DREAMING OF SOMNOLENCE: AN UPDATE IN INSOMNIA MANAGEMENT

Michael Howell

Introduction

Approximately 30% of all adults describe at least some degree of difficulty falling asleep or staying asleep. About one third of those (10% of adult population) will describe daytime dysfunction from insomnia (Roth 2007). In 2010 (the last year for which there is data) there were 5.5 million office visits for insomnia; from 1999 to 2010 the number of prescriptions written for sleeping medications rose from 5.3 to 20.8 million, a startling 293% increase (Ford et al 2014). Over half (55%) of patients on sleeping medication are taking a second sedating agent, while 25% are on an opioid analgesic (Bertisch 2014).

Prospective studies using large registries have linked insomnia, mortality, and stroke. Among a large nordic cohort insomnia symptoms predict all-cause mortality among men, but not women (Lalluka et al 2016). A Taiwan National Health database study noted that an insomnia diagnosis predicted stroke, most notably stroke in the young (Wu et al 2014). This link between insomnia and stroke was not seen in a separate, smaller database that only look at insomnia symptoms alone without a diagnosis (Helbig et al 2015).

Insomnia is particularly common among neurological disorders and typically indicates an increased disease burden. The majority of patients with Parkinson's disease (PD) suffer from insomnia (63%) with recent investigations demonstrating a direct link between insomnia severity and dopaminergic medication dosage (Ratti et al 2015, Zhu et al 2016). Among stroke patients insomnia symptoms are seen in 44% of survivors and predicts a decline in Health related quality of life measures (Tang et al 2015). Recently a study showed that over-the-counter sedatives are used to help promote sleep in nearly half of MS patients and correlated to daytime fatigue, suggesting that proper treatment of sleep disorders can better address MS fatigue (Braley et al 2015).

Insomnia predicts cognitive decline and mental disorders

Recent discoveries have highlighted the cognitive impairment from insomnia and growing evidence suggests that insomnia is a biomarker for future neuropsychiatric disorders. Attention, episodic memory, and working memory (an executive function) are relatively poor among insomniacs (Shekleton et al 2014, Fortier-Brochu et al 2014). Emotional perception, a critical facet of empathy, is impaired among patients with insomnia and may explain the poor social interactions often seen among patients with insomnia (Kyle et al 2014). Longitudinal studies have demonstrated that insomnia at baseline ultimately predicts anxiety, mood, and attention disorders in children (Armstrong et al 2014). Among patients with ADHD insomnia predicts later development of oppositional defiant disorder (Becker et al 2015). In elderly adults insomnia at baseline predicts cognitive decline 3-4 years later (Blackwell et al 2014).

Cognitive Hyper-vigilance

Historically the primary insomnias have organized into separate categories based upon various clinical features. According to the International Classification of Sleep Disorders-Second Edition (ICSD-2) these included: Adjustment insomnia, Psychophysiological insomnias, Idiopathic insomnias, and Paradoxical insomnia. However, in the recent published third edition of the ICSD (ICSD-3), these conditions have merged into one disorder, Chronic Insomnia Disorder. This change was made in recognition that cognitive hypervigilance is a unifying etiology in most cases of insomnia. Sleep becomes difficult to initiate and/or maintain due to a pathologically high increase in cortical arousal. This hyper-vigilance occurs 24 hours a day in contrast to other forms of sleep initiation difficulty (see below).

Pathophysiology-Recent Imaging Insights

Numerous studies have supported the hyper arousal theory of insomnia. Classic studies reveal greater high frequency EEG activity (typically beta) interfering with sleep onset, persistent through NREM sleep and even during middle of the day wakefulness. Functional imaging studies revealed a persistence of elevated glucose metabolism in the anterior cingulate relative to wakefulness as well as decreased activation during wakefulness in the lateral prefrontal cortex (both regions part of the default mode network).

More recently studies have demonstrated structural cortical abnormalities in regions of the default mode network and sensory regions. The default mode network (DMN) is a network of connected brain regions (mPFC, posterior cingulate, angular gyrus) when the brain is at wakeful rest (can include daydreaming, autobiographical tasks, social memory). During sleep there is normally a functional disconnection between the anterior and posterior regions of the DMN. Among patients with insomnia there is decreased structural connectivity between anterior and posterior regions of the DMN that was correlated with high scores (poorer sleep) on the Pittsburgh Sleep Quality Index (PSQI) (Suh et al 2016). Additionally, cortical thinning has been found in regions of the anterior cingulate, pre-central cortex, and lateral prefrontal cortex regions of the brain associated with insomnia related cognitive difficulties. The hyperarousal theory of insomnia suggests increased sensory processing associated with nocturnal mental rumination. Recently an imaging study demonstrated increased structural covariance between sensory regions and the default mode network in insomnia patients (Zhao et al 2015). So taking these two studies together there is a breakdown in the normal anterior to posterior disconnection in the default mode network at the same time there is an increase (likely pathological) in sensory processing that is interfering with sleep onset.

Sedating medications

One of the most vexing questions in clinical practice is when to prescribe a sedating agent (Stepanski 2005, Wohlgemuth 2005). Among neurology patient's insomnia is often chronic and thus a prescriber must determine whether to start an agent that may be needed for years.

A growing body of evidence regarding the risks of sleeping medications has underscored the need for novel therapeutic approaches. The commonly prescribed benzodiazepine and benzodiazepine receptor agonist can have lingering sedating effects, particularly among women and the elderly. Further, residual effects can lead to impaired driving even after 8 hours of sleep (Gunja 2013). These agents also increase the risk of falls, hip fractures, and exacerbate both mood and sleep related breathing disorders (Lin 2014;Li 2014). Sleepwalking is a well known side effect of benzodiazepine receptor agonists, especially when prescribed to patients with underlying Willis-Ekbom Syndrome (RLS) (see below) (Howell 2012, Howell 2015). Alarmingly, reports have also recently suggested that sleeping pills are associated with malignancy, Alzheimer's disease, and increased mortality (Kripke 2012, Billioti de Gage et al 2014)

Alternatively, sedating psychotropic medications such as trazodone and quetiapine are commonly prescribed for sleep initiation. However, their short-term efficacy is modest, long-term efficacy is poor, and safety in the general insomnia population is unknown (Mendelson 2005, Rosenberg 2006).

To a large degree chronic use of sedating agents can be avoided by rigorously excluding other easily mistaken disorders, especially prevalent in neurology patients. Further, common side effects often point to alternative etiologies as a source of sleep initiation failure.

Consider Other Etiologies

While difficulty initiating sleep is often attributed to a disorder of hyper-vigilance, circadian rhythm delay and RLS are often the diagnosis. This is especially true amongst neurology patients and thus extra scrutiny for these conditions is warranted.

Circadian Delay

It is difficult to exaggerate the effect modern lighting has had on our circadian rhythms. In 1700 total annual non-sunlight exposure was approximately 500 lumen hours. By 2010, our light exposure exceeded this baseline by three orders of magnitude (500,000 lumen hours). This artificial lighting is concentrated in the evening and

stimulates retinal ganglion cells that then signal the hypothalamic suprachiasmatic nucleus (SCN). The result is that our central circadian pacemaker, the SCN, promotes wakeful physiology long after the sun has set. Further, while our evenings are now often bathed in light we frequently delay our exposure to sunlight in the morning. This combination leads to a progressive delay in circadian rhythms (Manthena 2006, Reid 2011).

A patient with a circadian delay will have a similar presentation to those with cognitive hyper-vigilance when trying to fall asleep. They feel that their brain is fully aroused, and unable to "shut down". This experience is often stressful and may lead to nocturnal anxiety. However, distinct from cognitive hyper-vigilance, circadian delayed patients have severe difficulty waking up in the morning. They will often set several alarms clocks or have family members forcibly arouse them. They will sleep in late when possible. Importantly, if given the opportunity to go to bed several hours later they will often fall asleep without difficulty.

Therapy for Circadian Rhythm Delay:

- Bright light exposure (either sunlight or 10,000 lux light box) **first thing** in the AM for 30-120 minutes.
- Evening low dose melatonin 0.5-1mg po 4-6 hours prior to desired sleep onset.

Often the greatest hurdle in managing patients with a circadian delay is to convince them that the underlying problem can be addressed without a pharmaceutical agent. The timing of the light exposure and melatonin administration is critical as the phase response curves to these interventions quickly flatten out if the therapeutic window is missed.

Of note, many patients with circadian rhythm delays who have been chronically prescribed benzodiazepine receptor agonists will describe progressive inefficacy, AM sleepiness, and visual hallucinations.

Circadian Disruption in Neurodegeneration

Many insomnia complaints in patients with Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), are not in fact due to hyperarousal but instead these patients suffer from circadian disruption leading to misplaced timing of sleep propensity (Videnovic et al 2015). Decreased amplitudes of melatonin secretion and increased evening plasma cortisol levels have been noted in all three disorders resulting in in more fragmented sleep and decreased daytime wakefulness.

Among patients with Alzheimer's disease neuronal cell loss has been demonstrated in the suprachiasmatic nucleus (SCN) and the pineal gland. Additionally, there is a marked decrease in melatonin receptors in the SCN that coincided with a deposit of neurofibrillary tangles. These findings are associated with a decrease in CSF melatonin levels (even during the preclinical stages) and alterations in the normal variations in cortisol and body temperature. Clinically this pathology manifests as a progressive breakdown in day-night/wake-sleep stability and a delay in circadian rhythm (in contrast to the typical circadian advancement that occurs with normal ageing). This combination of nighttime sleep fragmentation and daytime napping is reinforced over time with a paucity of wakeful behavioral and cognitive cues stemming from immobility/decreased mental engagement. Ultimately, there is a complete breakdown in the 24-hour wake-sleep cycle which is the most common reason for institutionalization in the AD population. Traditional circadian therapies are helpful, particularly morning sunlight however melatonin is of limited efficacy due to the degeneration of melatonin receptors in the SCN noted above (Videnovic et al 2015).

Recent discoveries on the role of sleep in the clearance of insoluble CNS beta-amyloid suggest that sleep disruption may be a bidirectional relationship in cognitive impairment. These studies suggest that promoting sleep and circadian health may be neuro-protective however further studies are needed.

One interesting study of HD sheep noted that circadian rhythms appeared to normalize when HD sheep were kept with the normal sheep flock (Morton et al 2014) This study helps confirm that scheduled activity especially when combined with appropriate light exposure are powerful cues to reinforcing health circadian rhythms.

Utility of Cognitive Behavioral Therapy for Insomnia

Once circadian misalignment and RLS have been excluded as the cause of sleep initiation failure it is reasonable to consider conventional sedating agents. However, Cognitive Behavioral Therapy for Insomnia (CBT-I) is the most effective long-term treatment and the strategy most likely to result in a cure (Riemann 2009). Over the last several years, CBT-I has repeatedly been demonstrated to be a safe, efficacious therapy (Espie 2012, Mitchell 2012, Lovato 2014). As in-person therapy is often unavailable internet-delivered CBT-I treatments are effective and a good option for insightful and resourceful patients. As with all CBT treatments it is important to communicate to the patient up front the importance on behavioral change that is often difficult (Seyffert et al 2016). Recently CBT has been demonstrated to be effective in adults with Multiple Sclerosis and may often be a strategy to improve fatigue and mood symptoms in this population without pharmacotherapy (Clancy et al 2015). Among children with ADHD these behavioral sleep strategies have been shown to improve not only sleep but also daytime ADHD behaviors (Hiscock et al 2015).

Orexin-Based Therapeutic Agents

Narcolepsy, a disorder of excessive daytime sleepiness, is caused by dysfunction of the wake stabilizing peptide orexin. Suvorexant (40mg or 30mg), an orexin receptor antagonist was reported to be safe and efficacious over one year in patients with insomnia (Michelson 2014). More recently reports of lower dose suvorexant (20mg or 15mg-the FDA approved dosages) described sustained efficacy after three months. One study included a polysomnographic evaluation that noted an objective improvement in wake after sleep onset (WASO) with 23.1 fewer minutes per night as well as an increase in total sleep time (TST) per night of 27.5 minutes per night. There was no evidence of rebound or withdrawal symptoms after suvorexant was discontinued (Herring et al 2016). Pooled analyses from both dosage studies explored the effect of suvorexant on sleep architecture. Distinct from conventional sedative hypnotics suvorexant appears to have a small (1-2%) but consistently significant effect on increasing REM sleep (1-2% increase in % of TST) (Snyder et al 2016).

The most concerning suvorexant side effect is excessive daytime sleepiness and dosing is challenging as many patients have residual morning somnolence, even at low doses. Interestingly, suvorexant does not appear to suppress EEG power spectra nor does it appear to depress respiration unlike conventional sedatives (Ma et al 2014, Sun et al 2015, Sun et al 2015). Caution should be taken to avoid combining it with ethanol (Sun et al 2015, Sun et al 2015, Sun et al 2015).

References

Armstrong JM, Ruttle PL, Klein MH, Essex MJ, Benca RM. Associations of Child Insomnia, Sleep Movement, and Their Persistence with Mental Health Symptoms in Childhood and Adolescence. Sleep 37:901-9.

Becker SP, Langberg JM, Evans SW. Sleep problems predict comorbid externalizing behaviors and depression in young adolescents with attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry 2015 24:897-907.

Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National Use of Prescription Medications for Insomnia: NHANES 1999-2010. Sleep 37:343-9.

Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ. 2014 9:349.

Blackwell T, Yaffe K, Laffan A, et al. Associations of Objectively and Subjectively Measured Sleep Quality with Subsequent Cognitive Decline in Older Community-Dwelling Men: The MrOS Sleep Study. Sleep 37:655-63.

Braley TJ, Segal BM, Chervin RD. Hypnotic use and fatigue in multiple sclerosis. Sleep Med 2015 16:131-7.

Clancy M, Drerup M, Sullican AB. Outcomes of Cognitive-Behavioral Treatment for Insomnia on Insomnia, Depression, and Fatigue for Individuals with Multiple Sclerosis: A Case Series. Int J MS Care 2015 17:261-7.

DelRosso LM, Hoque R, James S, Gonzolez-Toledo E, Chesson AL. Sleep-Wake Pattern Following Gunshot Suprachiasmatic Damage. J Clin Sleep Med 2014 10:443-445.

Dolder CR, Nelson MH. Hypnosedative-induced complex behaviours : incidence, mechanisms and management. CNS Drugs 2008 22:1021-1036.

Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, Brown JS. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. Sleep. 2012 35:769-81.

Ford ES, Wheaton AG, Cunningham TJ, et al. Trends in Outpatient visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survery 1999-2010. Sleep 2014 37:1283-1293.

Gunja N. In the Zzz zone: The effects of Z-drugs on human performance and driving. J Med Toxicol 2013 9:163-71.

Helbig AK, Stockl D, Heier M, Ladwig KH Meisinger C. Symptoms of Insomnia and Sleep Duration and Their Association with Incident Strokes: Findings from the Population-Based MONIKA/KORA Augsburg Cohort Study. PLoS One 2015 10:e134480.

Herring WJ, Connor KM, Snyder E, et al. Suvorexant in Patients with Insomnia: Pooled Analysis of Three-Month Data from Phase-3 Ramdomized Controlled Clinical Trials. J Clin Sleep Med 2016 12:1215-25.

Hiscock H, Sciberras E, Mensah F, et al. Impact of a behavioral sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental mental health: randomized controlled trial. BMJ 2015. H68.

Fortier-Brochu E, Morin CM. Cognitive impairment in individuals with insomnia: clinical significance and correlates. Sleep 2014 37:1787-98.

Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open. 2012 2:epub.

Kyle SD, Beattie L, Spiegelhalder K, Rogers Z, Espie CA. Altered Emotion Perception in Insomnia Disorder. Sleep 37:775-83.

Li CT, Bai YM, Lee YC, et al. High Dosage of Hypnotics Predicts Subsequent Sleep-Related Breathing Disorders and Is Associated with Worse Outcomes for Depression. Sleep 2014 37:803-9.

Lallukka T, Podlipskyte A, Sivertsen B, et al. Insomnia symptoms and mortality: a register-linked study among women and men from Finland, Norway, and Lithuania. J Sleep Res 2016 25:96-103.

Lin FY, Chen PC, Liao CH, Hsieh YW, Sung FC. Retrospective Population Cohort Study on Hip Fracture Risk Associated with Zolpidem Medication. Sleep 2014 37:673-9.

Lovato N, Lack L, Wright H, Kennaway DJ. Evaluation of a Brief Treatment Program of Cognitive Behavioral Thearpy for Insomnia in Older Adults. Sleep 37:117-126.

Ma J, Svetnik V, Snyder E et al. EEG power spectral density profile of the orexin receptor agonist suvorexant in patients with primary insomnia and healthy subjects. Sleep 2014;37:1609-19.

Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005 66:469-476.

Michel MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract 2012 13:40.

Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014 13:461-71.

Morton AJ, Wood NI, Hastings MH, et al. Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. J Neurosci 2005 25:157-63.

Ratti PL, Negre-Pages L, Perez-Lloret S et al. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: Insights from a cross sectional evaluation of the French CoPark Cohort. Parkinsonism Relat Disord 2015 21:1323-9.

Reid KJ, Zee PC. Circadian rhythm sleep disorders. Handb Clin Neurol 2011 99:963-77.

Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonist and psychological and behavioral therapies. Sleep Med Rev 2009 13:205-14.

Rosenberg RP. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. Ann Clin Psychiatry 2006 18:49-56.

Roth T. Insomnia: Definition, Prevalence, Etiology, and Consequences. JCSM 2007 3:S7-10.

Shekleton JA, Flynn-Evans EE, Miller B, et al. Neurobehavioral Performance Impairment in Insomnia: Relationship with Self-Reported Sleep and Daytime Functioning. Sleep 37:107-16.

Seyffert M, Lagisetty P, Landgraf J, et al. Internet-Delivered Cognitive Behavioral Therapy to Treat Insomnia: A Systematic Review and Meta-Analysis. PLoS One 2016 11:e0149139.

Snyder E, Ma J, Svetnik V, et al. Effects of suvorexant on sleep architecture and power spectral profile in patients with insomnia: analysis of pooled phase 3 data. Sleep Med 2016 19:93-100.

Stepanski EJ. Hypnotics should not be considered for the initial treatment of chronic insomnia. JCSM 2005 1:125-128.

Suh S, Kim H, Dang-Vu TT, Joo E, Shin C. Cortical Thinning and Altered Cortico-Cortical Structural Covariance of the Default Mode Network in Patients with Persistent Insomnia Symptoms. Sleep 39:161-71.

Sun H, Palcza J, Rosenberg R et al. Effects of Suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with COPD. Respir Med 2015 109:416-26.

Sun H, Yee KL, Gill S, et al. Psychomotor Effects, pharmacokinetics and safety of the orexin receptor antagonist, suvorexant administered in combination with alcohol in healthy subjects. J Psychopharmacol 2015;29:1159-69.

Sun H, Palcza J, Card et al. Effects of Suvorexant, an orexin receptor antagonist, on respiration during sleep in Patients with OSA. JCSM 2015. [Epub ahead of print]

Tang WK, Grace Lau C, Mok V, Ungvari GS, Wong KS. Insomnia and health-related quality of life in stroke. Top Stroke Rehabil 2015 22:201-7.

Viana P, Rodrigues E, Fernandes C, et al. InMS: Chronic insomnia disorder in multiple sclerosis-a Portuguese multicenter study on prevalence, subtypes, associated factors and impact on quality of life. Mult Sclero Relat Disord 2015 4:477-83.

Videnovic A, Zee P. Consequences of Circadian Disruption on Neurologic Health. Sleep Med Clin 2015 10:469-480.

Wohlgemuth WK, Krystal AD. Hypnotics should be considered for the initial treatment of chronic insomnia. JCSM 2005 1:120-124.

Wu MP, Lin HJ, Weng SF, Ho CH, Wang JJ, Hsu YW. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. Stroke 45:1349-54.

Zhao L, Wang E, Shang X, et al. Cortical Structural Connectivity Alterations in Primary Insomnia: Insights from MRI-Based Morphometric Correlation Analysis. Biomed Res Int 2015. [Epub ahead of print]

Zhu K, van Hilten JJ, Marinus J. The course of insomnia in Parkinson's disease. Parkinsonism Relat Disord. 2016. [Epub ahead of print]