

## **Sleep Medicine Clinics Issue:**

A review of PAP therapy for the treatment of OSA

## **Title:**

Co-morbid insomnia and sleep apnea (COMISA): Assessment and management approaches.

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## **Disclosure Statement:**

DMW has no conflicts of interest to declare. AS and LL declare research funding and equipment support from the National Health and Medical Research Council (NHMRC), Flinders Foundation, ResMed, and Philips Respironics. AS is supported by a NHMRC Centres of Research Excellence grant (GNT1134954). LL has received research funding and is a shareholder of Re-time Aus. MC has received research funding from Brain Research UK and Chief Scientist Office.

## Key points

- ⌚ Approximately 30-50% of patients with obstructive sleep apnea (OSA) in sleep clinics report co-morbid insomnia symptoms.
- ⌚ Patients with co-morbid insomnia and sleep apnea (COMISA) have worse sleep, mental health, physical health, and quality of life, compared to patients with either insomnia or sleep apnea alone.
- ⌚ Patients with COMISA use positive airway pressure (PAP) therapy for fewer hours per night, compared to patients with sleep apnea alone. Consequently, it is important to identify and manage insomnia symptoms among patients with OSA.
- ⌚ Cognitive behavioral therapy for insomnia (CBTi) is recommended as the 'first line' treatment for insomnia. CBTi is an effective insomnia treatment in the presence of untreated OSA. CBTi may also reduce severity of OSA and improve adherence to PAP therapy in patients with moderate and severe OSA.
- ⌚ Many sleep clinics world-wide currently specialize in the diagnosis and management of OSA alone. Sleep clinics should incorporate insomnia assessment tools, and evidence-based insomnia treatment and referral pathways, to provide personalized care for patients with COMISA. Potential CBTi options include self-guided digital programs, brief behavioural treatment programs, and provision of CBTi from trained therapists or psychologists.

### Keywords:

COMISA, OSA, PAP therapy; PAP adherence, CBTi; cognitive behavioral therapy for insomnia

## Synopsis

Co-morbid insomnia and sleep apnea is a highly prevalent and debilitating condition that is more difficult to treat compared to insomnia alone or sleep apnea alone. Approximately 30-50% of sleep clinic patients with sleep apnea report co-morbid insomnia symptoms. Co-morbid insomnia is associated with lower adherence to positive airway pressure therapy for OSA. Management approaches that include targeted treatments for both insomnia and sleep apnea lead to the best treatment outcomes for patients with COMISA. Therefore, sleep clinics should incorporate insomnia and COMISA management pathways including access to cognitive behavioral therapy for insomnia.

## Introduction

Insomnia and obstructive sleep apnea (OSA) are the two most common sleep disorders and frequently co-occur<sup>1</sup>. The co-occurrence of insomnia and OSA in the same person was first recognised in 1973, however co-morbid insomnia and sleep apnea (COMISA) has only begun to receive an increased amount of research and clinical attention in the past 10-15 years<sup>2</sup>. COMISA results in greater morbidity for patients and more complex diagnostic and treatment decisions for clinicians compared to either insomnia or OSA alone<sup>2</sup>. There is evidence that adjunct assessment and management of co-morbid insomnia in people with OSA can contribute to improved sleep, mental health quality of life, and adherence to OSA therapy. Therefore, it is important to identify and manage co-morbid insomnia symptoms among patients with OSA in sleep clinic settings.

OSA is characterized by frequent collapse (apnea) and narrowing (hypopnea) of the upper airway during sleep that result in reduced oxygen saturation, changes in sympathetic activity, and cortical arousals from sleep. This commonly results in fragmented sleep architecture, frequent nocturnal awakenings, and daytime sleepiness and fatigue. OSA results from a combination of anatomical traits (e.g. reduced upper airway size) and non-anatomical traits (low respiratory arousal threshold, poor upper airway muscle response, and loop-gain)<sup>3,4</sup>. The most common index of OSA presence and severity is the apnea-hypopnea index (AHI), which represents the average number of apneas and hypopneas per hour of sleep. Approximately 10-20% of the general population have moderate OSA (AHI  $\geq$  15), although prevalence rates may be much higher<sup>5-7</sup>. OSA results in substantial societal costs through healthcare use, reduced quality of life, and reduced workplace productivity<sup>8,9</sup>.

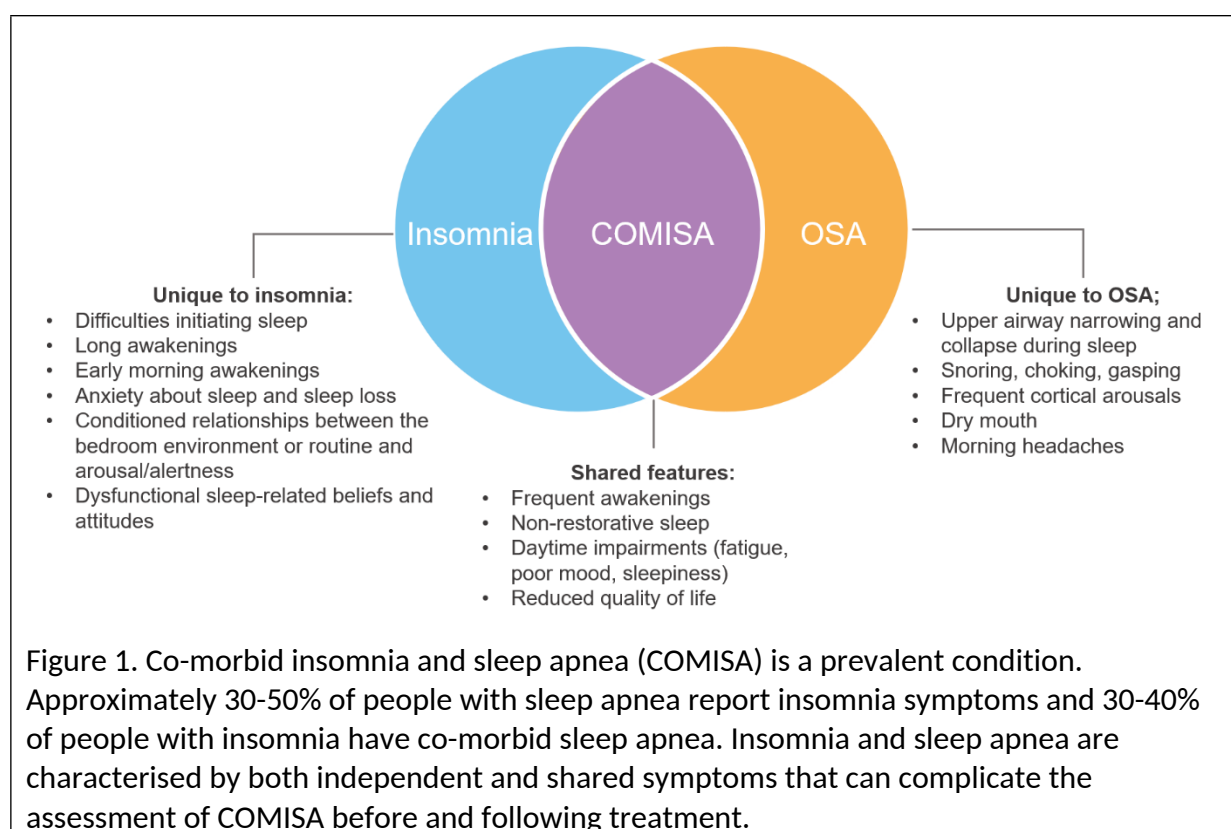
Insomnia is characterized by frequent self-reported nocturnal symptoms, and associated daytime impairments<sup>10</sup>. Nocturnal symptoms include difficulties initiating sleep, maintaining sleep, and/or undesired early morning awakenings, while common daytime symptoms include feelings of fatigue, concentration difficulties, lethargy, poor mood, difficulties with workplace productivity and increased effort to perform daytime activities<sup>11</sup>. Insomnia may be characterized as an acute (<3 months) or chronic condition ( $\geq$  3 months). Chronic insomnia occurs in approximately 6-15% of adults<sup>12,13</sup>, and is associated with reduced mental health<sup>14,15</sup>, and high societal costs through healthcare use, reduced productivity and impaired quality of life<sup>16</sup>. Insomnia frequently co-occurs with other sleep, mental and physical health problems<sup>15</sup>. When co-occurring with other conditions, insomnia symptoms should be conceptualized as a functionally independent 'co-morbid' condition, rather than a 'secondary symptom'<sup>17</sup>. This is because co-morbid insomnia often shares bi-directional relationships with other disorders<sup>18</sup>, responds to targeted insomnia treatment<sup>19</sup>, can undermine management of the co-morbid condition if untreated (e.g. depression<sup>20</sup>, sleep apnea<sup>1</sup>), and because treatment of the insomnia can also improve management of the co-morbid condition<sup>21,22</sup>. As discussed below, this also applies to management of co-morbid insomnia in the presence of OSA.

## Co-morbid insomnia and sleep apnea (COMISA)

### Prevalence of COMISA

The prevalence of COMISA has been investigated in different settings including sleep clinics specializing in management of OSA, specialist insomnia clinics, primary care settings,

military and veteran populations, and in the general population<sup>1,23,24</sup>. It is difficult to estimate the precise prevalence of COMISA, which differs depending on the setting, sampling methods, measures, and specific criteria applied to define each condition<sup>25</sup>. Importantly, the prevalence of COMISA also differs considerably, according to which condition is defined as the 'denominator'<sup>26</sup> (E.g. the prevalence of co-morbid OSA in patients with insomnia, the prevalence of co-morbid insomnia in patients with OSA, or the prevalence of COMISA in the general population). Approximately 30-40% of people with insomnia have co-morbid OSA, and 30-50% of people with OSA report co-morbid insomnia symptoms<sup>18</sup> (Figure 1). Most studies investigating the co-morbidity of insomnia and OSA in population-based samples have also reported that insomnia and OSA frequently co-occur<sup>24,26</sup>.



### Characteristics

Compared to people with insomnia alone or OSA alone, those with COMISA experience worse self-reported and objective sleep<sup>27-29</sup>, daytime function<sup>27,29</sup>, mental health<sup>30,31</sup>, and quality of life<sup>26,32</sup>. There is evidence that COMISA is also potentially associated with increased risk of cardio-vascular disease and all-cause mortality in population-based samples<sup>33-35</sup>. A recent study by Lechat and colleagues<sup>36</sup> used the Sleep Heart Health Study to investigate the association of COMISA, insomnia alone, OSA alone, and neither insomnia nor COMISA on risk of all-cause mortality. Participants with COMISA had an increased risk of all-cause mortality (HR = 1.47, CI = 1.06, 2.07) over 15 years of follow-up, compared to participants with neither insomnia/OSA. Insomnia alone and OSA alone were not associated with increased mortality risk. It is possible that the higher morbidity observed in people with COMISA may result from additive effects of the two overlapping sleep disorders, additional co-morbidities that may increase risk of COMISA and morbidity, or interactive effects

between the mechanisms and manifestations of insomnia and OSA on mental and physical health<sup>18,37</sup>. It is also possible that additional sleep-related circadian factors play an important role in the development of COMISA and associations with physical and mental health<sup>38</sup>. Bi-directional relationships between the underlying mechanisms and surfacing symptoms of insomnia, OSA and disturbed sleep, and the impact of these inter-relationships on overall health require further research<sup>18</sup>.

### Secondary versus co-morbid insomnia

Diagnostic criteria for chronic insomnia indicate that the sleep-wake difficulty should not be better explained by another sleep disorder<sup>10,39</sup>. Insomnia symptoms may be a direct consequence of apnea and hypopnea events among a sub-sample of patients with untreated OSA<sup>40</sup>. However, among most patients with COMISA, research indicates that the insomnia responds to targeted insomnia treatment<sup>29,41</sup>, and that insomnia symptoms frequently persist following management of the OSA alone<sup>40,42</sup>. Research has also demonstrated that independent treatment of both conditions improves overall management of patients with COMISA<sup>1,2,43</sup>. Furthermore, it is difficult to determine causal associations between insomnia and OSA according to baseline symptoms alone<sup>44,45</sup>, and there is evidence suggesting that insomnia and OSA share bi-directional relationships<sup>18</sup>. Therefore, insomnia should be conceptualized as a functionally independent ‘co-morbid’ condition with OSA to encourage targeted assessment and management approaches for both conditions.

### Sociodemographic factors in COMISA

Some sociodemographic groups may be at increased risk for COMISA but may have a varied clinical presentation that subsequently impacts diagnosis and management. For example, sex differences occur in the presentation of COMISA, with women more likely to report insomnia symptoms and men more likely to report witnessed apneas<sup>46,47</sup>. Additionally, the “disturbed sleep” OSA phenotype is more common among women than men with OSA<sup>48,49</sup>. Age is a known risk factor for both OSA and insomnia, and older age appears to be a risk factor for COMISA<sup>50</sup>. In regards to OSA treatment, both age and sex influence adherence to PAP therapy with younger women using PAP less regularly than older men<sup>51,52</sup>. Despite these age and sex differences in OSA clinical presentation, the treatment approaches and outcomes of COMISA therapies have not been evaluated comprehensively in women versus men or in younger versus older individuals.

Race and ethnicity are other important demographic factors to consider in the presentation and treatment of COMISA. In one study, the OSA “disturbed sleep” phenotype had the highest proportion of Blacks relative to the other four OSA subgroups<sup>48</sup>. Blacks may have increased prevalence of OSA relative to Whites but poorer adherence to both PAP therapy and cognitive behavioral therapy for insomnia (CBTi)<sup>53,54</sup>. Blacks, who on average sleep one hour less than White individuals, may find the sleep restriction component of CBTi particularly difficult, since their prescribed bedtime window (which is calculated based on their total sleep time) would be lower on average<sup>55</sup>. To date, differences in race/ethnicity have received insufficient attention in randomized controlled trials (RCTs) on COMISA. Thus, it is unknown if these could serve as moderators of treatment outcomes or whether treatments should be culturally/linguistically tailored or delivered via alternative pathways (e.g., from trusted community members such as community healthcare workers).

### Assessment of insomnia symptoms

Given that insomnia and OSA are both sleep disorders that impact daytime function, they share several overlapping symptoms (Figure 1). These shared symptoms can complicate the assessment and diagnosis of insomnia in the presence of OSA. For example, both insomnia and OSA result in more frequent nocturnal awakenings from sleep and are each associated with daytime impairments including poor mood, fatigue, and lethargy<sup>10,56</sup>. This 'shared symptoms' phenomenon can complicate assessment of insomnia symptoms before treatment and after treatment (e.g. assessing reduction in insomnia following PAP therapy). While OSA *and* insomnia result in more frequent brief awakenings from sleep, difficulties returning to sleep after awakening may be a unique symptom of insomnia.

In sleep clinic samples, simple self-report tools can be used to assess patients for insomnia symptoms. For example, the Insomnia Severity Index<sup>57</sup> is a 7-item self-report tool that measures severity of nocturnal and daytime insomnia symptoms. Higher scores indicate greater insomnia severity. The Sleep Condition Indicator<sup>58</sup> is an 8-item self-report questionnaire for insomnia that maps onto DSM-5 diagnostic criteria. Lower scores indicate worse sleep, with a score of 0-16 representing probable insomnia. Because both insomnia and OSA result in similar daytime symptoms, it is important to specifically focus on the presence of nocturnal insomnia symptoms, rather than only the 'total' insomnia score of the Insomnia Severity Index or Sleep Condition Indicator, in which daytime symptoms of OSA may contribute heavily to the total insomnia scores<sup>59,60</sup>.

One week self-report sleep diaries are a useful tool in the assessment of insomnia<sup>61</sup>. Patients can use sleep diaries to self-report their sleep and wake times, when getting out of bed each morning for one week. Average nightly sleep onset latency, sleep time, time in bed, wake after sleep onset, and sleep efficiency can be calculated at the end of the week. Sleep diaries can be used to provide an indication of the main types (e.g. sleep onset insomnia, sleep maintenance insomnia, early morning awakening insomnia), timing (e.g. an 'early' or 'late' timed body clock), and night-to-night variability/regularity of bedtime behaviors and insomnia symptoms.

### Management approaches for COMISA

An overview of management approaches for COMISA is presented in Box 1.

**Box 1. Overview of management approaches for COMISA**

- ⌚ Patients with confirmed/suspected OSA should be screened for insomnia symptoms and patients reporting insomnia should be assessed for high-risk OSA.
- ⌚ Treatments for both disorders should be made available to patients with COMISA.
- ⌚ Treatment sequence may be guided by the patient's chief complaint, severity and temporal onset of symptoms, lifestyle and occupation, co-morbid conditions, daytime sleepiness (motor-vehicle risk), and preference for treatment.
- ⌚ Patients with COMISA have worse acceptance and lower average nightly use of PAP compared to patients with OSA-alone. A sub-sample of patients with COMISA have adequate PAP use, which improves both the insomnia and OSA. Ongoing research aims to identify this sub-group, to improve precision medicine approaches.
- ⌚ Cognitive behavioral therapy for insomnia (CBTi) is the recommended 'first line' treatment for chronic insomnia. CBTi is an effective treatment in patients with COMISA and may improve PAP use in those with moderate and severe OSA. Although patients with insomnia alone rarely present with excessive daytime sleepiness, patients with COMISA that present with elevated daytime sleepiness should be monitored closely for increases in daytime sleepiness during the first 2-3 weeks of 'sleep restriction therapy'. See Table 4 for an overview of CBTi components.
- ⌚ Sedative-hypnotic medicines are the most common approach to manage insomnia. Early evidence indicated that certain sedative-hypnotics exacerbated OSA in some patients. More recent evidence suggests that specific medicines and combination-medicine approaches may be well tolerated in OSA patients with specific underlying phenotypic traits. Research on sedative-hypnotic medicine tolerance and effectiveness in COMISA is emerging.
- ⌚ Some non-PAP therapies for OSA (e.g. mandibular advancement splints, surgery) may be effective and well tolerated in specific patients with COMISA. Non-PAP therapies can also be limited by reduced adherence and effectiveness in patients with COMISA compared to those with OSA alone, and research to guide precision medicine approaches is needed.

### Insomnia symptoms reduce positive airway pressure adherence

Although continuous PAP therapy is the recommended first line treatment for moderate and severe OSA, many patients find it difficult to use pressurized masks for the duration of sleep<sup>62</sup>. Consequently, PAP therapy is limited by high rates of immediate rejection, and poor nightly use over time<sup>63</sup>. Patients with insomnia, who already have greater difficulties falling asleep at the start of the night, long awakenings throughout the night, and sleep-related anxiety and catastrophizing beliefs, may have greater difficulty accepting and using PAP therapy, compared to OSA patients without insomnia<sup>1</sup>. It is also suggested that mask discomfort, pressure leaks, and mechanical constraints may exacerbate pre-existing insomnia symptoms, and reduce PAP adherence<sup>64</sup>. Several case studies and pilot studies have provided important initial qualitative evidence of the impact of co-morbid insomnia on acceptance and use of PAP therapy<sup>65-67</sup>.

A large number of studies investigating the association of co-morbid insomnia symptoms with PAP acceptance and use are reported in Tables 1-3. Variability in study designs, samples, definitions of insomnia and measures of PAP adherence make it difficult to synthesize this literature into a single 'effect size' estimate. Most studies in this area suggest that patients with lower nightly PAP use are more likely to report insomnia symptoms (cross-sectional associations), and that pre-existing insomnia symptoms are associated with lower rates of future PAP adherence (longitudinal associations). Consequently, introducing PAP as the 'first line' treatment for COMISA may result in high rates of treatment rejection and sub-optimal adherence, thereby leaving both disorders untreated.

Table 1. Association of insomnia symptoms and adherence to Positive Airway Pressure therapy (1997 – 2013).

Study	N, age (mean), sex, BMI (mean)	Insomnia measure and prevalence	PAP outcome and effect of insomnia on PAP adherence
Weaver et al., 1997 <sup>68</sup>	32 patients with confirmed OSA, Age = 47, 81% male, BMI = 40.	After 1 month of PAP, 42% of patients reported difficulties initiating sleep, and 59% of patients reported frequent awakenings.	Patients were divided into 'consistent' vs 'intermittent' PAP users at 3-month follow-up. There was no difference in difficulties initiating sleep between patients characterised as 'consistent' (38%), versus 'inconsistent' (47%) PAP users. There was no difference in frequent awakenings between patients characterised as 'consistent' (44%), versus 'inconsistent' (80%) PAP users.
Smith et al., 2009 <sup>69</sup>	52 consecutive OSA patients recommended for PAP.	57% had at least 'moderate' difficulties initiating sleep.	Objective PAP use at 12 months. Average PAP use was lowest in patients with severe/very severe difficulties initiating sleep (2.7h/night), compared to those with mild/moderate (5.5h/night), or no difficulties initiating sleep (6h/night).
Nguyen et al., 2010 <sup>70</sup>	148 OSA patients, Age = 55, 82% male, BMI = 29.	49% of patients had a ISI score $\geq 15$ .	Objective PAP use and 'rejection' were assessed at 1 and 6 month follow-up. No difference in PAP outcomes were observed between patients with high/low ISI.
Wickwire et al., 2010 <sup>71</sup>	232 OSA patients, Age = 54, 56.5% male, BMI = 34.	16.6% reported difficulties initiating sleep, 23.7% reported difficulties maintaining sleep and 20.6% reported early morning awakening difficulties.	Average nightly PAP use and levels of adequate 'adherence' ( $\geq 4$ h/night on 70% of nights). After controlling for gender and age, difficulties maintaining sleep predicted lower PAP use and rates of PAP 'adherence' at follow-up (variable range of follow-up periods).
Pieh et al., 2012 <sup>72</sup>	73 OSA patients, Age = 55, 67% male, BMI = 31.	Regensburg Insomnia Scale (10-item questionnaire).	PAP use was assessed over 6 months of use. Insomnia symptoms at baseline were not associated with PAP 'rejection', but were associated with total PAP use over the first 6 months.
Bjornsdottir et al., 2013 <sup>40</sup>	705 patients with OSA, Age = 55, 80.6% male, BMI = 34.	Basic Nordic Sleep Questionnaire: 68% were classified with at least one insomnia subtype.	PAP use was assessed via objective and self-report data 2 years after PAP commencement. Difficulties initiating sleep and early morning awakening insomnia were associated with PAP discontinuation after 2 years.
Salepci et al., 2013 <sup>73</sup>	248 OSA patients using PAP (with follow-up data).	Self-reported 'difficulties initiating sleep' and 'sleep disturbances', assessed at follow-up appointments.	The proportion of patients with difficulties maintaining sleep reduced after PAP. Patients were characterized as PAP adherent ( $\geq 4$ h/night on 70% of nights) or non-adherent. Difficulties initiating sleep and sleep disturbances were more common among non-adherent patients.
Wallace et al., 2013 <sup>74</sup>	65 Hispanic or Latino veterans with OSA that used PAP and completed follow-up visit.	Average ISI score was 15.6, indicating moderate clinical insomnia.	At 1-week follow-up, there was no significant difference in ISI scores between PAP adherent vs. non-adherent groups. At 1-month follow-up, the non-adherent group had significantly higher baseline ISI scores ( $M = 17$ , $sd = 7$ ) compared to the adherent group ( $M = 13$ , $sd = 5$ ).

BMI = Body Mass Index, ISI = Insomnia Severity Index, OSA = Obstructive Sleep Apnea, PAP = Positive Airway Pressure.

Table 2. Association of insomnia symptoms and adherence to Positive Airway Pressure therapy (2014 – 2017).

Study	N, age (mean), sex, BMI (mean)	Insomnia measure and prevalence	PAP outcome and effect of insomnia on PAP adherence
Glidewell et al., 2014 <sup>42</sup>	68 OSA patients, Age = 48, 68% male, BMI = 32.	The first 3 items of the ISI were used to define insomnia. 78% of patients had insomnia (ISI sub-score $\geq 4$ ) and 22% had no insomnia.	Objective average nightly PAP use was measured over 1-2 months. There was no difference in average nightly PAP use between patients with and without insomnia.
Stepnowsky et al., 2014 <sup>75</sup>	241 OSA patients prescribed PAP, Age = 52, 66% male, BMI = 32.	The Pittsburgh Sleep Quality Index was completed after 2 and 4 months of PAP use.	PAP adherence was negatively associated with Sleep Quality scores at both 2 and 4-month follow-up. The association of baseline sleep quality with subsequent PAP adherence was not reported.
Mysliwiec et al., 2015 <sup>76</sup>	58 male military personnel with OSA treated with PAP. Age = 36, BMI = 31.	Insomnia (ICSD-3 criteria) classified in 64% of participants.	There was no difference in rates of insomnia, between participants that were adherent (61% insomnia), versus non-adherent (66% insomnia) at 4-6 week follow-up.
Wohlgemuth et al., 2015 <sup>77</sup>	207 OSA patients, Veterans, Age = 58, 94% male, BMI = 32.	Cross-sectional associations of ISI and PAP adherence were investigated at follow-up.	PAP data were used to identify three sub-groups; Non-adherers, Attempters, Adherers. Insomnia severity was higher in PAP 'Non-adherers' (M = 15.7) than 'Adherers' (M = 8.9).
Eysteinsdottir et al., 2016 <sup>78</sup>	796 OSA patients recommended PAP, Age = 54, 81% male, BMI = 33.	Difficulties initiating sleep, maintaining sleep, and early morning awakenings on the Basic Nordic Sleep Questionnaire.	PAP rejection within 1-year and objective PAP use over past month were investigated. Difficulties initiating sleep and early morning awakening insomnia were associated with PAP rejection. This effect was present in with BMI $\leq 30$ , but not those with BMI $> 30$ .
Gagnadoux et al., 2016 <sup>79</sup>	3,090 OSA patients with PAP follow-up data	Cluster analysis identified 5 clusters of OSA patients. Clusters 1, 4 had more insomnia symptoms.	PAP 'success' (defined as $\geq 4$ h use and improved sleepiness/overall health) was lower in clusters 1, 4, and 5 (representing 'female OSA', 'mildly symptomatic OSA', and 'co-morbid OSA' respectively).
Saaresranta et al., 2016 <sup>49</sup>	Cluster analysis of patients with OSA (n = 6,555). 1,067 had PAP data.	Physician diagnosed insomnia, subjective sleep latency $\geq 30$ min, self-reported sleep duration $\leq 6$ h and/or use of hypnotics.	Divided participants into four groups depending on presence vs. absence of insomnia and excessive daytime sleepiness. Trends for lower PAP adherence in groups with insomnia, and higher PAP adherence in group with sleepiness but no insomnia, after controlling for age, BMI and gender.
Lam et al., 2017 <sup>64</sup>	172 patients (123 with ISI data) presenting to a clinic for 'PAP-intolerant patients'.	ISI was completed before treatment.	Of patients with available ISI data, 59% had at least moderate insomnia. The most frequent reasons for PAP rejection/failure were; claustrophobia, mask discomfort, and sleeping difficulty.
Libman et al., 2017 <sup>80</sup>	29 female OSA patients, Age = 65, BMI = 32.	ISI, Sleep questionnaire (nightly awakenings, fatigue, sleepiness, sleep quality).	Self-reported PAP use was collected after 2 years. Participants were defined as 'adherent' vs 'non-adherent' ( $\geq 4$ h use on $\geq 80\%$ of nights). The ISI did not predict PAP adherence group.

BMI = Body Mass Index, ISI = Insomnia Severity Index, OSA = Obstructive Sleep Apnea, PAP = Positive Airway Pressure.

Table 3. Association of insomnia symptoms and adherence to Positive Airway Pressure therapy (2018 – current).

Study	N, age (mean), sex, BMI (mean)	Insomnia measure and prevalence	PAP outcome and effect of insomnia on PAP adherence
Cho et al., 2018 <sup>81</sup>	77 of 476 prospectively screened OSA patients with PAP follow-up data. Age = 51, 76% male, BMI = 26.	ISI $\geq 15$ was used to identify patients with insomnia (29%). Cross-sectional associations with PAP adherence were investigated.	Among the 77 patients with PAP data, there was no difference in adherence to PAP therapy between OSA patients with and without insomnia. There was no correlation between the ISI and PAP adherence.
El-Solh et al., 2018 <sup>82</sup>	72 Veterans with OSA and PTSD. Age = 50, 79% male, BMI = 34.	ISI $\geq 15$ was used to identify patients with insomnia at baseline (50%).	Participants with COMISA used PAP for fewer nights (33%) than those without insomnia (50%) at 12-week follow-up.
Philip et al., 2018 <sup>83</sup>	288 OSA patients. Age = 63, 69% male, BMI = 30.	Cross-sectional assessment of PAP adherence with insomnia (ISI), self-efficacy and other self-report data.	PAP adherence was negatively correlated with the ISI total score, and nocturnal insomnia item scores; difficulties initiating sleep, and difficulties maintaining sleep.
Fichten et al., 2018 (abstract) <sup>84</sup>	46 OSA patients prescribed PAP. Age = 54.	Self-reported difficulties initiating and maintaining sleep, and insomnia was assessed before and 1.5 years after PAP therapy.	20 of 46 participants were categorized as PAP-adherent at follow-up. Insomnia symptoms were less prevalent in the PAP adherent (20% had insomnia) than the non-adherent group (38% had insomnia).
Park et al., 2018 <sup>85</sup>	359 OSA patients. Age = 58, 78% male, BMI = 26.	The total ISI score, and itemized responses were investigated.	PAP adherence (defined as the use of PAP for $\geq 4$ h per night on 70% of nights) was observed in 46% of participants. Sleep onset insomnia symptoms (but not overall insomnia severity) were associated with PAP non-adherence.
Sawunyavisuth, 2018 <sup>86</sup>	53 OSA patients recommended PAP therapy, Age = 56, 62% male, BMI = 30.	Questionnaire assessing side effects resulting from trial of PAP. Included insomnia symptoms.	Following PAP trial, 12 patients (23%) did not purchase PAP and 41 patients (77%) did purchase PAP. Patients that did not purchase PAP indicated more insomnia symptoms, tightness of mask, cough and irritation resulting from PAP trial.
Wallace et al., 2018 <sup>87</sup>	53 Veterans with OSA that initiated PAP. Age = 50, 96% male, BMI = 34.	A ISI sub-score $\geq 6$ (three nocturnal items) was used to identify patients with insomnia (47%).	At 6-month follow-up, participants with co-morbid insomnia had significantly lower average PAP use (2.8h) compared to participants without co-morbid insomnia (4h/night). Participants with co-morbid insomnia also had a lower percentage of days with at least 4 hours use (32%), versus to those without co-morbid insomnia (50%).
Drakou et al., 2021 <sup>88</sup>	272 patients with suspected OSA, Age = 53, 74% male, BMI = 34. 160 recommended PAP.	Athens Insomnia Scale score $\geq 10$ .	Among patients with severe OSA and mild depression, those with insomnia were less likely to initially accept PAP therapy (25%) compared to those with no co-morbid insomnia (59%). There was no effect of insomnia presence on acceptance of PAP in patients with moderate OSA, or those without depression symptoms.

BMI = Body Mass Index, ISI = Insomnia Severity Index, OSA = Obstructive Sleep Apnea, PAP = Positive Airway Pressure.

### Improvements in insomnia after PAP

Although insomnia symptoms predict reduced adherence to PAP, a sub-group of patients with COMISA have adequate PAP use, and report improvement in insomnia symptoms following PAP therapy<sup>40,44</sup>. We recently reviewed nine studies investigating the effect of PAP therapy on improving insomnia symptoms and found that PAP improves insomnia by 20-50% from baseline levels<sup>18</sup>. An additional recent study by Lundetræ and colleagues<sup>44</sup> investigated the effect of insomnia symptoms on PAP use, and the effect of PAP use on improving insomnia symptoms in 442 patients with OSA. It was reported that although insomnia symptoms predicted worse adherence to PAP therapy, the proportion of patients reporting co-morbid insomnia decreased from 51% at baseline to 33% at follow-up. Insomnia improvements were larger among PAP-adherent patients.

These data indicate that some COMISA patients may experience insomnia symptoms as a result of untreated OSA. It is currently very difficult to identify this PAP-responsive sub-group using baseline symptoms alone. Some evidence suggests that greater OSA severity may be associated with more insomnia improvement during PAP<sup>42</sup>. However, higher AHI is also predictive of greater insomnia improvement following CBTi in patients with COMISA<sup>45</sup>. More frequent brief awakenings may also be more responsive to PAP treatment compared to sleep onset/late insomnia<sup>40</sup>. As evidence is still emerging, it is important to consider targeted treatments for each condition when a patient presents with COMISA. Decisions about treatment combinations and sequences should be guided by the patient's 'chief complaint', treatment preference, severity and onset of symptoms.

### Non-PAP therapies in COMISA

A handful of studies have also investigated the effect, and use of non-PAP therapies in patients with COMISA. Improvement of insomnia symptoms have been reported following upper airway surgery<sup>89</sup>, nasal dilator strip therapy<sup>90</sup>, and mandibular advancement splint therapy<sup>91</sup>. However, patients with COMISA may show reduced acceptance, use, and derive less therapeutic benefit from some of these therapies, compared to patients with OSA alone<sup>92,93</sup>.

### Sedative-hypnotic medicines

The use of hypnotic agents and combination pharmacotherapy to manage OSA in patients with specific phenotypes is an exciting emerging area<sup>94</sup>. Sedative-hypnotic medicines including benzodiazepines and 'z-drugs' are a common approach to manage insomnia<sup>95,96</sup>. However, they are not recommended as 'first line' treatment or a long-term management approach for insomnia, due to potential for dependence, side-effects, and tolerance to therapeutic dose<sup>97-99</sup>.

Hypnotic medicines may be well tolerated and improve sleep in specific OSA patients<sup>94</sup>. For example, a low respiratory arousal threshold is one of the main non-anatomical contributors to OSA pathogenesis<sup>4</sup>. At least one third of OSA patients have a low respiratory arousal threshold, in which they awaken to increasing respiratory effort and relatively minor airway narrowing, thereby perpetuating breathing instability<sup>18,100</sup>. Consequently, it is thought that increasing the arousal threshold may be a therapeutic target to improve overall airway stability in such patients. Ongoing research aims to investigate the low arousal threshold as a common mechanistic feature of OSA and COMISA<sup>18</sup>. Several studies have investigated the

effect of different hypnotic/combination agents in patients with OSA<sup>101</sup>. Messineo and colleagues<sup>102</sup> recently reported that zolpidem (10mg) results in an increase in objective sleep efficiency and respiratory arousal threshold, but no change in AHI, versus placebo, in patients with OSA and a low-to-moderate arousal threshold. A recent RCT by Cheng and colleagues<sup>103</sup> also investigated the effect of 10mg Lemborexant (a dual orexin receptor antagonist) in patients with mild OSA. It was reported that Lemborexant did not increase AHI, or reduce mean oxygen saturation, or percentage of sleep time with oxygen saturation <90%, versus placebo.

There is a growing trend in off-label anti-depressant and anti-psychotic medicines prescribed to manage insomnia<sup>15,104</sup>. Most studies investigating the effect of anti-depressants for insomnia have been limited to small samples and short-term follow-up<sup>105</sup>. Consequently, these medicines are not presently recommended for the management of insomnia<sup>15</sup>. Anti-psychotic medicines may also lead to a substantial AHI increase in patients presenting with insomnia symptoms<sup>106</sup>. Based on this limited evidence and potential for exacerbation of OSA, anti-depressant and anti-psychotic medicines are not currently recommended for the management of insomnia or COMISA.

#### CBT for insomnia (CBTi) is the most effective treatment for insomnia

CBTi is the recommended 'first line' treatment for chronic insomnia<sup>99,107,108</sup>. CBTi is a multi-component therapy that aims to identify and gradually reduce the underlying psychological, behavioral and physiological factors that maintain the insomnia condition<sup>109</sup>. CBTi includes several therapeutic components that may be tailored to patients' presenting symptoms and underlying features of the disorder (Table 4). Because CBTi targets the underlying causes of insomnia, it leads to improvements in sleep, daytime function, and mental health that are sustained long after therapy cessation. CBTi is commonly administered by trained therapists/psychologists over 6-8 weekly/fortnightly sessions, but has also been translated to self-guided reading, audio, and interactive online programs. A brief behavioral therapy for insomnia has been developed<sup>110,111</sup>, which distils the most effective educational and behavioral treatment components (stimulus control therapy, and bedtime restriction therapy) into a succinct 4-session program that can be delivered in a diverse range of healthcare settings<sup>112</sup>. As many patients with COMISA spend at least 4 weeks between their PAP titration and setup/initiation appointments, brief CBTi programs could be delivered without delaying commencement of PAP therapy.

Table 4. Components of cognitive behavioral therapy for insomnia (CBTi).

Component	Description
Education about sleep	<p>CBTi programs commonly begin with information about the process that control our sleep (2-process model).</p> <p>Sleep hygiene information is not an adequate stand-alone treatment for insomnia, but can be helpful in providing a treatment rationale for other active treatment components.</p> <p>Sleep information can also be used to provide accurate information about some of the common myths and misconceptions about sleep (see Cognitive Therapy below).</p>
Stimulus control therapy	<p>Instructions to help patients fall asleep quicker at the start of the night and following nocturnal awakenings;</p> <ol style="list-style-type: none"> <li>1. Use the bed only for sleep and intimacy,</li> <li>2. Get up at the same time each morning,</li> <li>3. Only go to bed when sleepy, do not 'try hard' to fall asleep,</li> <li>4. If not asleep within approximately 15-minutes, get out of bed and go to another room until sleepy again,</li> <li>5. Repeat steps 3 and 4 until asleep,</li> <li>6. Repeat steps 3 and 4 in the middle of the night when awake,</li> <li>7. Avoid daytime naps (especially long naps).</li> </ol>
Bedtime restriction therapy (also called <i>sleep restriction therapy</i> )	<p>Aims to reduce the 'conditioned' relationship between being in bed with a state of alertness and arousal. Patients are guided to temporarily reduce the time they spend in bed over multiple consecutive nights. This may result in a small amount of sleep loss during the first 1-2 weeks. Sleep pressure will increase during the first 1-2 weeks of therapy. This promotes quicker sleep onset and reduces the length of nocturnal awakenings. As patients begin sleeping for the large majority of time they spend in bed (85%), their time in bed can gradually be extended from week-to-week until a comfortable and satisfying equilibrium between their sleep efficiency (% of time in bed asleep), and daytime sleepiness is achieved. Typically, the prescribed time in bed is never reduced below 5.5 hours.</p>
Cognitive therapy	<p>Aims to identify and challenge the patient's maladaptive beliefs about sleep. These beliefs are replaced with more realistic ones that help the patient adopt a more accurate understanding of the impact of poor sleep on daytime functioning, sleep needs, and sleep medication. Techniques such as Socratic questioning or behavioral experiments are often part of cognitive therapy.</p>
Relaxation therapy	<p>Includes progressive muscle relaxation, mindfulness therapies, and meditation that aims to reduce alertness and arousal before bed and throughout the night. Relaxation exercises should be practiced over multiple days/nights to improve this cognitive skill, rather than as a once-off treatment.</p>

CBTi is an effective and safe treatment in the presence of untreated OSA<sup>29,41,113</sup>. Several case studies, pilot studies, and four recent RCTs (Table 5) have investigated the effect of CBTi on acceptance and use of PAP therapy. Evidence suggests that face-to-face CBTi interventions improve insomnia in the presence of OSA, can be safely delivered before OSA treatment, and may increase subsequent acceptance and use of PAP therapy in those with moderate and severe OSA<sup>114-117</sup>. Mixed results in this area (Table 5) highlight the need for further research to identify the most effective treatment sequence/s, interventions, and specific COMISA patients that are most responsive to CBTi before commencing PAP. There is also RCT evidence that CBTi reduces OSA severity through sleep consolidation<sup>22</sup>.

Adherence to CBTi in COMISA patients has not been evaluated yet, but there are specific issues that need attention, especially when CBTi and PAP therapy are provided simultaneously. For example, a patient with sleep onset insomnia symptoms might struggle to adhere to stimulus control instructions to get out of bed if unable to sleep (Table 4), as this would require removal and replacement of PAP equipment on each occasion. If stimulus control therapy is indicated as the best treatment for the insomnia, it could be initiated a couple of weeks before PAP commencement by which time repeated times out of bed should no longer be necessary. Another consideration for combined treatment is that some patients (particularly those including long reported periods awake in bed) being administered bedtime restriction therapy, will be asked to restrict their time in bed, in some cases as low as 5.5 hrs. This needs to be communicated to the care provider evaluating PAP adherence, who needs to acknowledge that PAP use will not be beyond those 5.5 hrs (assuming the patient is adherent to their prescribed time in bed). A move away from “PAP adherence based on hrs of use” towards “PAP adherence based on % of time in bed with effective therapy” is needed. This metric would be similar to psychologists using ‘sleep efficiency’ rather than ‘total sleep time’ to assess treatment-response to CBTi.

#### *Increasing access to CBTi in sleep clinics*

Despite strong recommendations that CBTi should be used as the ‘first line’ treatment for insomnia<sup>98,107,108</sup>, and evidence that CBTi is effective and safe<sup>118</sup> in the presence of co-morbid OSA, most clinicians and patients lack access to CBTi. This clear deficiency of CBTi requires attention. This may be achieved through embedding psychologists with training in CBTi in sleep clinics that specialise in OSA, or developing referral networks between sleep clinics and external ‘sleep’ psychologists. Secondly, CBTi programs have been translated to a brief behavioral therapy<sup>111</sup>, that may be delivered by existing PAP nurses, or other clinicians in sleep clinic settings. It may also be possible to up-skill family physicians, community health care professionals and social workers to administer this brief behavioral treatment for insomnia to improve availability<sup>112</sup>. CBTi may be delivered via telemedicine to increase access in rural/remote and underserved areas<sup>119</sup>. Finally, CBTi programs have also been translated to self-guided digital programs<sup>120</sup>. Digital CBTi is an effective treatment for insomnia that also improves co-morbid depression and anxiety symptoms<sup>121,122</sup>. At least one ongoing study is evaluating the effect of digital CBTi in patients with COMISA<sup>113</sup>. This research may inform the feasibility of a stepped-care system for management of insomnia in patients with COMISA.

Table 5. Randomized controlled trials investigating effect of CBTi on insomnia symptoms and PAP adherence in patients with COMISA.

Study	Sample characteristics	Design	Insomnia outcome	OSA outcome
Bjorvatn et al., 2018 <sup>117</sup>	164 patients with COMISA (Age M = 56, 71% male, BMI M = 32).	Parallel-arm RCT of a self-help book vs. sleep hygiene concurrent with PAP therapy, on insomnia symptoms and PAP adherence.	There was no between-group difference in change in insomnia symptoms from pre-treatment to 3-month follow-up.	There was no between-group difference in PAP adherence.
Sweetman et al., 2019 <sup>114</sup>	145 patients with COMISA (Age M = 59, 56% male, BMI M = 35).	Parallel-arm RCT of CBTi, versus no-treatment, on insomnia symptoms, and PAP acceptance/adherence in patients with untreated COMISA.	CBTi group experienced greater reduction in insomnia severity by post-CBTi/control, and 6-month follow-up, vs control.	CBTi group had greater initial acceptance (99 vs. 89%) and long term nightly use of PAP, vs. control (61 minutes difference).
Ong et al., 2020 <sup>115</sup>	121 patients with COMISA (Age M = 50, 55% male).	3-arm RCT of CBTi before PAP, CBTi concurrent with PAP, and PAP-only on insomnia symptoms and PAP adherence in 121 PAP naïve COMISA patients.	Compared to patients receiving PAP only, those receiving combined CBTi and PAP experienced greater improvement of the ISI. There was no difference between the groups that received sequential CBTi before PAP, versus concurrent CBTi and PAP.	There were no significant between-group differences in PAP adherence.
Alessi et al., 2021 <sup>116</sup>	124 veterans with COMISA (Age M = 63, 96% male).	Parallel-arm RCT of integrated CBTi + PAP adherence intervention, vs no-treatment, on insomnia symptoms and PAP adherence in veterans with COMISA.	Compared to the control group, the CBTi group experienced greater improvement in the ISI, self-report, and actigraphy measures sleep parameters.	Compared to the control group, the CBTi group had greater average nightly PAP use at 3 month (3.0, vs 1.9 h/night) and 6-month follow-up (2.4, vs 1.5 h/night).

CBTi = cognitive behavioral therapy for insomnia, PAP = positive airway pressure, ISI = Insomnia Severity Index, RCT = Randomized Controlled Trial. Adapted from Sweetman et al., (2019)<sup>2</sup>.

### *Proposed mechanisms*

The pathophysiology and developmental course of COMISA remains unclear and the exact mechanisms remain somewhat elusive because of the lack of research in this area.

Understanding the mechanisms underpinning COMISA is important, as this will likely improve precision medicine approaches for future patients, and potentially highlight areas for early intervention to prevent development and/or exacerbation of COMISA<sup>18</sup>. It is likely that there are multiple pathways that lead to the development of COMISA, so only a handful of mechanisms are discussed below.

#### *1) Effect of OSA on insomnia*

The most common proposed pathway is that OSA is a precipitating factor for insomnia, increasing risk of the development of chronic insomnia<sup>18</sup>. Specifically, arousals due to respiratory events result in sleep disruptions and increased sympathetic activity. Over time, the nocturnal increase in sympathetic activity associated with these respiratory events and awakenings could lead to periods of wakefulness, (mis)perceptions of multiple brief sleep periods as continued wakefulness<sup>123</sup>, feelings of frustration and anxiety about sleep loss, maladaptive behaviors and a state of chronic hyperarousal, one of the hallmark symptoms of insomnia disorder<sup>124</sup>. Over time, the insomnia condition may develop functional independence of the OSA, or remain partly dependent on respiratory-induced arousals/awakenings in some patients with COMISA.

Another possible mechanism is through rapid eye movement (REM) instability. Respiratory events disproportionally occur during REM sleep and light sleep in patients with OSA<sup>125</sup>. Respiratory events during REM sleep may lead to more frequent arousals and disruption of REM sleep. Riemann and colleagues proposed that such instability of REM sleep and frequent arousals might offer an explanation for the development of sleep maintenance insomnia, as these arousals contribute to the misperception of vivid dream mentation as wakefulness<sup>126</sup>. Although this proposed pathway does not explain the development of sleep onset insomnia symptoms, it is supported by research indicating that nocturnal awakenings in insomnia patients are often triggered by respiratory events<sup>127</sup>. This conceptualization is somewhat intuitive and consistent with the outdated conceptualization that insomnia is often secondary to co-occurring physical and mental health conditions (i.e. 'secondary insomnia'). However, as outlined above, PAP is not necessarily the most advantageous 'first line' treatment for all COMISA patients, especially those with sleep onset difficulties, or nocturnal awakenings *and* difficulties returning to sleep.

#### *2) Effect of insomnia on OSA*

A second, albeit less intuitive pathway, is that insomnia disorder leads to the exacerbation of OSA in patients with a pre-existing anatomical pre-disposition. It has been suggested that partial sleep deprivation experienced during periods of insomnia may compromise upper airway muscle tone<sup>128,129</sup>. The effect of sleep deprivation (including multiple nights of partial sleep restriction) on OSA severity and upper airway muscle tone in the context of insomnia and COMISA requires further research<sup>18</sup>. Alternatively, insomnia disorder that is characterized by a state of increased cognitive and physiological arousal during the day and night (hyper-arousal), may contribute to a reduced respiratory arousal threshold, one of the main non-anatomical traits of OSA<sup>4</sup>. A recent study demonstrated a small reduction of the AHI in COMISA patients following treatment of insomnia with CBT<sup>22</sup>. The authors speculate

that consolidating periods of fragmented sleep might improve airway patency, or that the increased homeostatic drive for sleep seen with sleep restriction therapy may lead to an increase in the respiratory arousal threshold. This preliminary data certainly supports the notion of providing CBTi prior to the initiation of PAP therapy.

### 3) *Common underlying pathophysiology*

Benetó and colleagues<sup>130</sup> speculate that the hypothalamic–pituitary–adrenal (HPA) axis might play an important role in the development of COMISA. The authors hypothesize a reciprocal relationship between OSA and insomnia mediated by activation of the HPA axis, which is caused by sleep fragmentation, reduced sleep duration and chronic sleep deprivation common to both conditions. The authors acknowledge an established evidence base for the effect of OSA on HPA axis activation, but that most of the research on insomnia has focused on the HPA axis activation as a cause for insomnia. Much less clear is the potential of HPA axis activation as a consequence of insomnia and cause for OSA, which would support their hypothesis of the HPA axis activation as the common link and mediator of the reciprocal relationship between OSA and insomnia. Research that links HPA activation and insomnia with objective short sleep duration supports the hypothesis that within this subgroup, HPA axis activation may be a consequence of insomnia. Additionally, metabolic syndrome has been proposed as a cause for OSA; metabolic syndrome in turn is a direct consequence of increased HPA axis activation. Together these results support the hypothesis that HPA axis activation may be a cause and consequence of each disorder, leading to a reciprocal relationship between insomnia and OSA.

It is likely that multiple pathways contribute to the development of COMISA. More longitudinal and experimental studies are needed to test possible mechanisms between insomnia and OSA. Certainly, information about these mechanisms will help guide our treatment approaches.

## Summary

Insomnia and sleep apnea are the two most common sleep disorders and frequently co-occur. COMISA results in greater morbidity for patients, and complex diagnostic and treatment decisions for clinicians. It is important for sleep clinicians to assess for insomnia symptoms among patients with suspected/confirmed OSA, and provide access to treatments for both disorders. Cognitive behavioral therapy for insomnia (CBTi) is an effective insomnia treatment in the presence of untreated OSA, and improves adherence to PAP therapy in patients with moderate/severe OSA. Many sleep clinics worldwide currently specialize in the diagnosis and management of OSA alone, and should consider incorporating insomnia and COMISA management pathways to improve outcomes for patients with COMISA.

## Clinics Care Points

- ⌚ Insomnia and sleep apnea frequently co-occur (COMISA). This results in worse sleep, daytime function, and quality of life, compared to either disorder alone.
- ⌚ It is important to implement evidence-based insomnia assessment and management approaches into sleep clinics worldwide to improve management of COMISA.
- ⌚ Clinicians may screen for insomnia symptoms in patients with suspected and confirmed OSA. Clinicians should be aware of the shared and unique symptoms of each disorder than can complicate the assessment and diagnostic process in patients with COMISA (Figure 1).
- ⌚ Patients with COMISA should be offered treatments for both disorders.
- ⌚ Patients with COMISA have lower nightly use of PAP therapy, compared to patients with OSA alone (Tables 1-3).
- ⌚ A sub-sample of patients with COMISA show adequate use of PAP therapy that improves symptoms of insomnia and OSA. There is currently insufficient evidence to identify this PAP-responsive group of COMISA patients before commencing treatment (i.e., precision medicine approaches). This is an important area of emerging research.
- ⌚ Cognitive behavioral therapy for insomnia (CBTi; Table 4) is the most effective and recommended 'first line' treatment for (co-morbid) insomnia. CBTi is effective and safe in the presence of mild, moderate and severe OSA. Patients should be monitored for increased daytime sleepiness during the first 1-2 weeks of 'bedtime restriction therapy' (one of the core therapeutic components of CBTi).
- ⌚ There is evidence that CBTi improves acceptance and use of PAP therapy among patients with co-morbid insomnia and moderate and severe OSA (Table 5).

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