MedSleep

# Sleep Matters®

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The official newsletter of MedSleep

## About MedSleep

MedSleep's network of clinics are committed to providing the highest quality sleep medicine services across Canada.

MedSleep is dedicated to improving health and promoting wellness by providing a comprehensive and patient-centered approach to the diagnosis and treatment of sleep disorders.

We strive to be pioneers in sleep medicine utilizing the latest in technology, promoting education, and participating in clinical research and the advancement of new treatments.

MedSleep clinics provide clinical consultation, diagnostic services (sleep testing) and treatment for the full spectrum of sleep disorders.

### DID YOU KNOW?

Our referral forms are now available electronically as fillable pdfs.

Contact us at: info@medsleep.com

# Novel research suggests an autoimmune basis of narcolepsy

**NARCOLEPSY IS A NEUROLOGICAL** disorder caused by the brain's inability to regulate sleep-wake cycles normally. The main features of narcolepsy are fatigue and cataplexy. The disease is also often associated with sudden sleep attacks, insomnia, dream-like hallucinations, and a condition called sleep paralysis. Its prevalence in the developed world is approximately the same as that of multiple sclerosis or Parkinson's disease. However, with increased public education about narcolepsy and physician training in the diagnosis and treatment of sleep disorders, these figures are expected to rise.

### Research discoveries at Stanford

Professor Emmanuel Mignot has studied the disease for 20 years at Stanford University School of Medicine. His research has shown how narcolepsy develops in genetically predisposed individuals. Hypocretin (also called orexin) is a neurotransmitter that regulates arousal, wakefulness and appetite.

Dr. Mignot's work has shown that T cells recognizing the protein of H1N1 virus (haemagglutinin) may develop a cross-reaction with hypocretin, thus destroying neurons producing this protein, and causing disorders of arousal.

Subsequent research confirmed that short fragments of haemagglutinin, consisting of 13 amino acids, are very similar to 2 equally short fragments of hypocretin. It causes T cells to respond immunologically against host protein, consequently leading to the development of narcolepsy. H1N1 virus is apparently not the only one which can cause this type of cross reaction with hypocretin, and may also occur in response to other pathogens.

The connection between H1N1 infection and narcolepsy was also confirmed by results of the research conducted at Beijing University People's Hospital. They showed that H1N1 outbreaks were correlated with increased narcolepsy morbidity about 6 months after the infection.

### MedSleep collaborating with Stanford

MedSleep has now entered into a collaborative research project with Dr. Mignot's group at Stanford. This study will contribute to the development of a patient registry for sleep disorders (including narcolepsy) and should reveal the genes and/or blood markers responsible for different sleep disorders. If one or more unique genes or blood markers could be identified, physicians would have a simple, minimally invasive test for aiding diagnosis of narcolepsy, and perhaps other disorders. ❖

## What's Inside?

**THE MULTIPLE HYPOTHESES** proposed to explain the function of sleep reflect our incomplete understanding. It is likely that sleep evolved to fulfill some sort of primitive function and has taken on multiple functions over time. Animals are most vulnerable when they are asleep. Evolution moves to minimize vulnerability. This would argue that sleep remains an essential physiologic process across all species.

Various interesting theories have been proposed regarding the function of sleep:

## Growth & Restoration

Anabolic activities are augmented during sleep. This facilitates somatic growth and development in children, and tissue repair and restoration in adults. There is also a bidirectional interaction between sleep and immune function, whereby sleep loss impairs immune function and immune challenge increases total sleep.

## Ontogenesis

REM sleep appears to be important for development of the brain. REM sleep occupies the majority of time of infant sleep, approximately 8 to 9 hours/day.


Among different species, the more immature the newborn, the more time it spends in REM sleep. The massive brain stimulation that occurs during REM-sleep appears to be essential to complete brain development after birth.

## Memory Processing

Many studies suggest that there is a correlation between sleep and the complex functions of memory. Harvard sleep researchers have proposed that an essential part of memory and learning consists of nerve cell dendrites sending information to the cell body to be organized into new neuronal connections. This process demands that no external information be presented to these dendrites, so that the "disconnect" of sleep becomes essential in order for memories and knowledge to be solidified and organized.

## Waste Clearance (the latest theory!)

A publication by L. Xie and colleagues in 2013 [1] explored the efficiency of the glymphatic system during sleep and provided the first direct evidence that the clearance of interstitial waste products increases during this resting state. They demonstrated that the changes in efficiency of CSF–ISF (interstitial fluid) exchange between the awake and sleeping brain were caused by expansion and contraction of the extracellular space, which increased by ~60% in the sleeping brain to promote clearance of interstitial wastes such as amyloid beta. They have hypothesized that the restorative properties of sleep may be partially linked to increased glymphatic clearance of metabolic waste products produced by neural activity in the awake brain. ❖

[1] Lulu Xie, et al. "Sleep drives metabolic clearance from the adult brain." *Science* 342 (6156): 373–377, 2013.

# What's new for the treatment of insomnia

The most recent addition to sleep-specific medications is **Silenor** (Doxepin 3 mg and 6 mg), which has been recently approved by Health Canada.

Silenor is a very potent antihistamine. Histamine is an excitatory neurotransmitter in the central nervous system, and the histamine blocking properties of Silenor are thought to be the reason for the sedative-hypnotic effect.

Recent clinical trials have shown clinical efficacy at doses of 3 and 6 mg for the management of insomnia (especially sleep maintenance insomnia). Doses greater than 6 mg are not indicated.

Silenor appears to have several advantages over other traditional sedative-hypnotic medications:

- Novel mechanism of action for sleep maintenance, mainly through potent antagonism of H1 receptors;
- No binding at the GABA-benzodiazepine receptor;
- Immediate and sustained efficacy over 3 months, without the development of tolerance;
- Good safety and tolerability profile; and
- No potential for physical dependence or withdrawal symptoms.

# Strategies for improving CPAP compliance

**CPAP IS THE FIRST-LINE TREATMENT** in obstructive sleep apnea. However, as in all chronic treatments, there is always the issue of noncompliance. Most patients perceive CPAP as somewhat uncomfortable and inconvenient. Furthermore, CPAP can cause unpleasant side effects derived from the mask interface, device noise (although much less with recent technical improvements), mucosal dryness, aerophagia, claustrophobia, etc. Thus noncompliance can be dependent on several different factors, all of which must be taken into account. Accordingly, the situation could be improved by increasing patients' awareness of the benefits of the treatment, and by establishing compliance targets that can easily be attained. Otherwise, the above mentioned drawbacks exert a negative influence, leading to abandonment of the treatment by approximately 23% of patients, mostly in the first year.

Although the effectiveness of the device depends on its regular use, there is some controversy over the minimum usage time needed to consider a patient as compliant and the treatment as beneficial. Some studies have found that approximately 4 hours of use per night creates a residual benefit in many domains. Generally, most studies have considered good adherence as use of the device for a minimum of 4 hours per night for 70% of the nights.

A recent review of the literature analyzed the factors influencing compliance with some interesting findings (Ward K, Hoare KJ, Gott M. "CPAP for OSA from the users' perspective? A systematic integrative literature review. "*Sleep Med Rev*. 2014 Aug;18(4):357-66). Most notable was the lack of association between apnea severity and compliance (or subjective response). By contrast, cognitive behavioral factors such as the patient's belief in their ability to complete tasks and reach goals, as well as outcome expectations, exert a great influence on compliance. Social support (especially from partners), and technical factors related to the device have the most significant effect on compliance. It is, therefore, important to encourage compliance through educational and cognitive behavioral techniques, with a special focus on the initial period of therapy. If a patient adapts and avoids abandonment in the early stages, then compliance is most often sustained.

## 10 ways to improve compliance

### 1 EARLY AND ONGOING ENCOURAGEMENT

Often the first suspicion of a sleep disorder arises from an office visit with the family doctor. Encouragement is needed from both the family physician and the spouse/partner/family member. Knowledgeable family doctors can help create a good "first impression" of CPAP. The patient and the spouse/partner need to be made aware of the health benefits of CPAP.

### 2 INITIATION OF CPAP THERAPY

A simple but comprehensive explanation of CPAP should be provided by the sleep physician when the patient is seen after the diagnostic sleep study. The patient is then referred to a reputable home-care company. Respiratory technologists (RTs) employed by those companies will again explain in detail what CPAP therapy entails, and which equipment is best suited. The home-care company is a very important educational partner. They troubleshoot any problems and provide continued encouragement. If a particular interface is not working well, they will try another design.

### 3 RAPID INDIVIDUAL FOLLOW-UP

Since the first few weeks of therapy tend to set the pattern of use, follow-up within the first month of CPAP therapy is essential. The home-care companies involved with the CPAP setup should also be included in follow-up. The first impression sets the stage for months and years to come. Correcting problems up front is critical.

### 4 MONITORING COMPLIANCE AND EFFICACY

Compliance should be checked somewhere between 3 and 6 months after the initial CPAP setup. Software now available in most CPAP devices allows for data download which provides accurate compliance data. The higher quality home care companies will track and provide download reports. Efficacy data is also available. Clinical follow-up to discuss the download data, and review any other issues affecting compliance with the patient continues to be essential.

### 5 LONG-TERM SUPPORT AND TROUBLE-SHOOTING

Many of the same activities from #4 also apply here. An annual office visit should be scheduled to check all the equipment and the hours/usage. Masks wear out and break, so an annual replacement should be in the plan. Changes in the patient's condition may warrant a change in CPAP pressure (i.e., weight loss may allow for a lower CPAP setting or vice-versa).

### 6 MASK FIT AND CHOICE OF INTERFACE

The fit and comfort of the CPAP mask is far more important than the type of CPAP device that the patient chooses. For example, patients with claustrophobia may tolerate nasal pillows or nasal prongs better than the nasal mask.

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## CPAP Compliance

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Pillows or prongs are also beneficial to interface with someone who has a mustache or is missing dental support needed for a nasal mask. Head straps should not be too tight and should not cause discomfort. An oronasal mask, or so-called full face mask, covers the nose and mouth, and may be a better choice for patients with nasal congestion or a persistent mouth leak.

### 7 NASAL CONGESTION, STEROIDS/ANTIHISTAMINES

Not being able to breathe easily through the nose creates a major barrier for compliance and adherence. For someone with congestion or sinusitis, nasal sprays with corticosteroids and antihistamines are essential. A full ENT assessment may be indicated for patients with ongoing upper airway congestion.

### 8 HUMIDIFICATION

Drying of the mouth and nose is a frequent complaint of CPAP users. Studies have examined heated humidification versus cold humidification and found that heated systems have better results. Patients generally have fewer complaints when using humidification.

### 9 CHOOSING THE RIGHT DEVICE

Continuous positive airway pressure (CPAP) was the initial standard for PAP therapy. Bilevel PAP therapy was then introduced and opened more options, allowing clinicians to set the baseline expiratory pressure and the peak inspiratory pressure. Next to be introduced was AutoCPAP, where the CPAP unit titrates the pressure up or down as needed to keep the upper airway open at the lowest effective pressure. This is ideal with positional apnea or apnea that is related to a specific sleep stage. Most CPAP units now come with a pressure-relief option, which provides a modest reduction in pressure at the very end of inspiration and beginning of expiration so patients do not have to breathe against the prescribed therapeutic pressure immediately (think of it as "BiPAP-lite"). Before the end of expiration, the pressure is restored to its therapeutic level to keep the airway open at the beginning of the next inspiration.

### 10 ON-LINE GROUP SUPPORT

Support groups have influence in many areas: sharing tips on how to cope with using CPAP. Support groups tend to increase the number of hours for CPAP use and can help encourage patients wanting to give up due to side effects or problems (http://www.apneasupport.org). ❖

## Canadian Sleep Statistics

We know how important it is to get a good night of sleep. Quantifying a "good night's sleep" is tricky because it is so variable and subjective. Most adults need somewhere between 7 and 9 hours of sleep every night to feel refreshed, underscoring the variability in what "enough" sleep means.

Comparing groups of people in different job and family situations can help to identify influences, apart from our bodies' physiology, that affects sleep.

Statistics Canada looked at how work, family characteristics and time stress affect sleep times of Canadians aged 15 and over. Gender differences were also examined. This article is based on data collected by Statistics Canada's 2010 *General Social Survey* (GSS).

According to the 2010 GSS, Canadians spent an average of 8 hours 18 minutes per day sleeping, but rates of sleep vary according to age. Among Canadians aged 15 and older, 15-24 year olds reported the most amount of daily sleep (8h 59 min), whereas the 35-44 age group reported the least (7h 57 min).

The sleep rates of senior age groups return close to those reported by younger Canadians: 8h 25 min among 65-74 year olds, and an additional 20 minutes for those 75 and older.


The lower levels of sleep reported by middle-aged Canadians can be explained partly by the "time stress" experienced by many people balancing family and work roles. In a previous GSS study, women and men with high levels of time stress reported getting 25 and 35 minutes less sleep (respectively) than those with low time stress.

Parenting can be costly to our "sleep hygiene." Survey respondents with children under the age of 15 at home slept an average of 17 minutes less than their childless counterparts, and those with two children slept 25 minutes less – echoing the results of similar U.S. studies.

Work also comes with a significant sleep-time cost. Canadians who work full-time report sleeping an average 24 minutes less per day than those not in the labour force. ❖

# Update on the management of Restless Legs Syndrome

**RESTLESS LEGS SYNDROME** (RLS) is a sensorimotor disorder characterized by an irresistible urge to move the lower limbs and, in some cases, the upper limbs. This urge is usually accompanied by sensory disturbances ranging from uncomfortable sensations to pain in the affected areas. Symptoms most often begin during inactivity, and can be somewhat relieved by movement. RLS follows a circadian pattern with symptoms most intense towards the evening and into the nighttime hours. RLS symptoms can range from relatively mild to severe, and from intermittent to intense daily distress. Severe RLS may have profoundly disruptive effects on sleep quality and daytime functioning.

Diagnostically, RLS is considered either primary, often occurring within families, or secondary, developing in association with other medical conditions (such as iron deficiency anemia, pregnancy, or end-stage renal disease).

## Prevalence and Etiology

RLS affects 5-10% of adults in North America. About one third of those with RLS symptoms are bothered sufficiently enough to seek medical attention. Women seem more susceptible to RLS than men, especially in relation to menstruation, pregnancy and menopause. RLS is more common in older adults although it can occur as early as the pre-school years. RLS is believed to be a central nervous system (CNS) disorder. RLS seems to run in families, consistent with a genetic origin in primary RLS. The exact cause of the disorder remains a mystery. One major theory is that a deficiency in brain iron, particularly within dopamine-containing neurons, may predispose to RLS. Brain iron deficiency may lead to a dysfunction of the dopamine pathways, giving rise to symptoms of RLS. As far as we know, RLS is neither a structural nor a neurodegenerative disorder, and most RLS patients have no neurologic comorbidities. Despite their definite response to dopaminergic medications, RLS and Parkinson's disease (PD) seem to have very different underlying etiologies, and one does not predispose to the other.

## Presentation

The description of the uncomfortable sensations is quite variable. The key element is the urge or need to move, though some patients will emphasize specific sensory symptoms.

Typical descriptors:

- "crazy legs."
- "It feels like a deep itch that I can't scratch."
- "painful."
- "burning… aching."
- "It feels like I have a toothache in my leg."
- "I have the heebie-jeebies in my legs."
- "My legs feel creepy, crawly."
- "It feels like I have worms crawling in my legs."
- "It feels like electricity in my legs."

RLS patients are often unable to ride comfortably as a passenger in a car or airplane, or attend the theater. If they do, they will most often choose isle seats in case they have to walk around for relief. They can have difficulty initiating and maintaining sleep, and they often suffer from fatigue, poor concentration, or a low mood during the day.

## RLS Primary Diagnostic Criteria

All four primary diagnostic criteria must be present in order to support a diagnosis of RLS:

1. An urge to move the lower limbs, with or without an uncomfortable sensory component. Sometimes the upper limbs are also involved.
2. Onset or exacerbation of the motor and sensory symptoms most often begin or worsen during periods of inactivity, particularly when lying down or sitting.
3. There is relief with movement. RLS symptoms are partially or totally relieved by movements such as walking or stretching; symptoms are relieved for at least as long as the activity continues. Mental activation also reduces symptoms.
4. There is a circadian pattern. RLS symptoms usually occur or worsen in the evening or at bedtime. Symptoms usually resolve by the morning.

An overnight sleep study is still considered to be the definitive test for the diagnosis of RLS. The sleep study will most often show significant periodic leg movements during sleep and pathognomonic motor restlessness before sleep and during waking intervals.

## Management

Certain medications may aggravate symptoms. These medications include anti-nausea drugs (prochlorperazine or metoclopramide), antipsychotic drugs (haloperidol or phenothiazine derivatives), antidepressants that increase serotonin, and some cold and allergy medications that contain sedating antihistamines. Iron studies (especially serum ferritin) need to be done because of the frequent association of RLS with iron deficiency (ferritin is the best measure of iron stores); CBC, $B_{12}$, folate, BUN, creatinine, and TSH screen are also recommended, as kidney disease, anemia, and hypothyroidism can all contribute to secondary RLS.

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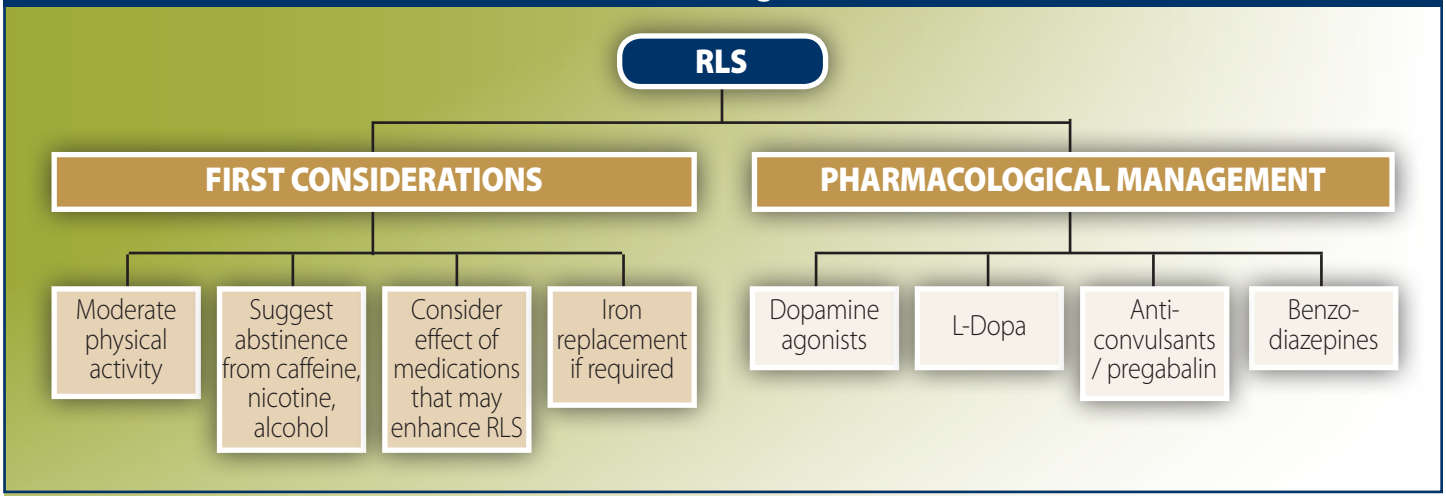
## Treatment algorithm

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When low normal (ferritin <50 µg/L) or abnormal (ferritin <30 µg/L) iron stores are suggested, iron repletion (e.g., ferrous gluconate) is indicated. Low iron stores are often associated with more severe RLS symptoms.

**Dopaminergic agents** Although usually used to treat Parkinson's disease, these medications have been shown to reduce symptoms of RLS and periodic leg movements during sleep when they are taken 2 hours before bedtime, and are considered a first line treatment. Requip (ropinirole) 0.25-0.75 mg and Mirapex (pramipexole) 0.25-0.75 mg are approved for the treatment of moderate to severe RLS. Both drugs are generally well tolerated. Good short-term results are typically seen with Sinemet (levodopa/carbidopa) 100/25 mg for managing intermittent RLS. A newer NEUPRO (rotigotine) 1-3mg/24hr has been recently approved in Canada. It is the first and only non-ergolinic dopamine agonist available as a transdermal patch. The efficacy has been well established, and this route of administration reduces the risk of augmentation (see below) noted with other oral dopaminergic agents.

Long-term use of these medications can lead to worsening of the symptoms in some individuals, where restlessness begins earlier in the day. This apparent progressive worsening is referred to as "augmentation." Fortunately, augmentation is reversible by removing the person from all dopamine-related medications. Another rare but important adverse effect that occurs is the development of impulsive or obsessive behaviors such as obsessive gambling or shopping. These behaviors can be reversed by stopping the medication.

**Benzodiazepines** These medications can help patients with a greater degree of sleep fragmentation, and, in some cases, may be required in addition to the dopaminergic symptoms. Clonazepam 0.5 mg is generally the first choice within this class of medications.

**Anticonvulsants** Gabapentin (Neurontin) and pregabalin (Lyrica) have been shown to be very effective in decreasing the sensory disturbances such as creeping and crawling sensations and nerve pain.

**Opioids** Codeine, propoxyphene, or oxycodone may be prescribed at night to diminish pain and help to relax individuals with more severe symptoms. These medications should only be considered as a last resort due to the high risk of dependency. ❖

# What is CBT insomnia treatment?

**COGNITIVE BEHAVIOURAL TREATMENT** addresses maladaptive behaviours and dysfunctional thoughts that contribute to chronic insomnia. This treatment is particularly helpful in individuals who have developed a conditioned or psychophysiological insomnia.

Typically for these individuals, sleep has become a central concern with intense fear surrounding the consequences of not being able to sleep. As a result of this fear of not being able to sleep, patients enter the sleep environment already in a heightened state of physiological arousal and are quick to jump to anxiogenic thoughts – *i.e.,* "If I don't sleep tonight, I am going to be completely dysfunctional tomorrow!".

In addition, in an attempt to ensure a better sleep, they might go to bed earlier than usual despite not being sleepy, or take afternoon or evening naps. These catastrophic thoughts and compensatory sleep behaviour unfortunately results in a worsening of the insomnia *(see figure below)*.

CBT is a structured therapy that can be provided on an individual or group basis. It typically involves 5 or 6 sessions and is presented in an educational format.

Patients are instructed about normal sleep physiology, including homesostatic and circadian factors that promote healthy sleep. With this background, they are taught several behavioural techniques *(i.e.,* bed restriction, stimulus control therapy, relaxation training) to optimize these factors and avoid compensatory strategies that will aggravate their insomnia. In addition to learning behavioural techniques, they are taught how to constructively challenge the dysfunctional thinking that intensifies their nocturnal anxiety.

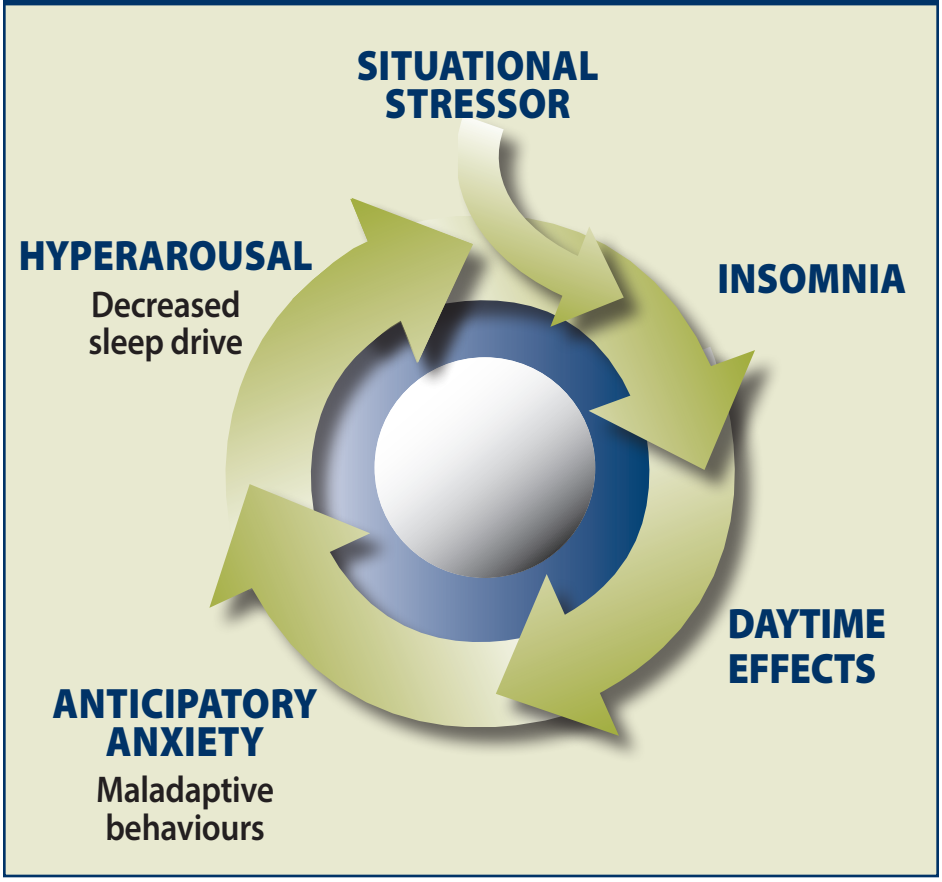
For example, a common scenario involves the tendency to catastrophize the impact of a bad night's sleep. Patients are gently challenged to examine whether in fact they have ever had satisfactory, productive days after a poor night of sleep.

Although short-term sleep restriction is unpleasant, it is usually time limited if one maintains optimal sleep scheduling, and it is not necessarily associated with catastrophic outcomes. As patients become increasingly aware of this, they are more readily able to manage their sleep anxiety and return to normal sleep patterns.

Patients are often surprised with the simplicity of the CBT strategies. However as with changing any behaviours, they often require the support, structure, and continuity provided by the program to sustain this new approach, especially during the initial phases of treatment when the insomnia can actually temporally worsen.

CBT for chronic insomnia has been well studied with several randomized, controlled trials showing a similar efficacy to hypnotic medications but with a more sustained effect. Current research is addressing optimal strategies to combine CBT with hypnotic medications. ❖

## THE CYCLE OF CHRONIC INSOMNIA



# MedSleep

**dedicated to achieving excellence in both the diagnosis and treatment of the full spectrum of sleep disorders, providing comprehensive evaluation and integrative treatment**

## ALBERTA

### MedSleep Calgary
Office phone: 403-254-6400
Office fax: 403-254-6403
Email: calgary@medsleep.com

#### Crowfoot
340-600 Crowfoot Cres NW
Calgary AB T3G 0B4

#### Evergreen
4101-230 Eversyde Blvd SW • Room 4
Calgary AB T2Y 0J4

#### Thorncliffe
14-5440 4 St NW
Calgary AB T2K 1A8

#### Chinook
203-5809 MacLeod Trail SW
Calgary AB T2H 0J9

### Northern Alberta Sleep Clinic
Office phone: 780-487-5333
Office fax: 780-487-3045
Email: edmonton@medsleep.com

#### Edmonton West
302-8702 Meadowlark Rd
Edmonton AB T5R 5W5

#### Edmonton South
106-2951 Ellwood Dr SW
Edmonton AB T6X 0B1

## BRITISH COLUMBIA

### MedSleep Burnaby
250-7155 Kingsway
Burnaby BC V5E 2V1
Office Phone: 778-379-3844
Office Fax: 778-379-4811
Email: vancouver@medsleep.com

### MedSleep Campbell River
Location TBA
Office Phone: 1-877-855-7431
Office Fax: 1-844-652-7386
Email: campbellriver@medsleep.com

### MedSleep Cowichan
160 Jubilee St
Duncan BC V9L 1W7
Office Phone: 250-597-7832
Office Fax: 250-597-8114
Email: cowichan@medsleep.com

### MedSleep Maple Ridge
110-20528 Lougheed Hwy
Maple Ridge BC V2X 2P8
Office Phone: 778-379-3844
Office Fax: 778-379-4811
Email: vancouver@medsleep.com

## BRITISH COLUMBIA *(continued)*

### Nanaimo Sleep Clinic
130-2124 Bowen Rd
Nanaimo BC V9S 1H7
Office Phone: 250-758-0060
Office Fax: 250-758-0063
Email: nanaimo@medsleep.com

### MedSleep Nelson
Location TBA
Office phone: 250-596-1870
Office fax: 250-596-1875
Email: nelson@medsleep.com

### MedSleep North Vancouver
901 3rd St W
North Vancouver BC V7P 3P9
Office phone: 778-379-3844
Office fax: 778-379-4811
Email: vancouver@medsleep.com

### MedSleep Penticton
140-1636 Main St
Penticton BC V2A 5G8
Office Phone: 236-422-3022
Office Fax: 236-422-3023
Email: penticton@medsleep.com

### MedSleep Prince George
226-100 Tabor Blvd
Prince George BC V2M 5T4
Office phone: 250-596-1870
Office fax: 250-596-1875
Email: princegeorge@medsleep.com

### MedSleep Vancouver
506-1755 West Broadway
Vancouver BC V6J 4S5
Office phone: 778-379-3844
Office fax: 778-379-4811
Email: vancouver@medsleep.com

### MedSleep Victoria / Langford
125-735 Goldstream Ave
Langford BC V9B 2X4
Office phone: 778-265-3383
Office fax: 250-391-8400
Email: victoria@medsleep.com

## NEW BRUNSWICK

### Moncton Sleep Institute
175-1273 Main St
Moncton NB E1C 0P4
Email: moncton@medsleep.com
Office phone: 506-383-5101
Office fax: 506-382-5162

## NOVA SCOTIA

### Medsleep Atlantic
114-250 Baker Dr
Dartmouth NS B2W 6L4
Office phone: 902-865-9698
Office fax: 902-407-4341
Email: halifax@medsleep.com

## ONTARIO

### Brampton Sleep Clinic
216-40 Finchgate Blvd
Brampton ON L6T 3J1
Office Phone: 905-456-3699
Office Fax: 905-456-8768
Email: brampton@medsleep.com

### Limestone City Sleep Lab
110-920 Princess St
Kingston ON K7L 1H1
Office phone: 613-547-9172
Office fax: 613-547-9910
Email: kingston@medsleep.com

### MedSleep Milton
205-611 Holly Ave
Milton ON L9T 0K4
Office phone: 905-636-9772
Office fax: 905-203-2882
Email: milton@medsleep.com

### MedSleep Pembroke
715 Mackay St
Pembroke Regional Hospital, Tower D
Pembroke ON K8A 1G8
Office phone: 613-735-2358
Office fax: 613-735-9301
Email: pembroke@medsleep.com

### Niagara Snoring & Sleep Centre
Niagara Falls Medical Centre
204-6453 Morrison St
Niagara Falls ON L2E 7H1
Office phone: 905-374-6453
Office fax: 1-888-905-6992
Email: niagara@medsleep.com

### Toronto - Etobicoke (Queensway)
### Queensway Sleep Lab
202-5359 Dundas St W
Etobicoke ON M9B 1B1
Office phone: 416-622-3266
Office fax: 416-622-7831
Email: queensway@medsleep.com

### Toronto - Eglinton (Midtown)
### Toronto Sleep Institute
507-586 Eglinton Ave E
Toronto ON M4P 1P2
Office phone: 416-488-6980
Office fax: 416-488-3998
Email: eglinton@medsleep.com

### Toronto - Thornhill
### Toronto Sleep Institute
208-390 Steeles Ave W
Thornhill ON L4J 6X2
Office phone: 905-709-9696
Office fax: 905-709-9764
Email: thornhill@medsleep.com

**info@medsleep.com • www.medsleep.com • 1-877-544-1418**
**Referral available in all major EMRs • For location & maps visit website or call us toll-free**