An expert view on sleep and multiple sclerosis

It is estimated that 70% of patients with multiple sclerosis complain about fatigue. In addition, more than 50% of MS patients, when asked about the quality of their sleep and sleep-related issues, complain that their sleep is inadequate, that they either have insomnia or that they feel un-rested after night time sleep. Wanting to understand more about fatigue and sleep disorders and their relationship to multiple sclerosis, Consultant Neurologist Mike Boggild, from the Walton Centre in Liverpool put a series of questions to Sleep Expert and Associate Professor of Neurology Michael Thorpy, from the Sleep Wake Disorders Center, Albert Einstein College of Medicine, New York. This article summarises their discussion.

Introduction by Dr Mike Boggild

A significant number of patients with multiple sclerosis report that they are fatigued. Fatigue is an important symptom to consider because it affects patients' social lives, occupations and other activities of daily living. A key question for neurologists is whether or not a fatigued patient may be suffering from an underlying sleep disorder, resulting in excessive sleepiness, and what action should be taken. In the UK we have relatively few neurologists and even fewer who specialise in sleep disorders. In addition, existing sleep services are overrun, so it would be unrealistic to refer every multiple sclerosis patient who complains of fatigue or excessive sleepiness. Wanting to know more about this and how MS specialists can best manage the problem of sleep disorders in multiple sclerosis, I approached US sleep expert, Dr Michael Thorpy. His views were most illuminating on the management options available to help alleviate these complex and troubling symptoms that, in my experience, affect at least two-thirds of patients.

How can fatigue and excessive sleepiness be differentiated?

About 70% of patients with multiple sclerosis complain about general fatigue. In addition, more than 50% of MS patients, when asked about the quality of their sleep and sleep-related issues, complain that their sleep is inadequate, that they either have insomnia or that they feel un-rested after night time sleep. So there seem to be two areas of fatigue; one of which is related, specifically, to sleep disturbance, while the other is related to general tiredness. These two areas are not the same and it is important to recognise this because their management strategies differ. Fatigue is a mental and physical tiredness that is independent of being sleepy. A patient who is sleepy has an increased propensity to fall asleep, and, will, for example, fall asleep quickly if they were put in a darkened room; a patient who is just fatigued will not. If a patient is suffering from excessive sleepiness, the focus is on establishing the issues that are affecting the quality or quantity of night time sleep or on specific neurological abnormalities that are causing an increased sleep predisposition during the day time that disturbs night time sleep. In a fatigued patient, the focus is on the primary disease process. In multiple sclerosis it is the direct consequences of the neurological disturbance associated with the disease, for example, depression, physical weakness and poor physical fitness that causes fatigue.

What factors underlie fatigue and excessive sleepiness?

Studies have shown that multiple sclerosis patients with severe fatigue have decreased cerebral metabolism, cortical metabolism and basal ganglia metabolism compared to multiple sclerosis patients without fatigue. The current thinking is that primary MS fatigue is probably due to some central nervous system disconnection between cortical and deeper structures. Depression also plays a role in MS-related fatigue. The first thing to do is to establish the factors that underlie the fatigue, then treat (pharmacologically or by other means) accordingly. It is also important to recognise that a patient may be using the word, ‘fatigue’, to describe sleepiness; patients do not tend to say ‘I am excessively sleepy’, or ‘I have severe sleepiness’, though this may be what they are suffering from. Instead, patients tend to use vague expressions such as ‘I have a loss of energy’, ‘I can’t concentrate’ or ‘I feel weak’. If a patient uses these sorts of expressions, they should trigger the question in the physician’s mind: Is this fatigue or is the excessive sleepiness symptomatic of a sleep disorder? In order to understand this better, a physician can ask direct questions about nocturnal sleep (amount of nocturnal sleep, quality of nocturnal sleep) and about any tendency for daytime sleepiness. Excessive daytime sleepiness is symptomatic

Trigger words patients use to describe they are sleepy

• ‘I have a loss of energy’
• ‘I can’t concentrate’
• ‘I feel weak’
of a sleep problem which could be due to sleep-wake dysregulation, sleep disruption or a circadian misalignment.

What sort of sleep problems might MS patients suffer from?

In multiple sclerosis patients with sleep disturbance, some patients may have primary insomnia, that is, insomnia unrelated to any psychiatric, medical or other identifiable reason.

In the general population, over 30% of people complain of primary insomnia, so this is likely to be an issue in multiple sclerosis patients, too. But, in addition, there are sleep problems that can occur more commonly in multiple sclerosis and cause disrupted sleep. For example, patients may experience leg-jerking movements, periodically, during night time sleep that affects sleep quality due to frequent arousals. Patients are unaware of these movements, and these are distinct from restless leg syndrome, which affects around 10% of the general adult population. Periodic leg-movements affect around 36% of multiple sclerosis patients and this is a symptom they are unaware of, unlike the feeling of restless legs. Periodic leg-movements occur every 30-40 seconds, particularly in the non-REM stage of sleep. And though patients are unaware of them, bed partners may be, so information from them can be very helpful in deciding if this is a factor contributing to sleepiness. Studies have not shown a greater prevalence of sleep apnoea in the MS population when compared with controls, but sleep apnoea occurs commonly in the general population, so some multiple sclerosis patients may also be affected by this sleep problem. Other unusual sleep disorders have been associated with MS, including REM-like features on multiple sleep latency tests that are similar to narcolepsy. There are some histocompatibility similarities between narcolepsy and multiple sclerosis that raise the issue that some of these patients may, in fact, have some specific, sleep-wake alteration that may predispose them to excessive sleepiness. If somebody with multiple sclerosis is spending a lot of time in bed during the day, there may be a tendency to develop prolonged napping and sleep during the day that takes away from night time sleep. This means it is important to ask about the whole sleep-wake pattern.

Can you explain the sleep/wake process?

Wakefulness and sleep (and the transition from one state to the other) are regulated by neuroanatomical, neurochemical and circadian systems, but no single brain centre is responsible for the whole sleep-wake cycle. Being awake involves two, parallel pathways that activate the cortex: one arises from neurones in the brainstem - the classical reticular activating system (RAS); the other a newly-characterised, neuronal projection from the hypothalamus that incorporates the sleep-wake ‘switch’. The latter involves three distinct hypothalamic structures that play a key role in promoting either sleep or wakefulness: the ventrolateral preoptic area (VLPO - sleep-promoting), the tuberomammillary nucleus (TMN - wake-promoting) and the suprachiasmatic nuclei (SCN - site of the ‘internal clock’ that regulates circadian rhythm).

The sleep-wake ‘flip-flop’ switch

One model of the normal sleep-wake cycle proposes that VLPO and TMN neurones inhibit each other, thus causing oscillations between wakefulness and sleep in a rhythm determined by the internal clock in the SCN. This is elegantly described by Saper et al who discuss the concept of a reciprocal switching circuit - or ‘flip-flop’ switch - which means the brain can be either ‘on’ (calm wakefulness) or ‘off’ (asleep). The two halves of the flip-flop circuit, by each strongly inhibiting the other, create a feedback loop that is bi-stable, meaning there are two possible stable patterns of firing, with a tendency to avoid intermediate states.

The self-reinforcing firing patterns of the flip-flop switch produce a degree of resistance to switching when one side is firing briskly, which confers stability to the system. So, what flips the switch? When major influences come into play, such as circadian sleep drive or an accumulated homeostatic need for sleep, the relative balance of mutual inhibition might gradually shift. When this pressure to change becomes great enough, the same feedback properties that allow the flip-flop circuit to resist change will suddenly yield and rapidly produce a reversal of the firing patterns. The flip-flop switch therefore changes behavioural state infrequently but rapidly, in contrast to the homeostatic and circadian inputs, which change continuously and slowly.

The relatively recent discovery of the neuropeptide, hypocretin (orexin), has thrown further light on how stability of this switch is maintained. It is now thought that hypocretin neurones might act as a ‘finger’, pressing the flip-flop switch into the ‘wakeful’ position, and preventing inappropriate switching into the ‘sleep’ position. It would follow that an unstable switch could lead to insomnia or to unwanted, rapid transitions into sleep during wakefulness, e.g. as seen in narcolepsy.
How should these problems be investigated?

The first thing is to understand the sleep-wake cycle by gleaning information with regard to sleep from a patient diary/sleep log. The next step is to determine, via symptom history, if there is anything to suggest a primary sleep disorder. If the patient has significant daytime sleepiness, and simple adjustments to sleep timing and pattern have been made but the problem still exists, electrophysiological tests are useful to see what is happening to the quality of night time sleep. In addition, a multiple sleep latency test gives objective information on sleep drive throughout the daytime. The Epworth Sleepiness Scale (ESS) is a particularly helpful scale to use with a patient that has an increased physiological drive for sleep. This scale provides useful information about sleepiness and its relation to everyday activities of daily living.

What questions can neurologists ask to elicit a potential sleep disorder?

If a patient answers yes to the questions listed below, this should alert a physician to a potential sleep disorder diagnosis:

- Do you gasp during sleep?
- Do you snore?
- Do you have difficulty falling asleep?
- Do you have difficulty remaining asleep or early morning awakening?
- Do your legs jerk while asleep?
- Do you take frequent daytime naps?
- Do you have breathing difficulties during sleep?
- Do you choke during sleep?
- Do you have difficulties falling asleep?
- Do you have difficulty remaining asleep or early morning awakening?
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Do patients develop tolerance to modafinil?

To date there have been over 200,000,000 patient days experience with modafinil and long-term, placebo-controlled studies in the US have shown that tolerance hasn’t developed over prolonged periods of time when using modafinil in narcolepsy patients. Such data does not yet exist for the MS population.

Key points:

- Fatigue and excessive sleepiness are two symptoms that differ in their clinical manifestation and management
- Patients who are fatigued may not report that they are also experiencing excessive sleepiness
- Many patients with MS may be excessively sleepy due to sleep disruption or an underlying sleep disorder
- Amantadine may be beneficial in treating mild cases of fatigue.

Modafinil 200mg – 400mg is effective in treating excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea-hypopnoea syndrome and moderate to severe chronic shift work sleep disorder.

Brian Simpson – A Case History

Brian Simpson was first diagnosed with multiple sclerosis in 2001 after presenting to his GP with an episode of blurred vision. He had also been experiencing spells of unexplained tiredness which, following the diagnosis of MS, were recognised as being disease-related symptoms. For Brian, such regular periods of fatigue and tiredness were a particular concern since his physically demanding job as a fireman required him to be alert and awake. He was well aware that suffering an episode of excessive sleepiness at work could endanger him and others’ safety and so he approached his GP to ask about possible treatment options.

Brian had previously been treated with amantadine, an established drug mainly used for the treatment of Parkinson’s disease, but which has some effect on MS fatigue. He tried the drug for several days, but experienced a variety of side effects and his neurologist offered him Modafinil as an alternative.

Brian was treated with Modafinil, 200 mg, to be taken first thing in the morning, and immediately began to feel the benefits. His energy levels whilst at work remained steady and continued to do so during the evenings at home with his family. Moreover, he suffered no major side effects.

As a result, he has continued with the treatment now for 12 months and remains enthusiastic about its effects. “Being on Modafinil allows me to play football on a Sunday in the park with my kids and it allows me, at work, to push myself further than maybe I would have done.” Treating his daytime excessive sleepiness with Modafinil has allowed Brian to be active, live a normal life and gain back some control over the disease.

(Patient’s name has been changed)