torontosleepinstitute

Sleep Matters™

The official newsletter of the Toronto Sleep Institute • Volume 2 – Edition 1

Medical Team

MESSAGE FROM THE MEDICAL DIRECTOR

New Location

On behalf of all the staff at Toronto Sleep Institute, I am pleased to announce that we have opened a new location in Thornhill.

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Changing Views on Insomnia

FOR OVER 20 YEARS, the teaching surrounding insomnia has emphasized that insomnia is a symptom and not a primary disorder. As such, treatment was directed at addressing the underlying disorder(s) with the anticipation that the insomnia symptom would resolve. In addition, it was advised that hypnotics should only be used for the short term, until the primary treatment of these underlying disorders became effective.

Insomina as a primary disorder

Although, it remains the case that medical disorders (especially pain disorders, respiratory disorders and impaired mobility) and psychiatric illness often contribute to insomnia, more recently following a 2005 NIH consensus conference, there are recommendations to reconsider insomnia as a primary disorder. This argument is based on more recent data demonstrating a unique set of physiological changes associated with insomnia. Furthermore, the insomnia syndrome is being reconceptualized as a disorder of "physiological hyper-arousal *across 24 hours*" and not confined to the sleep period.

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Finding suggestive of physiological hyperarousal are:

- increased metabolic rate,
- increased body temperature,
- increased heart rate,
- increased catecholamines, and
- increased PET brain perfusion.

Although patients with insomnia complain of daytime fatigue, daytime testing (multiple sleep latency test) paradoxically demonstrates increased levels of daytime alertness, consistent with a "24-hour hyper-arousal disturbance".

In addition, more and more studies suggest that insomnia has an independent impact on quality of life and function, suggesting that insomnia might be viewed as interacting with medical disorders rather than just a symptom. For example, it has been demonstrated that pain sensitivity increased with insomnia. In addition, recent evidence (Fava et al. *Biol Psychiatry* 2006) demonstrated that the improvement in mood disorders with antidepressant treatment does not necessarily correlate with improvement in sleep and the addition of a hypnotic agent to target co-morbid insomnia improves the anti-depressant response.

With these theoretical developments there is increasing consensus that chronic insomnia:

1) exists as a primary disorder,
2) is associated with significant impairment in function and quality of life, and
3) merits long-term treatment.

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Changing Views on Insomnia

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Novel Pharmacological Treatment

Traditional pharmacological treatment have utilized the benzodiazepines which have demonstrated efficacy but with concerns related to side effects including: somnolence, ataxia, amnesia, discontinuation effects (rebound insomnia and withdrawal syndromes) and dependence liability.

Subsequently there has been interest in non-benzodiazepine hypnotics which bind more selectively at the benzodiazepine-GABA receptor complex (zopiclone, zaleplon and zolpidem) and are thought to have less side effects and abuse/dependence potential.

Most recently though, there are multiple clinical trials evaluating novel hypnotic agents whose efficacy is thought to relate to different neurotransmitter systems including melatonin, substance P, calcium channel blockers and serotonin. It is expected that there will be several new compounds coming to market over the next several years.

Cognitive Behavioral Treatment

There have been increasing studies and consensus guidelines demonstrating efficacy comparable to hypnotic medications using Cognitive Behavioral Treatment which provides an excellent option for motivated individuals who prefer a non-pharmacological treatment. This treatment modality is offered individually or in groups for 6-8 sessions and addresses maladaptive behaviors and dysfunctional thoughts that perpetuate hyperarousal and insomnia.

Current research is addressing the utility of focused CBT components that might reduce the necessary number of sessions which are typically 6-8. There is also an interest in evaluating protocols that combine both CBT and pharmacotherapy.

Insomnia Medications

Introduction

A **WIDE VARIETY** of medications have the capacity to depress the functioning of the central nervous system. Those marketed for use specifically as sleep-aids are those that bind at and influence the γ-aminobutyric acid (GABA)-barbiturate-bendodiazepine receptor complex (*see figure 1*).

Chloral hydrate was the most popular sleep-inducing agent in the year 1900! It is perhaps the oldest example of a drug in this class that is still in common use today. With most of the older drugs, reduction in CNS activity is progressive and dose-dependant. This begins with simple sedation at low dose, through surgical anesthesia, culminating with fatal depression of cardio-respiratory regulation at higher doses. Specific binding of these older substances occurs primarily at the barbiturate receptor portion of the GABA receptor complex.

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Benzodiazepines:

The benzodiazepines (BDZs), and newer analogues, *cannot* induce a state of surgical anesthesia when used alone and are therefore much safer than the previously used barbiturates.

The problems associated with these medications are primarily related to *undesirable side-effects, psychological dependence and physical dependence*. These medications bind at the BDZ receptor portion of the GABA receptor complex (the $GABA_A$ receptor). Non-specific binding at the $GABA_A$ receptor does increase the tendency for unwanted side-effects, but problems encountered with these medications are more often related to inappropriate prescribing patterns, rather than the pharmacologic properties of the drug.

The effect of most benzodiazepines (BDZs) is mediated through non-specific binding at the GABA macromolecular receptor complex at the $GABA_A$ receptor (also termed the benzodiazepine receptor). With non-specific binding, the therapeutic vs side-effect profile of the drug is determined by the *phamacokinetic* properties (absorption, distribution, elimination) and the *pharmacodynamic* properties (receptor specificity, receptor affinity). BDZs that are rapidly absorbed have the benefit of a rapid onset of action. BDZs that are rapidly eliminated usually have a shorter duration of action. This can be associated with a higher dependence potential and withdrawal effects, but not always. If the BDZ has a high receptor affinity (eg, lorazepam), it binds tightly to the receptor, and is associated with increased side-effects upon discontinuation. If a *high receptor affinity* is combined with a *rapid elimination half-life*, the potential for withdrawal effects is greatly enhanced. This is the case with a medication such as triazolam.

The longer acting agents (eg. Nitrazepam) are more often associated with daytime sedation and/or confusion in the elderly.

Non-Benzodiazepine Hypnotics

Non-benzodiazepines (NBDZs) have a different chemical structure, but still bind at the BDZ receptor (the $GABA_A$ receptor). Zaleplon (Starnoc), Zolpidem (Ambien – USA only), and zopiclone (Imovane) are the three NBDZs currently available world-wide.

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Insomnia Medications

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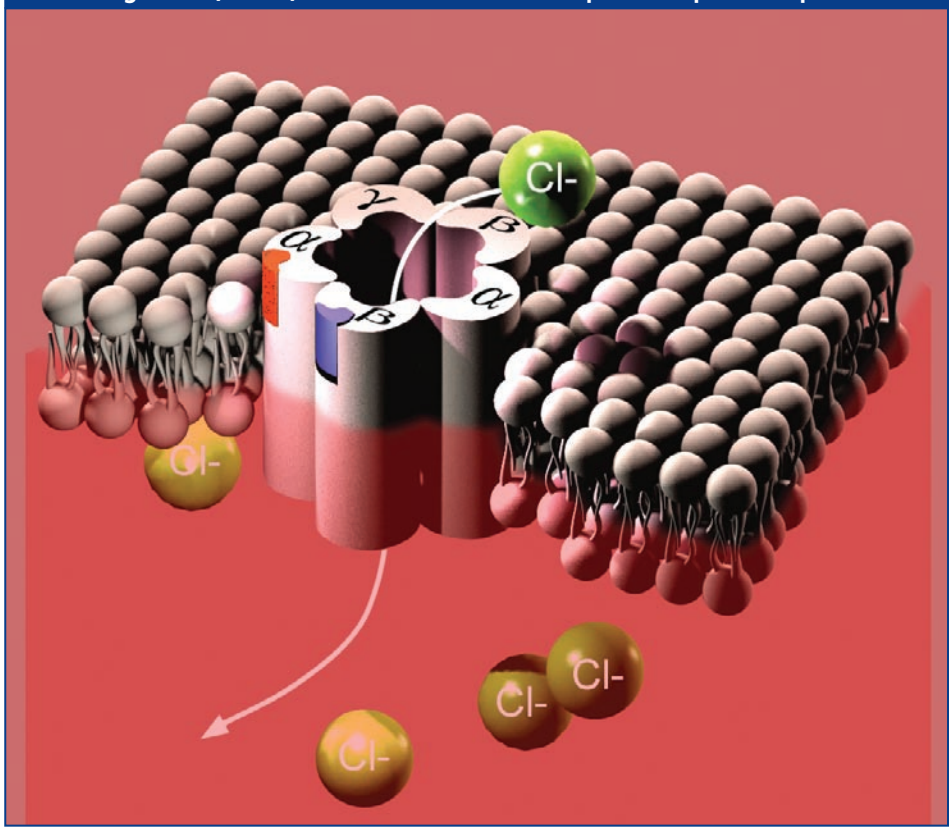
Zaleplon was discontinued in Canada last year, but this was due to economic factors rather than safety or efficacy. Attempts have been made to bring Ambien to Canada, but again economics (and politics) keep this superior sleep medication from coming to market in this country. Zopiclone (Imovane) remains as the safest and most efficacious medication specifically indicated to sleep induction.

Other commonly used off-label medications include trazodone, amitriptyline, quetiapine, risperidone. There have been some small trials demonstrative efficacy with low does trazodone however at this point in time there has been minimal research evidence supporting the use of the other agents for the treatment of primary insomnia.

Medications should only be used once all factors that may be contributing to the insomnia have been considered. Some factors may be beyond any obvious control, such as bereavement, exam stress, or even a genetic predisposition to poor sleep. However, other common contributing factors should be ruled-out, such as chronic pain, depression, anxiety, poor sleep hygiene, irregular sleep scheduling, and/or the presence of another primary sleep disorder.

Often proper management of these contributing factors will lead to a medication-free solution for the sleep disturbance.

Figure 1: (GABA)-barbiturate-benzodiazepine receptor complex



Hypnotic Medications

MEDICATION	T_{max} (Hrs)	$T_{1/2}$ (Hrs)	Sleep latency	Sleep efficiency	% SWS	% REM	Morning Sedation
Benzodiazepines:							
Temazepam	1	10	↓↓	↑	↓↓	---	↑
Triazolam	0.5	2	↓	↑	↑	↓	---
Oxazepam	3	16	↓	↑	↓	---	↑
Clonazepam	2	25	↓↓	↑	↓↓	↓	↑
Flurazepam	1.5	50+	↓↓	↑	↓↓	↓	↑↑
Non-Benzo:							
Zopiclone	0.5	6.0	↓↓	↑	--/↑	---	--/↑
Zaleplon	0.5	1.5	↓↓	↑	--/↑	---	---

New Location in Thornhill

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This location has been recently renovated with 6 diagnostic beds including one pediatric bed and will utilize the state of the art 32 channel Sandman diagnostic polysomnographic system. This location will also provide full consultation and clinic follow-up for the full spectrum of sleep disorders.

With the expansion of our facility, we are also excited to announce the addition of new physicians who will complement our multi-specialty consulting staff – including Dr. Abe Born (Respirology), Dr. Magdie Kohn (Respirology), Dr. Jack Shahin (Otolaryngology) and Dr. Eileen Sloan (Psychiatry).

In addition, we are pleased to announce the appointment of Dr. James MacFarlane as our Educational Director and Quality Assurance Consultant. Dr. MacFarlane is an Assistant Professor of Pediatrics & Psychiatry, University of Toronto, and a consultant to the Pediatric Sleep Program at The Hospital for Sick Children. He has extensive experience in both adult and pediatric Sleep Disorders Medicine, as well as a longstanding interest in Continuing Medical Education.

I hope you enjoy this issue of *Sleep Matters*. If there are any topics that would be of interest for future issues please let us know at: info@torontosleep.com

Sincerely,

Adam Blackman MD

Toronto Sleep Institute Insomnia Research Trials Program

We are currently involved in several trials studying novel hypnotic medications.

If you have any patients with primary insomnia who would be interested in participating in clinical research trials please have them contact:

416-488-6980 ext.6
www.sleepresearch.ca

torontosleepinstitute

DEDICATED TO ACHIEVING EXCELLENCE
in both the diagnosis and treatment of the full spectrum of sleep disorders, providing comprehensive evaluation and integrative treatment.

Please submit topics of interest for future issues to *Sleep Matters* ™ c/o info@torontosleep.com