, Nakajima T, Hayashida K, Honda M, Komada Y, et al. Health relatedquality of life among drug-naïve patients with narcolepsy with cataplexy, narcolepsy withoutcataplexy, and idiopathic hypersomnia without long sleep time. J Clin Sleep Med. 2008; 4: pp.572–578.

46. Dauvilliers Y, Bassetti CL, Principles and Practice of Sleep Medicine (Sixth Edition) 2017,e.4, c.91 Idiopathic Hypersomnia, pp.883–891.

47. Voderholzer U, Backhaus J, Hornyak M, et al. A 19-h spontaneous sleep period in idiopathiccentral nervous system hypersomnia J Sleep Res, 19 (1998), pp. 219–223.

48. Billiard M, S103 Polysomnographic features of narcolepsy types 1 and 2, and of idiopathic hypersomnia: Strengths and limitations, Clinical Neurophysiology, Volume 128, Issue 9,September 2017, pp. e212.

49. Billiard M, Idiopathic hypersomnia. In: Thorpy M, Billiard M, editors. Sleepiness: causes, consequence, and treatment. NY: Cambridge University Press; 2011. pp. 126– 35.

50. Rye D, 2013 Narcolepsy Network conference, What's in a Name? Understanding the Originsof the Terminologies for the Family of Hypersomnias.

51. Bassetti CL, Dauvilliers Y, Principles and Practice of Sleep Medicine (Fifth Edition) 2011, c.86. pp. 969-979.

52. Mindell JA, Bartle A, Wahab NA, Ahn Y, Ramamurthy MB, Huong HT, Kohyama J, Ruangdaraganon N, Sekartini R, Teng A, Goh DY, Sleep education in medical schoolcurriculum: A glimpse across countries Sleep Medicine, Volume 12, Issue 9, October 2011, pp. 928-931

51. Royal Australasian College of Physicians, 2013 Sleep Medicine Advanced Training Curriculum Adult Medicine Division, pp. 7.

52. Correspondence with Prof D Rye, 9 May 2015 and 3 August 2017

53. Correspondence with Prof Karel Šonka, 17 August 2015 and 7 August 2017

54. Correspondence with Prof Y Dauvilliers, 30 August 2017