Sleep Apnea and Insomnia: Emerging Evidence for Effective Clinical Management

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Abstract

Comorbid insomnia and sleep apnea (COMISA) are the most common co-occurring sleep disorders and presents many challenges to clinicians. This review provides an overview of the clinical challenges in the management of patients with COMISA with a focus on recent evidence regarding the evaluation and treatment of COMISA. Innovations in the assessment of COMISA have used profile analyses or dimensional approaches to examine symptom clusters or symptom severity that could be particularly useful in the assessment of COMISA. Recent randomized controlled trials have provided important evidence about the safety and effectiveness of a concomitant treatment approach to COMISA using cognitive-behavioral therapy for insomnia (CBT-I) with positive airway pressure (PAP). Furthermore, patient-centered considerations that integrate patient characteristics, treatment preferences, and accessibility to treatment in the context of COMISA are discussed as opportunities to improve patient care. Based on these recent advances and clinical perspectives, a model for using multidisciplinary, patient-centered care is recommended to optimize the clinical management of patients with COMISA.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that affects about 10% to 20% of middle to older aged adults [1] and is associated with excessive daytime sleepiness, cardiovascular sequelae, neurocognitive deficits, and depression [2-6]. Respiratory events result in sleep fragmentation and poor sleep quality. It is also common for people with OSA to have difficulty falling and/or staying asleep. Given that chronic insomnia is considered a distinct disorder [7,8], comorbid insomnia and sleep apnea (COMISA) are the most common co-occurring sleep disorders, with a global prevalence between 18% to 42% [9], and a prevalence between 29% and 67% among patients presenting for treatment. COMISA is associated with increased medical (e.g., cardiometabolic conditions) and psychiatric morbidity (e.g., mood disorders, post-traumatic stress disorder), and worse daytime functioning relative to each condition alone [10-18]. As a result, clinical management of COMISA is often very challenging.

Currently, there are no definitive guidelines for evaluating and treating patients with COMISA. Traditional approaches based upon clinical lore and older diagnostic nomenclature are being challenged by recent innovations and emerging data that support multidisciplinary approaches with considerations based on patient-centered care. This shift includes utilization of symptom profiles or phenotypes that transcend diagnostic categories, treatment combinations using various specialties and sequences, and consideration of patient characteristics and preferences throughout the process of clinical care. The purpose of this review is to provide an overview of the clinical challenges associated with the management of patients with COMISA. Emphasis is given to recent evidence from randomized controlled trials (RCT) and perspectives in patient-centered care that can optimize clinical management of COMISA.

Clinical Challenges

Traditional Approaches to the Assessment of COMISA

The traditional approach to assessing sleep disorders is to conduct a clinical interview/exam and, if indicated, to conduct a laboratory-based polysomnography (PSG) test. The clinical pathway is driven by provisional diagnosis and tends to be parallel (see Figure 1). If the referral is for OSA, or if the chief complaint is

suggestive of OSA (e.g., snoring, witnessed apneas), the clinical evaluation typically involves: 1) a clinical interview to ascertain nocturnal signs and symptoms and daytime indications of sleepiness/fatigue, 2) a physical examination of the oropharynx and assessment of other conditions that could be causing the sleep disturbance, and 3) a laboratory polysomnography (PSG) or home sleep apnea test (HSAT). If the referral is for insomnia or if the chief complaint is suggestive of insomnia (e.g., difficulty falling and/or staying asleep), the clinical evaluation typically involves: 1) a clinical interview with emphasis on the sleep/wake patterns (e.g., bedtimes, waketimes), sleep hygiene considerations, and psychological features (e.g., racing thoughts in bed), 2) prospective sleep/wake diaries and/or actigraphy monitoring for 1 to 2 weeks, and 3) self-report questionnaires, which can include global symptoms of insomnia (e.g., Insomnia Severity Index, Pittsburgh Sleep Quality Index) or questionnaires to assess common comorbid conditions such as mood or anxiety scales.

<Insert Figure 1 about here>

For patients with COMISA, the evaluation process is less clear and may include several potential clinical dilemmas. First, the presenting complaint or reason for referral (insomnia or OSA symptoms) could lead the clinician to make different decisions regarding the evaluation pathway. PSG is not recommended in the standard assessment of insomnia, and therefore, patients whose primary complaint is difficulty falling or staying asleep might not receive a PSG or HSAT prior to initiating treatment for insomnia. This can result in occult OSA remaining undiagnosed and undertreated. Similarly, patients who present with OSA symptoms are less likely to complete prospective sleep diaries or actigraphy monitoring, which could result in undiagnosed or undertreated comorbid insomnia. Furthermore, the clinician's specialty and clinical environment could influence decisions in the evaluation pathway. For example, pulmonary specialists might be more inclined to focus on OSA assessment (e.g., PSG, HSAT) for patients with COMISA while behavioral specialists (i.e., psychiatrist, psychologist) might be more inclined to focus on assessing insomnia. Finally, questionnaires commonly used to assess insomnia alone are not validated in patients with COMISA, potentially resulting in misdiagnosis of comorbid insomnia when the underlying disorder is OSA alone [19]. As a result, patients with COMISA may find

that these traditional pathways for OSA and insomnia do not fit their condition and they are at risk for receiving suboptimal treatment.

Innovations in the Assessment of COMISA

In contrast to the traditional approach, recent innovations using symptom profiles are looking beyond the presenting complaint or diagnostic categories, which could be particularly useful in the assessment of COMISA. There are indications that the subtype of insomnia (i.e., difficulty falling asleep, staying asleep, or early morning awakenings) can impact the rate of co-occurrence with OSA [12,20]. Chung [20] found that sleep maintenance and early morning awakenings were the most common subtype of insomnia associated with OSA. In a large population-based study of people with OSA, 16% had sleep onset insomnia, 59% had sleep maintenance insomnia, and 28% had early morning awakenings [21]. Empirically-driven clinical and population-based studies using OSA symptoms have identified COMISA as a common OSA phenotype. In a study using the Icelandic Sleep Apnea Cohort (ISAC) with moderate to severe OSA, three symptom clusters were described: 1) minimally symptomatic, 2) disturbed sleep, and 3) excessively sleepy [13]. Approximately one-third (32.7%) of the cohort belonged to the "disturbed sleep" group, one characterized by insomnia symptoms and restless sleep. A similar study conducted on an international clinical sample (Sleep Apnea Global Interdisciplinary Consortium [SAGIC]) described two additional clusters (upper airway symptoms with sleepiness and upper airway symptoms dominant) with a lower prevalence (19.0%) of the "disturbed sleep" group [22]. Compared to the other clusters, the "disturbed sleep" group contained the highest proportion of females, black individuals, and greatest levels of obesity. Using similar OSA symptoms in the Sleep Heart Health Study among individuals with moderate to severe OSA, Mazzotti et al [23] found four OSA clusters, with a 12.2% prevalence of the "disturbed sleep" type. One important limitation in this literature is that relatively few studies have included validated insomnia assessments in the analyses, which might account for the variability of the prevalence of COMISA across studies [24]. Crawford et al [25] conducted latent profile analyses on a sample using diagnostic criteria for insomnia and found that the "mild insomnia" subtype had significantly a greater percentage of OSA (70%) compared to the other subtypes (~50%). These studies serve as examples of how

data-driven approaches could move the field beyond reliance on the presenting complaint and potentially avoid clinician bias.

Traditional Approaches to the Treatment of COMISA

Although there are well-established treatments for OSA and insomnia separately, there are no definitive guidelines for how to combine or integrate these treatments in the case of COMISA. The traditional approach to COMISA has been to treat OSA and insomnia separately (see Figure 1). Typically, OSA treatment is considered primary and thus the first-line treatment for COMISA has followed the guidelines for OSA treatment [26]. The gold standard treatment for OSA is positive airway pressure (PAP), with oral appliances, upper airway stimulation, or surgery considered when appropriate [26]. Insomnia treatment is considered secondary, typically when the insomnia persists after OSA is well-controlled or when patients fail OSA treatments (e.g., low PAP adherence). The gold standard treatment for insomnia is cognitive-behavior therapy for insomnia (CBT-I), which has substantial evidence supporting effectiveness and safety [27,28] (see Table 1 for summary of CBT-I components). However, CBT-I is typically delivered by a sleep psychologist or similarly trained mental health provider and there is a limited number of qualified CBT-I providers. As a result, hypnotics are frequently used by patients with COMISA.[29] This traditional approach is centered on the working hypothesis that the insomnia symptoms are secondary to OSA and thus it should resolve with optimal OSA treatment.

<Insert Table 1 about here>

There is accumulating evidence that this sequential approach is sub-optimal and does not address several clinical issues. First, when insomnia is present with OSA, there is evidence that the insomnia symptoms are associated with low adherence to PAP [21,30,31]. Regular use of PAP can be very challenging given that only about 30% to 50% of OSA patients are regular long-term users of PAP [32-34]. Furthermore, the Centers for Medicare and Medicaid Services (CMS) reimbursement policy require patients to demonstrate adequate adherence to PAP within the first 3 months, defined as usage of the PAP device for at least 4 hours per night on 70% of nights during a consecutive 30-day period. As a result, patients with COMISA are at particularly high

risk for not meeting these expectations and losing reimbursement for PAP therapy. Second, pharmacological treatment of insomnia in patients with COMISA could potentially exacerbate daytime sleepiness or have other adverse effects (e.g., increased risk of motor vehicle accidents). Third, patients who do not perceive any benefits from PAP therapy or who do not receive appropriate treatment for insomnia might be dissatisfied with their sleep treatments.[35].

Given these clinical dilemmas and lack of clear guidelines, prospective clinical studies have sought to gather evidence about concomitant treatments for COMISA. In one of the first studies to use CBT-I in COMISA, Krakow et al [36] reported on a case replication series of patients who received CBT-I first, followed by receiving an OSA treatment (PAP, oral appliance, or surgery). They found that 47% reported clinically significant improvements after CBT-I compared to 88% who reported clinically significant improvements after receiving both treatments. Furthermore, many patients were not initially interested in, or ready for OSA treatment as the initial treatment. Using a mixed-methods approach, Ong et al [35] found that patients generally preferred to receive a combination of treatments using CBT-I and PAP but there was uncertainty about the optimal timing of initiating insomnia treatment. These studies exemplify the importance of concomitant treatments targeting both insomnia and OSA in patients with COMISA.

Evidence from Recent RCTs on COMISA

Three recent RCTs have been published examining CBT-I and PAP for COMISA. Sweetman et al. [37] compared CBT-I versus a treatment as usual control prior to receiving PAP treatment in 145 patients with COMISA. Compared to the control condition, those in the CBT-I group demonstrated greater average nightly adherence to PAP by 61 minutes (p = 0.023, d = 0.38) and higher initial PAP treatment acceptance (99% vs. 89%; p = 0.034). Furthermore, those who received CBT-I showed greater improvement on global insomnia severity as measured by the insomnia severity index. A second report from this RCT examined weekly changes in sleep patterns and daytime sleepiness. Sweetman and colleagues [38] found a 15% increase in sleepiness the week after administering sleep restriction therapy as part of CBT-I. However, the levels of sleepiness subsided to pre-treatment levels in the subsequent weeks while sleep patterns generally improved. A third report from this

RCT [39] examined the impact of CBT-I on OSA severity and found a 7.5 point greater decrease in AHI from pre to post treatment in the CBT-I group compared to a no-treatment control group.

Ong et al [40] conducted a 3-arm RCT on 121 adult patients with COMISA using a partial factorial design to compare the timing of treatment initiation with CBT-I and PAP. Compared to PAP alone, the concomitant treatment arms reported a significantly greater reduction from baseline on the ISI (p=.0009) and had a greater percentage of participants who were categorized as good sleepers (p=.044) and remitters from insomnia (p=.008). No significant differences were found between the sequential (CBT-I followed by PAP) versus concurrent treatment models on any outcome measure. In contrast to the findings from Sweetman et al. [37], no significant differences were found between the concomitant treatment arms versus PAP only on PAP adherence.

A third RCT by Bjorvatn et al. [41] examined 164 adults with COMISA who received CBT-I delivered using bibliotherapy (i.e., self-help book) compared to a sleep hygiene control concurrent with initiation CPAP treatment. The authors found that both groups reported reductions in insomnia severity with no significant between-group differences, which the authors attributed to improvements from receiving CPAP.

Collectively, these RCTs support the effectiveness and safety of using therapist-delivered CBT-I in patients with COMISA. Specifically, a 4-session CBT-I prior to, or concurrent with PAP is superior to PAP alone on insomnia outcomes while bibliotherapy-delivered CBT-I is insufficient. Additionally, no serious adverse events related to CBT-I were reported and the increase in sleepiness resulting from sleep restriction therapy was temporary [38]. This suggests that CBT-I is safe, although sleepiness should be monitored throughout treatment. The evidence is not entirely clear if CBT-I can also improve adherence to PAP. It is possible that the conflicting findings might be due to the inclusion of mild OSA in the Ong et al study [40] whereas the Sweetman et al study [37] included only moderate to severe OSA (AHI ≥ 15). Alternatively, the conflicting findings might be the result of differences in sampling. The Sweetman et al [37] study recruited primarily from sleep clinics and Ong et al study [40] recruited from the community, many of whom were not seeking treatment and did not know they had sleep

apnea prior to participating in the study. Finally, the Sweetman et al study revealed an intriguing finding that CBT-I can potentially decrease OSA severity.

Clinical Considerations for Patient-Centered Care

In addition to the emerging evidence for assessment and treatment, patient-centered care should also consider patient characteristics, treatment preferences, and accessibility to treatment. This section reviews clinical considerations that have not received sufficient attention in COMISA but could improve assessment and personalization of treatment in patients with COMISA.

Demographics and Socioeconomic Status

Patient demographics are an important consideration in the assessment and treatment of COMISA. Some studies have found sex differences in the clinical presentation of COMISA, with women more likely to present with insomnia symptoms and men more likely to report witnessed apneas [42,43]. Furthermore, the OSA phenotype with "disturbed sleep" is more common among women than men with OSA [22,44]. Age is a known risk factor for OSA and insomnia independently and older age appears to be a risk factor for COMISA [45]. One study that examined both sex and age found a significant interaction between these two risk factors [46]. The highest prevalence of COMISA in men occurred between age 45 and 55, but the highest prevalence of COMISA in women occurred above age 55. In regards to OSA therapy, both age and sex influence adherence to PAP therapy with younger women using PAP less regularly than older men [47,48].

Race and ethnicity are also important demographic factors to consider in the presentation and treatment of COMISA. In one study, the OSA phenotype with "disturbed sleep" had the highest proportion of Blacks relative to the other four OSA subgroups [22]. Blacks are known to have increased prevalence of OSA and more severe disease burden relative to whites but poorer adherence to PAP therapy [49]. Furthermore, in clinical samples, Blacks have been reported to have poorer adherence to CBT-I therapy than White individuals [50]. Blacks, who on average sleep one hour less than white individuals, may find the sleep restriction component of CBT-I particularly challenging [51]. One study examining sex and ethnicity found that among those with OSA, White

women were most likely to report sleep maintenance insomnia while Hispanic women were most likely to report sleep onset insomnia [43].

Socioeconomic status (SES), such as level of education and marital/civil status should also be considered as part of patient-centered care. Low SES individuals are known to have greater risk of OSA and more disruptive, less efficient sleep [51]. Furthermore, lower SES individuals continue to have reduced adherence to PAP therapy compared to higher SES individuals [52]. In RCTs of insomnia, lower SES individuals have been found to have significantly higher rates of dropout [53]. The presence of a regular bed partner can impact the patient's presenting complaint and reason for treatment, as individuals who are married or have a regular bed partner might be more motivated to seek treatment and also to adhere to treatment. Ong et al [40] found that a high level of education and being married were both associated with better PAP use among COMISA patients, indicating that SES stability might improve treatment outcomes. This also suggests that those with low SES might benefit from additional patient education and individuals who do not have a regular bed partner might benefit from additional peer support.

Treatment Preferences

Although very little is known about the treatment preferences of COMISA patients, a mixed-methods study [35] provided important insights on the patient perspective of COMISA. First, COMISA patients were more inclined to define their sleep problem by their symptom profile (problems falling asleep or problems staying asleep) rather than by the diagnostic category (insomnia or OSA). Thus, clinicians should be cognizant of the patients' primary complaint, since presenting them with a treatment plan (e.g., starting with CPAP) that is inconsistent with their main complaint (e.g., problems falling asleep) might be counterproductive. A second finding revealed that COMISA patients were confused by having multiple sleep practitioners, rather than one "sleep doctor". For these patients, having two different treatments presented might be confusing and even conflicting. Since multidisciplinary teams are particularly well-suited to manage COMISA [54], patient education might be an important consideration to explain the process and benefits of this approach.

Treatment Accessibility

The COVID-19 pandemic has raised the importance of flexibility in access to clinical services, which is another important aspect of patient-centered care. Fortunately, management of COMSIA is adaptable to this environment given the rise of HSAT, telemedicine, and digital health. Clinical assessment of COMISA can be conducted using a combination of telehealth visits and online questionnaires to gather clinical information and HSAT to evaluate the presence of OSA. Many PAP machines can be adjusted automatically (i.e., auto-PAP) without face-to-face contact and most PAP machines use can be monitored remotely through the internet. Similarly, CBT-I can be conducted remotely using telehealth models which can increase access to a behavioral sleep medicine (BSM) provider, particularly in rural areas or when a BSM provider is not located nearby. Alternatively, automated digital CBT-I programs are available and preliminary results from an RCT suggest that it can improve insomnia symptoms but do not significantly improve PAP adherence or daytime sleepiness.[55] See Table 2 for further information on CBT-I delivery options.

<Insert Table 2 and Figure 2 about here>

A Model for Effective Clinical Management of COMISA

Progress to date has provided evidence to shift the clinical management of COMISA towards a multidisciplinary, patient-centered approach (see Figure 2). Rather than working exclusively from a provisional diagnosis or within specialties, a comprehensive multidisciplinary assessment should be conducted with input from behavioral, pulmonary, and other relevant specialties. This allows clinicians with various backgrounds to utilize their expertise with the respective diagnostic tools to develop a more comprehensive symptom profile. For example, pulmonary specialists can focus on symptoms related to sleep-disordered breathing and daytime sleepiness through a history and physical exam and PSG/HSAT data. Behavioral specialists can focus on symptoms related to insomnia and hyperarousal by using sleep diaries and actigraphy and assessing sleep-related behaviors. Patient considerations (e.g., preferences, demographics) and accessibility options (e.g., telehealth) and assessment of other sleep disorders (e.g., restless leg syndrome) and comorbidities (e.g., mood disorders) that could impact treatment decisions should also be conducted as part of this process by

both specialists. The data gathered can then be synthesized to develop a symptom profile to guide discussion among the multidisciplinary team regarding the most appropriate treatment approach. For many patients, an ideal combination would be a 4-session CBT-I delivered by a BSM provider early in the course of treatment along with PAP therapy initiated concurrently or shortly after CBT-I that is managed by a pulmonary or sleep specialist. Considerations should be given to patient preferences and accessibility of treatment with alternatives for digital CBT-I or telehealth monitoring. As part of this process, patient education about these treatments along with a discussion of the goals, expectations, and potential barriers can be useful to develop a treatment plan that prioritizes outcomes that are clinically important and personally relevant to the patient. After treatments are delivered, follow-up assessment on key outcomes of each treatment should be conducted to monitor treatment adherence and progress as part of quality care [56,57]. This includes AHI reduction, daytime alertness, and PAP adherence for PAP and insomnia remission/response for CBT-I. If needed, alternative treatment modalities can be considered. Since the current evidence is still inconclusive to provide specific guidelines on whether all patients with insomnia should receive a PSG/HSAT or the optimal sequence of treatments, this model for COMISA management encourages a dimensional assessment approach, patient engagement, and multidisciplinary expertise to help guide decision making.

Future Directions

Future research should continue to build upon these findings and investigate other areas that can improve precision and personalization of care. First, research is needed to validate data-driven assessment approaches for COMISA and to inform the implementation of these methods in clinical settings. The rise of wearable technologies and machine learning can provide an avenue to collect “real-world” data from patients and synthesize these into symptom profiles. Second, research is still needed to provide guidance on the optimal treatment combination or sequence. For example, are there patients with COMISA who should receive PAP first? Should patients be assessed at certain intervals during the treatment pathway to determine if they should continue with their current treatment or add another treatment? RCT designs such as the sequential multiple assignment randomized trial (SMART) can provide insights to these questions. Third, specific research is needed on patient-centered factors, such as demographic variables, patient preferences, and various delivery

methods that can enhance patient engagement and impact treatment response (e.g., culturally-tailored CBT-I, linguistically-tailored education on OSA and PAP). Finally, future studies should consider other treatment combinations beyond CBT-I and PAP. For example, what is the effectiveness of behavioral approaches combined with an oral appliance or upper airway stimulation? Integrating CBT-I with other cognitive-behavioral strategies for PAP adherence (e.g., motivational interviewing) could also be useful and preliminary findings from a recently completed RCT [58] has reported benefits for a broad CBT intervention. Future investigations such as these can provide more specific data to inform best practices for managing patients with COMISA.

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Figure Captions.

Figure 1 Caption. This figure illustrates the traditional model for clinical management of comorbid insomnia and sleep apnea (COMISA). The presenting complaint or reason for referral serves as the basis for provisional diagnosis (insomnia or OSA) which then leads to parallel clinical pathways. If insomnia is suspected, the assessment typically involves a clinical interview with sleep diaries, actigraphy, and questionnaires used as appropriate. The standard treatment is cognitive-behavioral therapy for insomnia (CBT-I) with short-term use of hypnotic medications appropriate in certain situations. If OSA is suspected, the assessment typically involves a clinical interview and exam followed by a PSG or HSAT, with questionnaires used as needed. The standard treatment is positive airway pressure (PAP) with other treatments such as oral appliance, upper airway stimulation, or surgery considered when appropriate.

Figure 2 Caption. This figure illustrates a working model for a patient-centered, multidisciplinary approach to the management of comorbid insomnia and sleep apnea (COMISA). Rather than working from a provisional diagnosis, pulmonary and behavioral specialists can use their relevant expertise in diagnostic tools to generate a symptom profile. Based on the findings from this comprehensive assessment, concomitant treatments using PAP and CBT-I should be considered. Follow-up assessment on key outcomes should be conducted after receiving each treatment (e.g., AHI reduction for PAP, insomnia remission for CBT-I) to determine if further treatment or alternative approaches are needed. Considerations of patient characteristics, treatment preferences and accessibility, treatment adherence and satisfaction are central throughout this process.