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APPROACH TO INSOMNIA IN THE ELDERLY: PRACTICE CONSIDERATIONS IN PRIMARY CARE FOR COMPLEX PATIENTS

Soojin Chun
MSc, MD, FRCPC(C)
Geriatric Psychiatrist, Royal Ottawa Mental Health Centre, Lecturer, University of Ottawa

Elliot Kyung Lee
MD, FRCP(C), D.ABSM, AASM, F.APA
Sleep Specialist, Royal Ottawa Mental Health Centre, Assistant Professor, University of Toronto

Corresponding Author:
Soojin Chun
Soojin.Chun@theroyal.ca

Abstract

Insomnia is one of the most common symptoms for which geriatric patients to seek medical attention. Insomnia in the elderly is often associated with multiple psychiatric and medical comorbidities and negative health consequences. Multiple medical problems and medications can contribute to the development of insomnia symptoms. In particular, common symptoms associated with sleep disturbances include pain, mood problems and memory complaints. Each of these factors can interact with each other to exacerbate patient symptomatology and have a bidirectional relationship with sleep. Sleep-disordered breathing in particular is frequently overlooked in the geriatric population yet is highly prevalent and can contribute to one or all of pain, mood and memory complaints. This article will explore how these factors may interact in the context of a common but complex clinical presentation of a geriatric patient in clinical practice and will conclude with some practical suggestions for further evaluation and management for this patient.

This article has been peer reviewed.

Conflict of Interest: None

This article was published in December 2019.

Key words:
psychiatric disorders, dementia, pain, sleep

Key Points:

1. Sleep has a bidirectional relationship with a number of problems including pain, memory and depression symptoms. These problems may also interact to exacerbate each other.
2. Insomnia is an important symptom to identify, recognize and treat appropriately in geriatric patients. This can come from a variety of factors. Insomnia will worsen virtually every other symptom a patient has (pain, mood, memory, etc.). Appropriate recognition and treatment can improve clinical outcomes.
3. Common medications used in the geriatric population can frequently be associated with insomnia.
4. Sleep-disordered breathing is common in the geriatric population and is frequently under-recognized. Clinicians should maintain a high index of suspicion for sleep-disordered breathing in geriatric patients who present with memory difficulties and/or depressive symptoms.

Case

A 70-year-old male is assessed by his family doctor with the chief complaint of "poor sleep." He reports having difficulty falling asleep at night and wakes up frequently during the night. He feels tired during the day and often needs to nap after lunch hour. His wife reports that they have been sleeping in separate bedrooms for the past year as he is "very restless" at night. He complains of pain in his knees and back that keeps him up at night. He wakes up to go to the bathroom two or three times a night, but he's always had a "small bladder." He admits he snores at night but "that's nothing to worry about." He is concerned that his insomnia is impacting his ability to function during the day, as he "can't think straight." His wife reports that he is very irritable and seems very unmotivated to do things around the house despite him taking his medications regularly.

His medical history includes chronic obstructive pulmonary disease (COPD), hypertension, hypercholesterolemia, osteoarthritis, coronary artery disease and history of palpitations/arrhythmia. He does not have any history of primary sleep disorder.

His psychiatric history includes major depressive disorder and generalized anxiety disorder. He has never had any psychiatric admission in the past.

His current medications include propranolol, hydrochlorothiazide, atorvastatin, sertraline and mirtazapine. He takes acetaminophen with codeine (8 mg) at times for arthritis pain. He does not have any drug allergies.

On social history, he drinks half a glass of wine at dinner every night. He never smokes. He drinks three large cups of coffee every day "to stay awake." He does not use any illicit substance.

On physical examination, his weight is 182 lb and his supine blood pressure is 144/80 mmHg with HR 80 beats per minute (BPM). His standing blood pressure is 120/65 mmHg with HR 92 BPM. Cardiovascular and respiratory exams are normal. Neurological exam reveals mild resting tremor in bilateral upper extremities. His gait is slow but stable without any gait aid. He reports feeling "unsteady" while walking. His MOCA score is 22/30, showing difficulty with visual perception and delayed recall.

More details will be introduced later in this article.

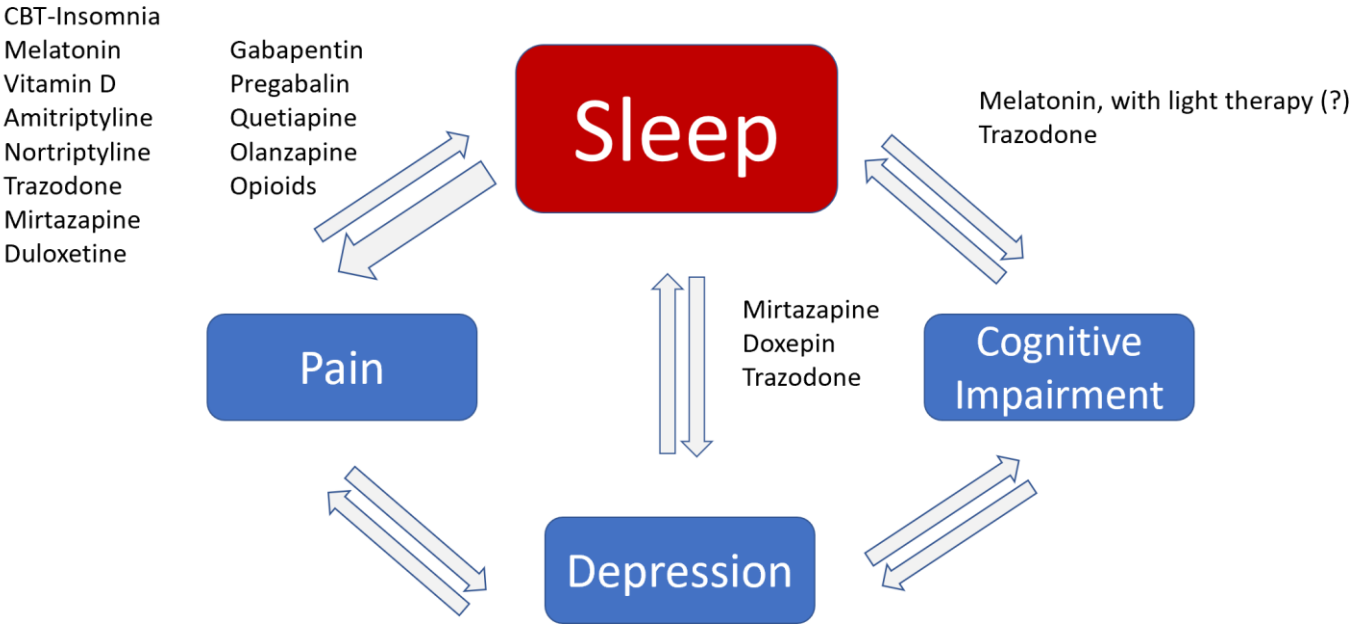
Introduction

Insomnia is one of the most common symptoms for which geriatric patients to seek medical attention. Insomnia in the elderly is often associated with multiple psychiatric and medical comorbidities and negative health consequences. The prevalence of insomnia increases to up to 40% of people older than 65.[1,2]

There are number of changes in sleep that occur with aging that were described in our previous paper (to view the article, please click here)[3]. Unfortunately, many of these changes almost always are negative in nature and often cause distress and an overall decline in quality of life.[4] Insomnia disorder is characterized by a "predominant complaint of dissatisfaction with sleep quantity or quality" according to the diagnostic criteria from DSM-5.[5] It is widely understood that insomnia is frequently multifactorial in origin. Therefore, an approach to insomnia requires a stepwise evaluation of predisposing, precipitating and perpetuating factors.[3]

The purpose of this follow-up article is to delineate a practical approach to chronic insomnia with comorbid medical factors including pain symptoms, memory impairment and/or depression in the geriatric population with primary practitioners in mind. These factors can all be interrelated and may mutually affect each other (See Figure 1). We will use the case introduced at the beginning to review important considerations and contributing factors to insomnia with one or a combination of these common comorbidities and discuss when to refer patients with insomnia symptoms to geriatric psychiatry and/or a sleep disorders clinic for further evaluation. For the purposes of this discussion, this review will focus on major neurocognitive disorder, Alzheimer's type, when discussing memory complaints and association with sleep problems, although there are significant data linking sleep disturbances to other neurocognitive disorders (e.g., Lewy body dementia, Parkinson's dementia, vascular dementia and others).

Figure 1: Bidirectional relationship between depression, pain, cognitive impairment and sleep complaints. Note that pain problems may also exacerbate cognitive impairment, though they are not associated with the development of a neurocognitive disorder, but both depression and sleep complaints may be associated with cognitive disorders. Medication considerations are listed for symptom clusters, but overall evidence is small and clinical judgment is important to guide selection.



Initial Assessment

A careful and thorough history needs to be obtained to assess predisposing, precipitating and perpetuating factors for insomnia symptoms. If the history indicates a possible primary sleep disorder, such as restless legs syndrome, obstructive sleep apnea or Rapid Eye Movement (REM) sleep behaviour disorder, it is unlikely that insomnia symptoms would improve without first addressing the primary sleep disorder by a sleep specialist. See our previous article for screening questions (Table 1: Common sleep disorders, screening tools click here)[3] In particular, it would be important to speak to the bed partner about any history of movement abnormalities noted during the night or dream enactment behaviour. These findings could suggest a diagnosis of a movement related sleep disorder such as periodic limb movement disorder or REM behaviour disorder (RBD), where patients lose the paralysis of REM sleep and subsequently have the ability to act out their dreams, sometimes resulting in injury to themselves or their partner.[6] In such cases, a referral to a sleep specialist for evaluation by polysomnography is strongly recommended, particularly if there is a comorbid history of memory complaints. Up to 75% of patients with RBD will subsequently develop an alpha synucleinopathy disorder, including possibly Parkinson's disease, Lewy body dementia and/or multisystem atrophy within 10 years of the initial RBD diagnosis.[6]

If the patient's history reveals possible active medical and/or psychiatric conditions, then interventions to address these conditions are crucial in minimizing insomnia symptoms. It is important to understand that sleep disturbances in older adults are frequently associated with pre-existing systemic medical condition(s).

Examples of medical conditions associated with disturbance of sleep are shown in Table 1.

Table 1. Medical conditions associated with disturbed sleep

Cardiovascular disorders	Congestive heart failure (CHF), nocturnal angina
Respiratory disorders	Chronic obstructive pulmonary disease (COPD), asthma
Endocrine disorders	Hypothyroidism, hyperthyroidism
Gastroenterological disorders	Gastroesophageal reflux
Neurological disorders	Stroke, migraine, neuromuscular degenerative disorders, nocturnal seizures, Parkinson's disease, major neurocognitive disorders
Pain disorders	Arthritis, fibromyalgia, neuropathic pain, cancer, headache/migraine
Genitourinary disorders	Nocturia, benign prostate hyperplasia (BPH)

Sleep symptoms are very common in psychiatric conditions and therefore it is crucial to screen for primary psychiatric disorders (other than insomnia disorder), such as major depressive disorder, bipolar spectrum disorder, anxiety and/or substance use disorder. More recently, insomnia disorder is now viewed as a separate entity in DSM-5, rather than secondary to a psychiatric illness, raising the importance of making an independent diagnosis and treating accordingly in the context of a major psychiatric illness.[5]

Once major medical and psychiatric conditions are ruled out or addressed, it is crucial to have a thorough review of the patient's medication list. There are numerous medications commonly used in the older population that have been known to stimulate arousal centres and result in iatrogenic insomnia (Table 2). Unfortunately, many of these medications are used to treat comorbid medical/psychiatric conditions precipitating insomnia. Effort should be made to either minimize or discontinue these medications if possible, while carefully weighing anticipated benefits versus drawbacks of such actions. The timing of medications should also be reviewed so that activating/stimulating medications are taken earlier in the day.

Table 2: Medications and other substances that can contribute to insomnia

Psychiatric	Antidepressants: Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) Psychostimulants: methylphenidate, modafinil Cholinesterase inhibitors: e.g. donepezil, rivastigmine and galantamine
Cardiovascular	Angiotensin converting enzyme inhibitors (ACEI), diuretics, alpha-blockers (ARB), beta-blockers, calcium channel blocker, statins
Respiratory	Bronchodilators (e.g. Salbutamol), theophylline
Neurological	Anti-Parkinson's: dopaminergic agonist, such as Levodopa
Gastrointestinal	H2 blockers: Ranitidine, Cimetidine
Analgesics	Chronic opioid use
Others	Caffeine, nicotine, alcohol, glucocorticoid

Other contributing factors, such as acute and chronic stressors should be discussed during the initial assessment of insomnia. Behavioural and psychological factors, such as poor sleep hygiene, unrealistic expectations of sleep, environmental disturbances (e.g., pets, bed partner, use of electronics such as an iPad) should be discussed. See the 6Ps in the Evaluation Section of our previous article (click here).

Back to Our Case

There are several medical conditions that may be contributing to sleep difficulties in this patient, including COPD and chronic pain in the context of osteoarthritis. Several medications that he takes may worsen sleep, including his atorvastatin, hydrochlorothiazide and propranolol. Statin drugs have been associated with insomnia in some but not all studies. A large meta-analysis by Broncel and colleagues did not find an association between statin drugs and insomnia,[7] though several other investigators have found a relationship. It has been suggested that more lipophilic statins such as lovastatin, atorvastatin and simvastatin are more likely to cause insomnia than hydrophilic drugs such as rosuvastatin and pravastatin.[8] The mechanism by which insomnia occurs is not known, though some speculate that reduced cholesterol on cell membranes may affect serotonin receptor activity, possibly precipitating insomnia symptoms.[8] Diuretic medications may contribute to nocturia, which has been associated with increased mortality for elderly patients, particularly with more than three episodes per night.[9] Beta-blockers have frequently been associated with insomnia symptoms. This is thought to occur as a result of a blockage of sympathetic signalling to the pineal gland resulting in decreased production of melatonin, a soporific hormone normally needed to facilitate sleep onset and maintenance.[10] Propranolol in particular has been associated with a higher risk of insomnia in elderly patients, in part due to its high lipophilicity and resultant high blood brain barrier penetration.[11]

While these conditions have been associated with poor quality sleep, it is important to consider whether there may be any other problems that compromise sleep.

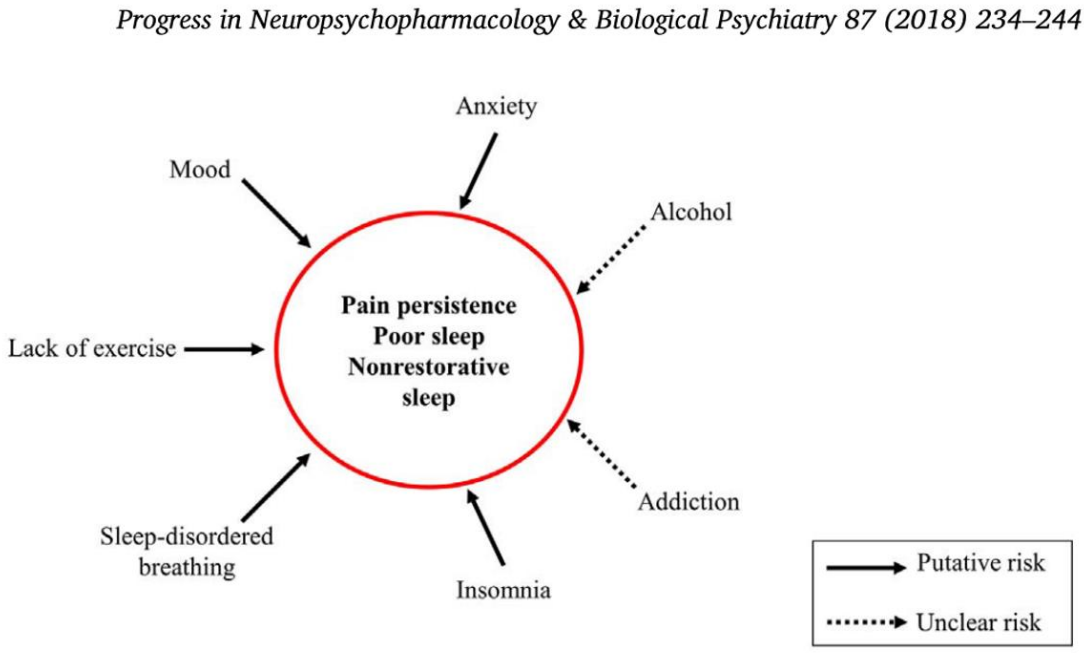
Clinical Questions

1. Can pain play a role in sleep difficulties? Can a sleep disorder play a role in pain? How is this relationship defined?
2. How are sleep and major depressive disorder related?
3. Can a sleep disorder play a role in memory difficulties?

Pain and Sleep

Pain and sleep have a complicated, bidirectional relationship (see Figure 1). Up to 50-80% of patients with chronic pain conditions will identify sleep disturbances.[12] A number of factors may influence the risk of pain and sleep being connected, including negative mood states, anxiety, lack of exercise, drug use and comorbid sleep disorders (see Figure 2). Acute or chronic pain can interfere with quality and/or quantity of sleep in the elderly. Pain can trigger poor sleep quality and fragmentation of sleep thus reducing sleep's restorative benefits.[13] Poor sleep quality, including insomnia, is known to exacerbate pain.[14-16] Impaired sleep, however, is a more consistent predictor of pain than vice versa.[17] Pain increases cortical arousals and sleep deprivation increases pain sensitivity via reduced opioid receptor affinity.[18] An increase in proinflammatory cytokines is also seen with sleep deprivation.[12]

Figure 2: Important risk factors influencing pain and sleep (reprinted from *Prog Neuropsychopharmacol Biol Psychiatry*, 87(Pt B), Marshansky, S. et al., Sleep, chronic pain and opioid risk for apnea, 234-244, 2018, with permission from Elsevier.



In general, non-pharmacologic methods including cognitive behavioural therapy (CBT) are recommended for treatment of insomnia and pain symptoms if possible. Benzodiazepine drugs may be considered for short-term relief of insomnia symptoms associated with pain by improving muscle tension and anxiety, but long-term use should be avoided due to potential side effects including neurocognitive difficulties, depression, fall risk, driving crash risk and addiction risk. Long-term use of benzodiazepines has not been associated with improvement of insomnia or pain symptoms.[12] While several other sedating drugs such as Z-drugs are often prescribed for insomnia symptoms, these have not been shown to be effective in treating sleep disturbances and/or pain symptoms when these conditions coexist.[19] Furthermore, these drugs should be avoided due to addiction risk and potential for worsening underlying and unrecognized sleep-disordered breathing.[14] Melatonin has been shown to have some benefits for sleep initiation and maintenance as well as nociceptive properties, due to both its soporific effects and anti-inflammatory effects.[20] Vitamin D has garnered interest as a possible immunomodulatory molecule that may mitigate pain symptoms for patients with chronic musculoskeletal pain, possibly mediated via inhibitory effects on COX-2.[21] Patients with lower 25 hydroxyvitamin D (<20 ng/ml) levels frequently have been identified as experiencing more pain symptoms.[13,21] Other studies have suggested amitriptyline can be helpful for sleep disturbances associated with pain, but quality studies are lacking.[22] Caution is warranted in the elderly due to its high anticholinergic activity and potential for neurocognitive side effects. Nortriptyline, a metabolite of amitriptyline, can also be

considered as this medication has fewer anticholinergic effects than amitriptyline. Trazodone and mirtazapine have been identified in small studies to have some benefit for pain and sleep symptoms.[12] Duloxetine, an SNRI has been associated with improvement in depressive symptoms and pain problems, but may worsen sleep disturbances.[23] Limited data suggest atypical antipsychotics such as quetiapine and olanzapine may be helpful for sleep parameters and have analgesic properties, but side effects can be significant including weight gain and prolongation of QT interval; consultation with a psychiatrist is recommended if use of these medications is considered.[12] Multiple studies suggest efficacy for the alpha 2 delta drugs including gabapentin and pregabalin for decreasing sleep latency, increasing sleep continuity and increasing deep sleep with accompanying analgesic properties for neuropathic pain, as well as antidepressant and anxiolytic properties, making these drugs reasonable to consider for this context.[12,20,23] Caution is warranted if considering these medications due to their potential cognitive side effects. While cannabinoids have been assessed for their nociceptive properties and soporific effects, their use in the elderly has not been comprehensively evaluated for these symptoms.[20,24] Although the elderly may find cannabinoids more appealing as a "natural" substance and perceive less harms from these substances, caution is needed as these substances may increase gait instability, cognitive impairment, myocardial infarction and other cardiovascular complications, as well as psychotic symptoms (for full review see "Medical Cannabis for Older Patients"[25]). Opioid use can be considered if pain is significant, but multiple lines of evidence demonstrate sleep-disordered breathing occurring in up to 70-85% of patients who use these medications, including central sleep apnea, as well as obstructive sleep apnea.[26] Long-term opioid use also suppresses slow wave sleep, which may paradoxically promote long-term development of pain problems.[27] Consequently, significant caution is warranted when considering use of these drugs.

Major Depressive Disorder and Sleep

Multiple studies confirm a relationship with sleep disturbances and the development of a major depressive disorder. Sleep disturbances are a significant risk factor for the development and recurrence of a major depressive episode and may represent a prodrome for this condition in older individuals.[28] A systematic review and meta-analysis by Bao and colleagues demonstrated that the inverse is also true, that depression increases the risk of sleep disturbances developing in the elderly by 70%.[29] Several studies suggest a link between a depressive episode and subsequent shorter sleep durations in the elderly.[30] Chronic shorter sleep durations may alter the hypothalamic pituitary adrenal axis, which may be a mechanism that perpetuates the development and/or exacerbation of a major depressive episode.[31] Consequently, since depression and sleep disturbances co-occur frequently and mutually exacerbate each other, this emphasizes the need for prompt identification and treatment of both of these conditions to ensure optimal outcomes. Depression symptoms may also be a prodromal presentation for the emergence of a neurocognitive disorder.[32] The presence of multiple physical comorbidities may further strengthen the relationship between depression and incident sleep disturbances and vice versa, thus further highlighting the need for early identification and treatment.[33,34]

The Canadian Network for Mood and Anxiety Treatments (CANMAT) has published guidelines in 2016 on the use of pharmacotherapy for the treatment of mood disorders in the elderly population (to view the article, please click here).[32] While a full review of these options is beyond the scope of this review, CANMAT guidelines suggest a first-line treatment for major depressive disorder could include an SSRI, SNRI, Mirtazapine, Bupropion or nortriptyline. With the presence of insomnia, a 2018 Cochrane review (to view the article, please click here) found limited evidence to support the use of SSRIs specifically for insomnia symptoms, but some modest evidence to suggest improvement of insomnia symptoms with low dose doxepin, or trazodone.[35] There was no evidence to suggest benefit with amitriptyline, a commonly prescribed tricyclic antidepressant for insomnia in the elderly.[35] Mirtazapine in particular may have benefits for insomnia symptoms in patients with late life depression likely due to its antihistaminergic properties and 5-HT2C antagonism, particularly in those with complex medical problems.[36] Caution is warranted with mirtazapine use, however, as it has been identified to cause or worsen symptoms of restless legs syndrome and period limb movement disorder in some patients.[37]

Sleep, Memory and Neurocognitive Dysfunction

Sleep and neurocognitive disorders likely have a bidirectional relationship. As neurocognitive disorders progress, there is a typical progression of insomnia symptoms and deterioration of sleep. Progression of insomnia symptoms and sleep deprivation has been implicated in increased cerebral amyloid beta (Aβ) deposition.[38] Consequently, targeted modifiable risk factors are of utmost importance to decrease progression to Alzheimer's disease. Sleep is increasingly being examined as a potential avenue for treatment of and/or to decelerate progression of these disorders. Emerging data is implicating sleep-disordered breathing as a modifiable risk factor for the progression of neurocognitive disorders including Alzheimer's disease.[39]

Sleep has been posited to play an important role in clearing metabolic waste products from the brain via the glymphatic system.[40] The glymphatic system is a group of perivascular channels around cerebral blood vessels that is particularly active during sleep and has been implicated in clearing metabolic waste products for the brain, including Aβ.[38,40] While the existence of this system is proven in animals, emerging evidence is also identifying the function of this system in humans with diffusion tensor magnetic resonance (MR) imaging.[38,41] During sleep, there is a marked increase in interstitial space, which results in accelerated clearance of Aβ. Interestingly, clearance has been shown to be most rapid in the lateral position.[38] Sleep deprivation has been linked with increased deposition of Aβ and other metabolic waste products[38,42] and increased deposition has been linked with sleep disturbances suggesting a bidirectional relationship between these factors.[43]

Sleep and Neurocognitive Disorders, Including Alzheimer's Type

Neurodegenerative disorders are frequently associated with sleep disturbances through a variety of mechanisms including alterations in neurotransmitter activity and changes in circadian stability.[44] These disorders often have associated degenerative effects on brain nuclei in the anterior and posterior hypothalamus and basal forebrain that play key roles in regulating sleep and vigilance. The suprachiasmatic nucleus (SCN) in particular is affected by aging and neurodegenerative processes.[45] This nucleus plays a key role in the consolidation of circadian rhythms and acts as a biological clock or pacemaker. Decreased cerebrospinal fluid (CSF) melatonin levels and changes in melatonin receptor expression are seen in patients with major neurocognitive disorder, Alzheimer's type and these changes can predate the onset of cognitive symptoms.[46,47] Decreased slow wave (deep) sleep and REM sleep as well as other sleep disturbances are also seen.[47]

Pharmacotherapy for Sleep Disturbances in Neurocognitive Disorders

Studies of pharmacotherapies for sleep disturbances in patients with neurocognitive disorders are generally lacking. A large 2016 Cochrane review (to view the article, please click here) of randomized placebo controlled trials of medications for sleep disturbances in patients with neurocognitive disorders found such studies for melatonin, trazodone and ramelteon (a melatonin agonist not available in Canada).[47] Overall results were judged to be of low quality. No evidence of significant benefit or significant side effects were seen in studies of melatonin or ramelteon, while modest evidence of benefit, including increased total sleep time and sleep efficiency was seen with trazodone 50 mg administered for two weeks. The size of the trial, however, was very small (30 subjects), limiting the generalizability of these findings.[47] The authors were unable to find trials of other medications commonly used to treat sleep disturbances in this patient population.

Xu and colleagues conducted a systematic meta-analysis of melatonin use for sleep disorders and cognition in dementia and found evidence of an improvement in total sleep time (24.32 minutes) with marginal benefits in sleep efficiency with no evidence of change in cognitive function.[48] Given that melatonin levels are known to be lower in patients with Alzheimer's disease, several investigators have studied melatonin administration for insomnia symptoms in these patients but data have produced mixed results. Some studies have suggested some benefits for these patients, in terms of reduced sleep latency and improved sleep quality, while other studies have shown no effect at all and some even showing increased aggression.[44,49] Dowling and colleagues performed an experiment where subjects received 5 mg of melatonin over 10 weeks, 2-3 hours before bedtime (i.e. 5:00 to 6:00 p.m.) in 16 subjects with Alzheimer's disease and evidence of disturbed rest activity rhythms. This melatonin dose was estimated to produce a peak physiologic level 10-1000 times

normal levels within one hour of administration for eight hours. These subjects also received light exposure (>2500 lux) from 9:30 to 10:30 a.m. Monday to Friday during the same time period. Compared to control subjects, patients in the combination melatonin plus light therapy group experienced more daytime activity, less daytime somnolence and improved diurnal rest activity patterns.[50] These results suggest that timed melatonin administration combined with light therapy might be more helpful than melatonin administration alone but further work is needed to replicate these findings.

OSA in the Elderly – Under-recognized, Undertreated

Obstructive sleep apnea (OSA) is a common condition characterized by repeated partial or complete airway obstructions in breathing during sleep leading to intermittent hypoxemia, sleep fragmentation, sympathetic activation and sleep deprivation. OSA is frequently associated with numerous comorbidities, including cardiovascular disease, cognitive dysfunction, depression and decreased quality of life.[51] This condition may be seen frequently in the elderly, in up to 70% of men and 56% of women over the age of 60 years.[52-54] Braley and colleagues assessed the prevalence of OSA in a sample of community dwelling American elderly subjects as part of the National Health and Aging Trends Study (NHATS) using the STOP BANG questionnaire (to view the STOP BANG Questionnaire in Table 1 please click here). Using a cutoff of 3 for this test (since every patient would score at least 1 by virtue of their age), 56% of patients were determined to be at high risk for OSA. Among these patients, 8% had an evaluation for OSA and in 94% of these cases, the diagnosis was confirmed.[51]

OSA is frequently under-recognized in the geriatric population for a variety of reasons. Insomnia is a frequent symptom of OSA, but is overlooked.[55] Other common symptoms of OSA in the geriatric population include frequent nocturnal urination, postoperative delirium and gait disturbance.[56] However, more than 77% of patients over the age of 65 may report nocturia symptoms disturbing sleep.[57] Potential etiologies include overactive bladder, decreased bladder capacity associated with aging, benign prostatic hypertrophy, diabetes mellitus and edematous states such as those associated with heart failure and/or kidney dysfunction.[9] These associations make this symptom easy to overlook. Elderly patients with three or more episodes of nocturia per night in particular should be routinely screened for OSA, since three or more nocturia episodes has been predictive of severity of sleep-disordered breathing and increased mortality.[9,58] Patients with OSA also show increased stride to stride variability of stride time (STV).[59] Increased STV has been associated with a higher risk of falls and disability.[60] Furthermore, treatment of OSA has been demonstrated to improve gait parameters.[61] Body habitus and male sex are often identified as significant risk factors for OSA, but these factors become insensitive to identifying sleep-disordered breathing in the geriatric population after the age of 60.[62] Furthermore, common signs and symptoms of OSA, including snoring, hypertension and sleepiness during the day may frequently be attributed to normal effects of aging.[51] As a result of frequent under-recognition and undertreatment, these patients are often prescribed hypnotic agents for symptomatic relief, which may worsen problems with breathing in sleep as well as causing confusional arousals.[18,63]

OSA and Effects on Memory, Neurocognitive Disorder – Alzheimer's Type

Obstructive sleep apnea is linked to memory and neurocognitive impairment, as well as depression, through a variety of mechanisms including hypoperfusion, endothelial dysfunction, intermittent hypoxemia and neuroinflammation.[6] While a variety of factors likely play a role in the development of Alzheimer's disease, the earliest (preclinical) signs of Alzheimer's include the development of insoluble Aβ plaques, which can initially be detected by observing a reduction in CSF soluble Aβ 42 levels, often 10-15 years before cognitive symptoms are identified.[64] Untreated OSA has also been associated with reductions in CSF soluble Aβ 42 levels and these reductions are ameliorated if CPAP treatment is used.[65] A longitudinal study by Sharma and colleagues demonstrated a direct correlation between the severity of OSA and subsequent amyloid burden over a two-year follow-up period.[66] Although not all studies agree, the most frequent deficits seen in geriatric patients with OSA include vigilance, attention, memory executive function and mental flexibility.[67,68] OSA has been associated with earlier and continuing cognitive decline in the elderly.[69] Treatment of sleep-disordered breathing with CPAP therapy has shown reduction in progression of neurocognitive difficulties and even

improved cognition.[39,70] Taken together, these findings suggest OSA is a modifiable risk factor for the subsequent development of Alzheimer's neurocognitive disorder.[71]

OSA and Effects on Major Depressive Disorder

Increasing data is also suggesting a link between OSA and depression. Two prospective longitudinal studies indicate OSA confers a twofold increased risk of developing a major depressive disorder.[72,73] Those with a major depressive disorder are five times more likely to have a history of OSA compared to the general population.[74] Insomnia may be a presenting symptom of a depressive disorder along with pain in the geriatric population[75] but is often dismissed as a normal part of aging. Like neurocognitive disorders, hypoperfusion, endothelial dysfunction, intermittent hypoxemia and neuroinflammation have all been implicated as potential mechanisms, suggesting common pathways may link OSA to both depression and neurocognitive disorders.[56] Serum brain derived neurotrophic factor (BDNF) has been strongly connected with major depressive disorder and several investigators have observed lower serum BDNF and hippocampal damage in patients with OSA compared to healthy controls.[67] Furthermore, treatment of OSA with CPAP has also been shown to improve depressive symptoms in the elderly population.[76,77]

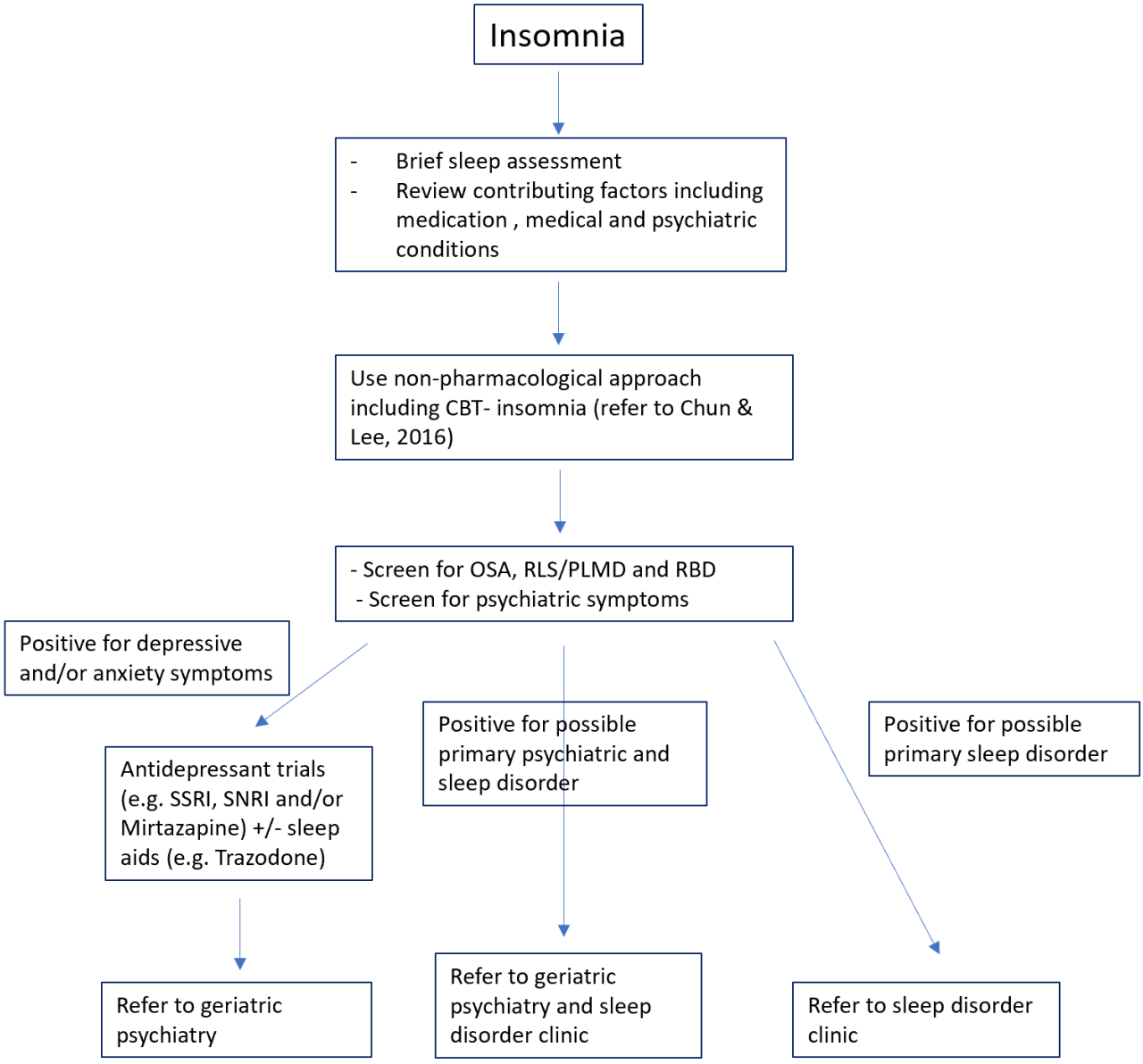
Case Summary

This patient has a complex constellation of symptoms and potential disorders that may interact to contribute to his ongoing mood, pain and memory difficulties. See Figure 3 for a suggested algorithm for assessment and management suggestions for this patient. Given this patient's history of insomnia difficulties, daytime fatigue and memory complaints, a sleep medicine consultation is warranted, particularly with a history of snoring. Even in the absence of this symptom, a sleep study should be considered. There is growing evidence linking OSA to memory difficulties and the atypical presentation of this condition in the older population. Further supporting evidence to suggest a sleep medicine evaluation is indicated includes the cardiovascular history for this patient and as well as the psychiatric symptoms suggestive of an underlying persistent and treatment resistant major depressive disorder. Other causes of sleep disturbances should also be considered including RLS/PLMD and RBD. Most notably, unrecognized sleep-disordered breathing (SDB) can contribute to one or all of this patient's problems, including pain, depression and memory complaints. Since SDB is quite treatable with continuous positive airway pressure (CPAP) for instance, such treatment can help with depression, pain and memory symptoms given the known bidirectional relationship of these symptoms to sleep. OSA is increasingly being considered as a risk factor for the development of neurocognitive disorders including particularly Alzheimer's type and vascular dementia.

Pharmacotherapy options are very limited for patients with a history of sleep complaints and memory difficulties, with only melatonin demonstrating some limited benefits. Adding light therapy to melatonin could be considered. Given the history of persistent depressive symptoms and memory complaints, referral to geriatric psychiatry would be indicated for optimization of management for depressive symptomatology and further cognitive assessment. Medications that could be considered include duloxetine or nortriptyline each with important potential side effects to consider.

Figure 3: Algorithm for diagnostic evaluation of insomnia in elderly patient with sleep complaints.

OSA – obstructive sleep apnea; RLS – restless legs syndrome; PLMD – period limb movement disorder; RBD – REM sleep behaviour disorder



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