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Authors

Sankari, Abdulghani

Badr, M

Martin, Jennifer

et al.

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Impact Of Spinal Cord Injury On Sleep: Current Perspectives

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Abdulghani Sankari ^{1,2}
M Safwan Badr ^{1,2}
Jennifer L Martin ^{3,4}
Najib T Ayas⁵
David J Berlowitz ⁶⁻⁸

¹Department of Internal Medicine, John D. Dingell VA Medical Center, Detroit, MI, USA; ²Department of Internal Medicine, Wayne State University, Detroit, MI, USA; ³Geriatric Research, Education and Clinical Center, VA Greater Los Angeles Healthcare System, North Hills, CA, USA; ⁴Geriatric Research, Education and Clinical Center, David Geffen School of Medicine at the University of California, Los Angeles, CA, USA; ⁵Department of Medicine, The University of British Columbia, Vancouver, BC, Canada; ⁶Department of Physiotherapy, University of Melbourne, Melbourne, Australia; ⁷Department of Physiotherapy, Austin Health, Melbourne, Australia; ⁸Institute for Breathing and Sleep, Austin Health, Melbourne, Australia

Abstract: Sleep disorders are commonly encountered in people living with spinal cord injury (SCI). Primary sleep disorders such as sleep-disordered breathing (SDB), sleep-related movement disorders, circadian rhythm sleep-wake disorders, and insomnia disorder are common conditions after SCI but remain under-recognized, underdiagnosed and therefore remain untreated for a majority of patients. Sleep disturbances in people living with SCI are associated with significant impairments of daytime function and quality of life. Previous reviews have described findings related mainly to SDB but have not examined the relationship between other sleep disorders and SCI. This narrative review examines various sleep abnormalities and related functional and physical impairments in people living with SCI. It discusses new evidence pertaining to management, highlights existing limitations in the literature and recommends future directions for research.

Keywords: SCI, sleep-disordered breathing, leg movements, circadian rhythm sleep disorders, insomnia

Introduction

Sleep disorders are more common in individuals with spinal cord injury (SCI) than in the general population and likely contribute to reduced societal participation and quality of life.¹ Poor sleep quality is a consistent patient-reported outcome in populations with chronic SCI.²⁻⁶ Multiple factors may adversely influence sleep after SCI including very high rates of sleep-disordered breathing (SDB), particularly in those with high thoracic and cervical level injuries,⁷ high frequency of abnormal legs movements during wake and sleep,⁸ and poor sleep quality. The latter may be due to pain, insomnia and/or sleep-wake circadian rhythm disturbances.^{9,10} Subsequently, individuals living with SCI report daytime symptoms such as fatigue, excessive day time sleepiness,^{11,12} difficulties with concentration, and impaired quality of life. Furthermore, fatigue and excessive daytime sleepiness, have been associated with pain,¹³ depression,¹⁴ side effects of medications, spasticity,¹⁵ discomforts related to posture¹⁶ and autonomic dysfunction¹⁷ in people living with SCI. Interestingly, recent studies suggested that SCI does not in itself result in significantly impact of fatigue on health-related quality of life.¹⁸ However, approximately 40% of individuals with SCI were reported to be at risk of experiencing psychological disorder, such as depression and anxiety disorder.

In this narrative review and commentary, we examine the impact of SCI on sleep and daytime function. This paper is written to summarize current perspectives, provoke discussion and dialogue and to support the clinical practice of spinal,

Correspondence: Abdulghani Sankari
Division of Pulmonary, Critical Care and Sleep Medicine, 3990 John R, 3-Hudson, Detroit, MI 48201, USA
Tel +1 (313) 745-6033
Fax +1 (313) 745-8725
Email asankari@wayne.edu

rehabilitation, neurology, respiratory and sleep health professionals who provide care for people living with the complex co-morbidities of SCI. This paper is not intended to be a comprehensive systematic review; rather we have reviewed the existing literature exploring health risks due to the coexistence of sleep disorders and SCI. Of the recognized sleep disorders, we discuss and summarize the current evidence for the evaluation and management of the most prevalent and well-described conditions in SCI patients: sleep-disordered breathing (SDB), circadian rhythm sleep-wake disorders (CRSWD), insomnia, and periodic legs movements during sleep. Finally, we present the challenges faced in the management of these disorders and identify future directions for research.

Sleep-Disordered Breathing In SCI

Sleep-disordered breathing (SDB) is highly prevalent after SCI. While many studies noted the increased frequency of obstructive sleep apnea (OSA),^{10,19} there are reports of increased hypoventilation at sleep onset,²⁰ central sleep apnea (CSA) and narrow CO₂ reserve, a marker of increased susceptibility to CSA in cervical SCI.²¹ The severity of SDB is characterized by the apnea-hypopnea index (AHI) which is the number of times the airway narrows or closes per hour of sleep with arousals or desaturations of 3 or 4%. SDB is common in the general population of adults, with moderate to the severe disease present in approximately 10% of middle-aged (30–49 years) men, 3% of middle-aged women, and higher rates in older adults of both sexes.²² SDB seems to develop quickly after the onset of SCI; in a study by Berlowitz and colleagues, 62% of individuals with SCI assessed by full polysomnography (PSG) had SDB by four weeks post-injury. The study conservatively estimated that 10% of the cohort may have had SDB prior to the injury, indicating most developed SDB after the injurious event.²³ Chronically, SDB has a prevalence of 40–91% in SCI patients.^{2,24–28} The prevalence in people with paraplegia does not appear significantly different from what is seen in the general population; however, the literature is less comprehensive in this group owing partly to difficulties in completing diagnostic testing in patients with limited mobility.

Multiple mechanisms predispose to the development of SDB in SCI.²⁹ These include increase upper airway collapsibility,³⁰ a reduced dilator muscle responsiveness/effectiveness,³¹ a reduced arousal threshold,³² and an unstable ventilatory control system.²¹ The increased upper airway collapsibility can be due to multiple physiological

and/or anatomical factors. These include obesity (as indicated by increased specific measures of body habitus such as weight, body mass index (BMI), waist, abdominal, and neck girth) which is associated with OSA in both SCI²⁴ and the general population.³³ Obesity leads to narrowing of the upper airway by deposition in pharyngeal tissues including the tongue in both the general population and in SCI,^{22,34} in addition to the effect of reducing lung volume on decreased upper airway caliber during sleep.³⁵ In chronic SCI, most authors have observed associations between OSA prevalence and increasing age, BMI and neck circumference,^{24,25,27,36} but these relationships appear weaker in the acute, post-injury period.²³ Many individuals with SCI receive medications to control other symptoms that can affect breathing, including sedatives, muscle relaxants, and narcotics.³⁷ In addition, there is some cross-sectional evidence that loud snoring (a cardinal symptom of OSA) is associated with the use of anti-spasticity medications and obesity in SCI.³⁸

The loss of sympathetic modulation to the airways with resultant unopposed parasympathetic activation may result in bronchoconstriction in individuals with SCI,¹⁷ and in increased nasal resistance in tetraplegia.³⁹ Increased nasal resistance may contribute to upper airway narrowing by increasing negative pressure in the upper airway. There is no evidence that links bronchoconstriction to sleep disturbance in SCI and while a pilot study of the effect of nasal congestion in tetraplegia suggested a potential reduction in OSA severity,³⁹ the experiment requires replication with larger numbers and perhaps alternative decongesting medications.⁴⁰

Abnormalities of ventilatory control may also contribute to breathing instability and SDB after SCI. A recent study showed that the genioglossus reflex response to negative upper airway pressure (a protective reflex to maintain upper airway patency) was reduced in people with both OSA and SCI compared to those with OSA but without SCI. However, the mechanical corollary for this physiologic derangement is yet to be established.³¹ Also, accumulating data suggest that some patients with cervical spinal injuries may also experience CSA, perhaps related to a sleep onset hypoventilation and increased plant gain and a corresponding decrease in the CO₂ reserve.^{20,21,41} These physiologic abnormalities may predispose to upper airway collapse and consequent upper airway obstruction by reducing upper airway tone during periods of central apnea.⁴² Although these studies had small sample sizes and the underlying etiology of these ventilatory control abnormalities are unclear, it suggests the possibility that the mechanisms driving the increased prevalence and severity of SDB in

SCI may be different to those observed in the general population. Whether this may eventually lead to specifically tailored therapies for SDB in SCI is currently under research investigation.

Sleep-disordered breathing in tetraplegia may also be an etiologically bi-phasic disorder; acutely caused by the cervical SCI with partial resolution during injury recovery, only to increase again with age, weight gain, ongoing chronic intermittent hypoxia and the use of medications that compromise respiration.^{7,23,24} An association between cognitive performance and the severity of SDB has been described acutely after tetraplegic injury, impairments that persisted after adjustment for the known confounders of age and pre-injury estimates of verbal intelligence.⁴³ It is further suggested that an individual with acute tetraplegia and undiagnosed or untreated SDB may participate less in rehabilitation⁴⁴ due to sleepiness and fatigue⁴⁵ and therefore be less engaged in activities that improve quality of life and maintain functioning over time.

Consequences Of Sleep Disordered Breathing In SCI

Consistent with findings from individuals without SCI, people with chronic SCI and SDB suffer reduced cognitive function⁴⁶ that can be observed early after injury. A study of 104 people with acute tetraplegia by Schembri and colleagues found that severe OSA (AHI > 30) was associated with poorer attention, information processing, and recall compared to milder OSA.⁴³ The deficit in attention and information processing observed in those with severe OSA was large; equivalent to the expected decline after 31 additional years of aging. The substantial cortical reorganization has been well described after SCI⁴⁷⁻⁴⁹ and further research is required to understand the relative importance and time course of changes in generalized central nervous system inflammation,^{50,51} deafferentation,⁴⁹ functional connectivity,⁴⁸ and SDB.⁴³

People with SDB often report poor sleep quality and daytime sleepiness. Treatment with CPAP significantly improves daytime sleepiness in the general population with SDB.^{52,53} Likewise, untreated SDB is strongly associated with the incidence of cardiovascular and cerebrovascular disease including hypertension, strokes, and myocardial infarction.⁵⁴ The impact of SDB on cardiovascular health in SCI has not been well studied, though one study of 50 patients with tetraplegia noted increased cardiac medication use in patients with sleep apnea.²⁷ Given the high rates of cardiovascular disease in SCI patients, the associations between SDB and cardiovascular risks in SCI need to be further studied.¹²

Periodic Leg Movements

Periodic Leg Movements (PLM) are characterized by periodic episodes of repetitive and highly stereotyped limb movements, typically big toe and ankle dorsiflexion which is often accompanied by knee and hip flexion.^{8,55} The associated Restless Leg Syndrome (RLS), is characterized by uncomfortable leg sensations usually prior to sleep onset that causes an almost irresistible urge to move.⁵⁶ Both conditions can result in considerable disruption to sleep quality and are typically associated with excessive daytime sleepiness. Up to 80% of RLS patients also experience PLMS (Periodic Leg Movement syndrome), defined as five or more PLM events per hour of sleep.⁵⁷

The prevalence of periodic leg movement disorder (PLMD) appears to be markedly elevated in people with SCI. While the majority of previous samples are small and clinic-based rather than true population estimates, the prevalence in those with a lesion above T10 has been reported to range from approximately 50–100%.^{55,58-68} As detailed previously, SDB is also highly prevalent in tetraplegia,^{23,24} which precludes the diagnosis of PLMD according to the ICSD-3. For this reason, the American Association of Sleep Medicine (AASM) PLM scoring rules exclude events that occur from 0.5 seconds prior to or following a scored respiratory event. While some studies investigating PLMs excluded participants with SDB;⁵⁷ others have included participants with SDB and excluded PLM events adjacent to respiratory events as per the AASM rules,⁵⁹ and other authors made no reference to possible co-existent SDB.^{66,68} Peters et al recently collated 262 clinical and research sleep studies in people with tetraplegia.⁸ Similarly to the 2015 Prosperpio paper,⁵⁹ Peters excluded PLM events as per the AASM rules and observed an estimated prevalence (proportion with a PLM rate of > 15 events per hour) of 58%. No significant difference was observed in PLM prevalence or severity between participants with or without SDB. The arousal index was associated with the SDB severity, but not with the PLM index.⁸ Similarly, Salminen et al published a clinical case strongly suggesting SDB and PLM are independent phenomena in tetraplegia.⁵⁸ As such, it appears that PLMD is common in SCI, especially in tetraplegia and is not substantially modified in prevalence or severity by SDB.

Effect Of SCI On Circadian Rhythm Sleep-Wake Disorders (CRSWD)

There is evidence that the circadian rhythmicity of melatonin is disrupted in tetraplegia. Following a complete

cervical SCI, the afferent input of somatic and autonomic fibers below the SCI is disrupted and the efferent sympathetic innervation of the pineal gland via the superior cervical ganglion is interrupted. During the daytime, light striking the retina stimulates afferent pathways through the suprachiasmatic nuclei that in turn pass to the superior cervical ganglion and onward to the pineal gland to inhibit melatonin production. Darkness removes this inhibition and melatonin production ensues. The fibers from the suprachiasmatic nuclei travel with the sympathetic fibers which exit the spine between the first and sixth thoracic levels before ascending outside the spinal cord to the superior cervical ganglion. Fibers then pass back into the cortex and innervate the pineal gland. In 2000, Zeitzer and colleagues showed that complete cervical SCI, which cuts the suprachiasmatic nuclei to superior cervical ganglion pathway, is associated with near abolition of circadian melatonin rhythmicity and a markedly reduced circulating level.⁶⁹ These findings have been replicated by others.^{70–74} Other endocrine rhythms similarly modified by circadian influences, such as cortisol and thyroid-stimulating hormone, do not appear markedly affected by cervical SCI, however, the temperature is affected.⁷⁵ Thijsen et al observed a substantial phase advancement of temperature in tetraplegia. Core temperature phase and amplitude of change in paraplegia were not different from the non-disabled control participants. The temperature phase advance observed in tetraplegia may be yet another contributor to the poor sleep quality reported in this group.

Whether SCI affects sleep timing per se is similarly unclear. Delayed REM onset has been reported in a community survey and home PSG study of 78 people with tetraplegia.²⁴ Participants with motor and sensory complete lesions (ASIA A, $n=35$ mean REM latency in minutes of 145 (SD=82)) took significantly longer to attain first REM than those with incomplete lesion (AIS B-E, $n=43$, 94(58.5) minutes) although OSA was also more severe in those with complete lesions potentially confounding this finding. Further, while sleep complaints in SCI are frequent,^{6,10,19,24,76–78} and anecdotally, delayed sleep phase is reported in SCI, the relative contribution of environmental, social and physiological effects remains unclear. As detailed above,⁷⁵ temperature phase is substantially advanced in tetraplegia but it is unclear if or how this interacts with melatonin dysregulation to affect sleep. Highly prevalent PLMD and SDB further complicate symptomology, diagnosis, and management.

Effect Of SCI On Insomnia

Insomnia is highly prevalent in the general population, with estimates ranging from 15–30%, and women having a 1.4 times higher risk than men for insomnia.⁷⁹ Insomnia disorder, defined as difficulty falling or staying asleep that persists for at least three months, occurs at least three nights per week and is accompanied by daytime consequences, is likely less common, but estimates still suggest rates of 10–20% in the population.⁷⁹ A recent study using the Sleep Heart Health Study Sleep Habits Questionnaire found that 57% of SCI individuals had insomnia symptoms,⁷⁸ although it is not clear that these individuals would meet criteria for insomnia disorder as they also had significantly higher risk for SDB and had greater differences in weekday/weekend sleep which may be associated with insufficient sleep rather than insomnia disorder. This does suggest that evaluation for insomnia disorder is useful in understanding the effect of other sleep disorders experienced by individuals with SCI and can affect the choice of treatment.

Evaluation Of Sleep Disorders In Individuals With SCI

SDB is underdiagnosed in this population, and this is likely true for other sleep disorders as well.⁸⁰ Given the high prevalence of sleep disorders in SCI, any substantial sleep-related complaints should be further evaluated so that appropriate treatment can be initiated. Common symptoms include daytime fatigue/sleepiness, poor quality sleep, nocturnal awakenings, and witnessed apneas. These symptoms are not specific and further assessment is usually required to identify the correct diagnosis. The gold standard for diagnosis of SDB and periodic legs movements is full night attended PSG in the sleep laboratory; however, access to these facilities is often limited with substantial wait times.⁸⁰ In addition, many laboratories are not equipped to handle the requirements of individuals with SCI (eg, lifts, special beds for pressure care, adequate staff) representing another barrier to diagnosis. Home sleep apnea testing may provide an alternative diagnostic tool for SDB in these patients. This could include full PSG (including EEG recording) in the patients' homes, which similar to what is done in sleep laboratories (Type II studies). However, costs and resources required for these are substantial, and often not feasible outside of a research setting. Another possibility is truncated Type III or oximetry studies, which record some of the physiologic signals included in PSG but lack

others (e.g. EEG and EMG). These systems can be more easily set up in the home and have been used for SCI screening.⁸¹ The study by Bauman et al coupled a Level III device with transcutaneous carbon dioxide monitoring and observed similar sample prevalence (81%) as has been previously described, albeit at the upper end of the prevalence estimate ranges. A more recent study suggests that the incorporation of a tetraplegia-specific questionnaire with oximetry had reasonable sensitivity (77–83%) and specificity (81–88%) in detecting moderate to severe SDB.⁸⁰ The Graco et al model was compared with full PSG and as such is currently the best-validated, population-based screening approach available.

Management Of Sleep Disorders In Individuals With SCI

Treatment Of Obstructive Sleep Apnea

Treatment of SDB in people living with SCI is challenging, although substantial symptomatic improvements may be observed in many individuals. Although not studied in SCI, lifestyle interventions including exercise and weight loss⁸² should be encouraged as these have positive effects on SDB in the general population, and there is no reason to assume a lack of benefit in SCI.⁸³ The most commonly used treatment for SDB is continuous positive airway pressure (CPAP) which consists of a mask attached to the nose/face that administers a positive pressure to the upper airway preventing its collapse during sleep. CPAP is effective in eliminating obstructive events during sleep and improving oxygenation. One of the major limitations of CPAP is poor adherence, with only about 50% of patients being able to adhere to the therapy on a long-term basis.⁸⁴ Given the challenges related to arm strength/mobility in tetraplegia, and additional factors such as increased nasal congestion, it is perhaps not surprising that only 20–50% of people with chronic SCI and SDB are reported to adhere with CPAP.^{2,25,27,85,86} The less claustrophobic nature of nasal pillows may mean that they are well suited to tetraplegic users and the lower pressures required by many CPAP users with tetraplegia allows for greater flexibility in interface choice as leak is less likely at lower pressures.⁸⁷

The nature of the barriers to diagnosis and management of sleep disorders in SCI has recently been explored qualitatively through interviews with 20 specialist spinal medical practitioners from the UK, USA, Canada, Europe, and Australia.⁸⁸ Commonly reported barriers to independent

management practices were lack of skills, low confidence about capabilities, and the belief that SDB management was outside their scope of practice. The three spinal units independently managing SDB were well resourced with multidisciplinary involvement and “clinical champions” to lead the program.

The experiences of people living with SCI and comorbid SDB and the relationships of these experiences to concordance with CPAP prescription has also been reported recently.⁸⁶ Sixteen people with SCI and newly diagnosed SDB were provided with CPAP and participated in semi-structured interviews one month later. Usage was then reviewed at one, six and 12 months. The perceived balance of benefits versus burdens strongly influenced the ongoing level of use in study participants. Burden attributed to CPAP use was common and included mask discomfort and physical and emotional problems. Adherent participants were motivated by the immediate daytime benefits to mood, alertness, and reduced sleepiness. There was a tendency for patients to fail to recognize symptoms of SDB until after they were treated with CPAP. These practical challenges to the use of CPAP for SDB in tetraplegia and the uncertainty as to the real benefit of the therapy in SCI likely limit the ability of clinicians to provide evidence-based advice to their patients and for people with SCI to value the therapy.

Berlowitz et al recently assessed the effectiveness of CPAP in among individuals with acute SCI.⁸⁹ One hundred and sixty patients were randomized to CPAP or no CPAP for three months. Sleepiness was significantly improved with CPAP ($p=0.01$) though other cognitive parameters were unchanged. One issue was that CPAP adherence was relatively low in the study (2.9 hrs/night, with 21% achieving >4 hrs per night) despite only randomizing patients who were able to tolerate a three-day CPAP run-in period. The fact that sleepiness was improved with CPAP despite only partial adherence is encouraging and suggests that if adherence could be improved, more substantial benefits could be achieved.

Whether other ventilator modes, such as bilevel therapy, might be more effective in this patient group has been explored in a recent case series.⁹⁰ A combination of bilevel PAP support (for upper airway dysfunction) and bilevel PAP with volume assured pressure support (for SDB plus hypoventilation during sleep but not daytime) were used to support people with SCI (74% quadriplegia) and SDB over 12 months. If those lost to follow-up in this

cohort paper are assumed to be non-adherent, then overall PAP use of 28% at 3 months is similar to the 21% observed in the *COSAQ* (CPAP treatment for obstructive sleep apnea after acute quadriplegia) study, suggesting that the type of PAP is not a determinant of adherence.

An additional but frequently overlooked confounder to the interpretation of PAP use in clinical studies is the influence of government or privately funded diagnosis and treatment on practice. If, for example, an accident compensation system will only support one PAP device per patient, almost regardless of complexity, then clinicians and patients may well choose a more complex device. Conversely, if reimbursement requires a “step-wise” increase in complexity of treatment with evidence of failure before progression (CPAP to bi-level to controlled ventilation), then practice may well be different. Increased sleep onset ventilatory instability²⁰ and a reduced carbon dioxide reserve²¹ may well predispose people with tetraplegia to pressure support induced central apnea and sleep fragmentation. In such a case, CPAP at low pressures may be best while similarly, controlled (timed) ventilation could be indicated. We are unaware of any papers that have directly compared different PAP therapies for acceptance, usage, and efficacy in SCI as has been reported in conditions such as obesity hypoventilation syndrome.⁹¹ This paucity of literature impedes evidenced-based care and should be considered in future research priority setting exercises.

Other alternative treatments for SDB include upper airway surgery,^{92,93} hypoglossal nerve stimulation,⁹⁴ and dental appliances.⁹⁵ We are not aware of studies of these modalities in SCI, but anecdotally, some patients may respond physiologically and symptomatically and they may be considered in selected cases where risks do not outweigh the possible benefits. A recent pilot, cross-over controlled trial assessed the potential for nasal decongestion to reduce the AHI in tetraplegia.⁹⁶ No significant difference in SDB severity was observed although a trend to less severe respiratory events (more hypopneas versus apneas) was observed, similar to that observed in the general population with SDB.⁴⁰ More research into these alternative treatment measures is clearly necessary in cases of SCI.

Treatment Of Periodic Leg Movements In SCI

The origin of PLMs in the general population is generally not well understood. The clinical effectiveness of dopaminergic

agents led to the conclusion that the central brain or hypothalamic dysfunction drove the peripheral events. PLMs predominate in non-rapid eye movement (NREM) sleep in the general population, but in contrast, a number of case reports and series in SCI suggest that PLM may be observed throughout REM and without clear periodicity.^{8,55,57,58,66,68} This observation strongly suggests that PLM after SCI arises peripherally rather than centrally. Interventions which alter cortical arousal in SCI do not necessarily result in a reduction in PLM and similarly, inhibition of PLM does not necessarily reduce sleep disruption.^{56,58} Further, a recent case series evaluated PSG data in both SCI and Multiple Sclerosis from a spasticity clinic population who were typically referred for refractory “spasticity” despite often maximal anti-spasticity therapy. The study explored the possibility that spasticity was, in fact, undiagnosed and/or untreated PLM and showed a substantial reduction in PLM index and arousals from sleep in those with confirmed PLM (≥ 15 per hour of sleep) treated with a low dosage of pramipexole.⁹⁷ Taken together, these data suggest that there is likely clinical utility in SCI, especially where movements predominate in supine and during sleep, in assuming the distressing movements are PLM, not excess spasticity and treated with dopaminergic agents as first-line therapy. Polysomnography will obviously assist with differential diagnosis and more controlled trials are needed.

Treatment Of Insomnia In SCI

There are multiple challenges in treating insomnia disorder among individuals with SCI. First, pharmacological agents have a number of adverse effects that may be even more significant among individuals with SCI. For example, fall risk among those who ambulate may be elevated further, and impaired cognition may be exacerbated. As a result of these and other concerns, pharmacological therapy is recommended only after cognitive-behavioral therapy for insomnia (CBT-I) has been attempted.⁹⁸ CBT-I is a multi-component psychological treatment that includes behavioral techniques (stimulus control, sleep restriction therapy, sleep hygiene and relaxation/arousal reduction strategies) plus cognitive therapy to address sleep-related thoughts and beliefs. While no formal studies of CBT-I have been conducted in SCI, a systematic review found evidence that cognitive-behavioral therapies, in general, are helpful for anxiety, depression, adjustment, and coping problems.⁹⁹ Furthermore, there are studies of CBT-I treatments, using an adaptation of the standard behavioral techniques (e.g.,

eliminating the recommendation to get out of bed in the middle of the night if unable to sleep; addressing disease-specific cognitions) in populations with functional impairments,¹⁰⁰ and this approach may be extrapolated to SCI. Overall, SCI should not prevent people from being offered the best-available evidence-based treatment for insomnia disorder if the person is interested in a non-pharmacological approach.

There is also evidence that insomnia disorder can increase the risk for intolerance of positive airway pressure (PAP) therapy for SDB.¹⁰¹ As a result, it may be necessary to address insomnia symptoms when PAP therapy is initiated as patients with SCI already have significant challenges to PAP use due to limitations in physical function and other factors as outlined earlier.⁸⁶

Treatment Of CRSWD In SCI

Despite the clear abnormalities of circadian control in SCI and the availability of melatonin, little work has been undertaken to understand its potential therapeutic role in SCI, particularly in tetraplegia. Chronic melatonin supplementation is often used by people with blindness to counter circadian desynchronization brought on by their visual impairment and the associated jet-lag type symptoms.^{102,103} People living with tetraplegia are essentially 180 degrees out of circadian phase all of the time and as such, appropriately timed exogenous melatonin may offer unique opportunities for sleep-onset insomnia and sleep phase entrainment.

A small size pilot study⁷¹ and two subsequent randomized controlled, cross-over trials^{72,104} have demonstrated the safety of exogenous melatonin in tetraplegia. While the studies suggested some subjective improvements in sleep, both trials were underpowered statistically to demonstrate any effect on objective sleep variables. More recently, Kostovski and colleagues have shown that exogenous melatonin administration in tetraplegia can normalize clock gene expression in peripheral blood.⁷⁴ The symptomatic and longer-term physiological effects of these changes are as yet unknown.

Future Directions

Despite the increased prevalence of sleep disorders in individuals with SCI, the majority are under-recognized and untreated with several challenges in their management. Future studies could focus on the following knowledge gaps:

- Studies to determine the epidemiology and clinical manifestations of sleep disorders in individuals with

SCI are sorely needed. One particular challenge is that the parameters used for disease definition were based on observations in the general population.

- Individuals living with SCI often suffer from more than one sleep disorder, and studies on combined treatments for those with multiple sleep disorders are warranted.
- The underlying mechanisms of sleep disorders remain unclear and likely are related to physiological and behavioral changes that follow SCI. There is a critical need to identify mechanistic pathways using human as well as animal models. Such knowledge will inform the development and the testing of novel pharmacological treatments that are both effective and tolerable.
- Management of sleep disorders in this population remains a challenge given the complex clinical presentations and care needs. Likewise, there is a need to examine the positive impact of treating sleep disorders on societal participation, quality of life and function.
- The comparison of different PAP therapies for acceptance, usage, and efficacy in SCI remains unstudied.
- The effect of non-pharmacological treatments such as respiratory muscle training/exercises, dental appliances or nerve stimulation on treating SDB in SCI can inform alternative treatments when PAP therapy is not well-tolerated.
- The effect of non-pharmacological treatments such as behavioral interventions on treating insomnia and the adaptation and testing of CBT-I in SCI can lead to impactful improvements in daytime functioning and facilitate adjustment to PAP therapy in individuals with comorbid SDB and insomnia disorder.

Conclusion

The extant literature on the impact of SCI on sleep is limited and heterogeneous. While advances have been made recently on understanding the mechanisms and optimizing management of SDB after chronic SCI, other sleep disorders remain unstudied. Future studies could identify the particular expression of the disease, assess new therapies beyond traditional treatments, and determine predictors of treatment efficacy. A focus on developing standardized approaches along with measures of treatment efficacy could also provide more information on the efficacy of individual treatment components. A multidisciplinary approach to management is recommended given the overlap of sleep disorders and other co-morbid conditions in individuals

with SCI. A comprehensive management approach should include behavioral and pharmaceutical therapies, and be aligned with ongoing management and rehabilitation goals.

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