Chinese Guidelines for the Diagnosis and Treatment of Insomnia Comorbid with Obstructive Sleep Apnea in Adults (2024 Edition) Postprint

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Abstract

The co-occurrence of insomnia and obstructive sleep apnea (OSA) is termed comorbid insomnia and obstructive sleep apnea (COMISA). The prevalence of COMISA in the general population ranges from 0.6% to 19.3%, with main manifestations including difficulty falling asleep, frequent awakenings, early morning awakening, poor sleep quality, snoring with apnea during sleep, non-restorative sleep, daytime sleepiness, fatigue, decreased attention, impaired memory, mood disorders, and reduced quality of life, which can lead to multi-system adverse outcomes and increased all-cause mortality. Therefore, the diagnosis, differential diagnosis, and standardized treatment of COMISA are of significant importance. This guideline was developed by the Sleep Study Group of the Neurology Branch of the Chinese Medical Doctor Association and the Sleep Medicine Professional Committee of the Chinese Medical Doctor Association, who organized domestic experts in the field of sleep medicine. Based on the current status of COMISA diagnosis and treatment practices both domestically and internationally, and through literature evidence review and extensive discussion, this guideline summarizes and consolidates aspects of epidemiology, etiology and risk factors, pathophysiological mechanisms, clinical manifestations, assessment methods, diagnosis, differential diagnosis, and treatment, providing a decision-making basis for the diagnosis and treatment of COMISA to guide clinical practice.

Full Text

Preamble

Guideline · Consensus

Chinese Guideline for Diagnosis and Treatment of Co-morbid Insomnia and Sleep Apnea in Adults (2024 Edition)

Issuing Organizations: Sleep Medicine Committee, Chinese Medical Doctor Association; Sleep Disorders Group, Neurology Branch, Chinese Medical Doctor Association

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Abstract

Abstract When insomnia and obstructive sleep apnea (OSA) coexist, this condition is referred to as comorbid insomnia and sleep apnea (COMISA). The prevalence of COMISA in the general population ranges from 0.6% to 19.3%. It is primarily characterized by difficulty falling asleep, frequent nighttime awakenings, early morning awakening, poor sleep quality, snoring or apnea during sleep, unrefreshing or nonrestorative sleep, excessive daytime sleepiness, fatigue, attention impairment, memory impairment, emotional disorders, and impaired quality of life. COMISA can lead to adverse outcomes in multiple organ systems and increased all-cause mortality. Therefore, establishing standardized guidelines for the diagnosis, differential diagnosis, and treatment of COMISA is of significant clinical importance. This guideline was developed by the Sleep Medicine Committee of the Chinese Medical Doctor Association and the Sleep Disorders Group of the Neurology Branch of the Chinese Medical Doctor Association, organized by domestic sleep medicine experts. Based on current domestic and international COMISA diagnosis and treatment practices, it was formulated through comprehensive literature review and extensive expert discussion. The guideline summarizes evidence on epidemiology, etiology and risk factors, pathophysiological mechanisms, clinical manifestations, assessment methods, diagnosis, differential diagnosis, and treatment, providing a basis for clinical decision-making and guiding medical practice.

[**Keywords**] Insomnia; Obstructive sleep apnea; Comorbidity; Diagnosis and treatment; Guidelines

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1. Guideline Development Methodology

To standardize the diagnosis and treatment of COMISA, relevant domain experts developed the *Chinese Guideline for Diagnosis and Treatment of Comorbid Insomnia and Sleep Apnea in Adults* based on evidence-based medicine and consensus discussion. This guideline provides clinicians with a more comprehensive, standardized, and practical diagnostic and treatment protocol for adult COMISA.

The guideline was organized by the Sleep Disorders Group of the Neurology Branch and the Sleep Medicine Committee of the Chinese Medical Doctor Association, with participation from domestic sleep medicine experts. Based on current domestic and international COMISA diagnosis and treatment practices, and through extensive literature review and discussion, the guideline was finalized.

According to the *WHO Handbook for Guideline Development* (2015) and the *Guiding Principles for Developing/Revising Clinical Diagnosis and Treatment Guidelines in China (2022 Edition)* published in the *Chinese Medical Journal*, the guideline working group evaluated relevant guidelines, consensus statements, and literature, and used the GRADE method for evidence quality assessment and recommendation grading (Table 1 and Table 2). Literature searches were updated through June 2024. After screening, 142 articles and 41 guidelines/consensus statements were included, comprising 127 English and 15 Chinese publications. For important areas where ideal evidence could not be found in existing literature, expert consensus based on clinical experience was used.

Through systematic review, this guideline addresses four major clinical questions: (1) diagnostic and differential diagnostic methods and criteria for adult COMISA suitable for Chinese populations; (2) etiological and complication assessment methods for COMISA; (3) treatment approaches for COMISA; and (4) comprehensive diagnostic and treatment pathways and processes for COMISA.

Table 2. GRADE Evidence Quality Grading and Definition

Grade	Definition
High (A)	Very confident that the true effect is close to the estimated effect
Moderate (B)	Moderately confident in the effect estimate: true effect may be close to estimated effect, but could be substantially different
Low (C)	Limited confidence in the effect estimate: true effect may be substantially different from estimated effect

Grade	Definition
Very Low (D)	Very little confidence in the effect estimate: true effect is likely substantially different from estimated effect

2. Epidemiology

The prevalence of COMISA in the general population ranges from 0.6% to 19.3%. Among patients with insomnia symptoms, the comorbidity rate of OSA reaches 13.6% to 77.5%, while among OSA patients, the proportion with insomnia symptoms ranges from 23.4% to 88% [2-6]. In OSA patients, the prevalence rates of insomnia as the main complaint, any insomnia symptom, difficulty falling asleep, sleep maintenance difficulty, and early awakening are 38%, 36%, 18%, 42%, and 21%, respectively [9].

3. Etiology and Risk Factors of COMISA

3.1 Age and Gender

The prevalence of COMISA increases with age. It peaks between ages 45-55 years in males and after age 55 years in females, with comparable prevalence rates between genders. Among COMISA patients, the proportion of males ranges from 45.8% to 56.9% [3-5, 10].

3.2 Obesity

Obesity is a major risk factor for OSA, and OSA can in turn exacerbate obesity [11-12]. Insomnia patients with concurrent obesity or overweight are prone to developing COMISA. Studies in overweight populations report a COMISA prevalence of 11.37% [13], while among bariatric surgery candidates, the proportion ranges from 27% to 37.28% [14-15]. Research shows that BMI in COMISA patients is comparable to that in OSA patients and higher than in patients with insomnia alone or control groups [3-5].

3.3 Genetic Factors

While familial aggregation patterns for insomnia have not been definitively established, the incidence of insomnia is higher in monozygotic twins compared with dizygotic twins, and the proportion is also higher in first-degree relatives than in the general population [16]. Individuals with a family history of OSA have a 2-4 fold increased risk, with genetic predispositions in craniofacial structure abnormalities, obesity, and reduced respiratory center sensitivity [17]. There

are significant genetic overlap regions between OSA and insomnia, though local gene associations remain unclear. COMISA may express clinical manifestations of OSA and insomnia through different genetic pathways [6].

3.4 Use of Benzodiazepine Receptor Agonists (BZRAs)

BZRAs are commonly used to improve insomnia symptoms but can reduce respiratory center sensitivity to hypoxia and hypercapnia, decrease upper airway dilator muscle tone, and lead to upper airway collapse, ultimately inducing or worsening OSA. In OSA patients, recurrent upper airway collapse causes sleep apnea and hypoxia, while also activating the HPA axis, increasing cortisol secretion, and subsequently causing physiological hyperarousal and sympathetic nervous system excitation, leading to repeated nighttime awakenings/arousals, increased N1 and N2 sleep, and reduced N3 sleep. BZRA use is more common in COMISA patients than in the general population [4], and these drugs increase the risk of OSA in insomnia patients, with associations related to current use and cumulative dose [18].

3.5 Alcohol, Smoking, and Caffeine

Alcohol causes sleep fragmentation in the second half of the night, increased wake after sleep onset (WASO), and reduced REM sleep [19]. It decreases respiratory center sensitivity to hypoxia and hypercapnia, makes the upper airway more prone to collapse, and prolongs apnea duration by inhibiting central arousal mechanisms [20]. Alcohol increases the risk of both insomnia [19, 21] and OSA [20], and alcohol withdrawal can trigger insomnia [19], though the proportion and frequency of alcohol consumption in COMISA patients show no significant difference compared with the general population [3, 5].

Nicotine's central excitatory effects can cause insomnia and chronic upper airway inflammation that worsens respiratory disorders. Therefore, smoking increases the risk of both insomnia [22] and OSA [23], with higher smoking rates observed in COMISA patients compared with the general population [5].

Caffeine typically prolongs sleep latency (SL), reduces total sleep time (TST) and sleep efficiency (SE), decreases slow-wave sleep, and increases N1 sleep and awakenings, with dose- and time-dependent relationships [24]. While caffeine is often used to improve daytime sleepiness in OSA, some studies suggest it may increase OSA risk [23].

3.6 Somatic and Psychiatric Comorbidities

Hypertension, cardiovascular disease, diabetes, cerebrovascular disease, and psychiatric disorders are more likely to co-occur with COMISA [3-5, 25].

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4. Pathophysiological Mechanisms

Current research on COMISA pathophysiology explores the bidirectional interactions between the two disorders [26-28]. Chronic insomnia patients exhibit physiological hyperarousal, sympathetic activation, HPA axis overactivity, and disordered cortisol secretion rhythms, leading to increased cortisol, adrenocorticotropic hormone, and norepinephrine secretion. This increases nighttime awakenings, destabilizes sleep and breathing, increases N1 and N2 sleep, and decreases N3 sleep. During N1 and N2 sleep, upper airway muscle tone decreases, causing airway collapse, increased CO2 responsiveness, lowered respiratory arousal threshold, enhanced loop gain, and instability of respiratory center control in light sleep, ultimately leading to OSA. Additionally, chronic insomnia often causes fatigue, increased food intake, and reduced activity, resulting in weight gain, decreased lung capacity, and reduced upper airway anatomical volume, further predisposing to upper airway collapse and OSA.

In OSA patients, recurrent upper airway collapse causes sleep apnea and hypoxia while also activating the HPA axis, increasing cortisol secretion, and subsequently causing physiological hyperarousal and sympathetic excitation, leading to repeated nighttime awakenings/arousals, increased N1 and N2 sleep, reduced N3 sleep, increased nocturia, and disturbed sleep perception, ultimately worsening insomnia symptoms.

Although the two sleep disorders can influence each other, studies suggest their severity may have a non-linear relationship [29]. Long-term use of noninvasive positive pressure ventilation (NPPV) in OSA patients can improve mild insomnia symptoms but is ineffective for severe insomnia, particularly sleep-onset and early-morning awakening types [30]. Thus, hyperarousal caused by obstructive respiratory events can only partially explain insomnia symptoms in COMISA. For some severe and special types of chronic insomnia, mechanisms may relate to long-term maladaptive cognitive-behavioral patterns, individual traits, or genetic factors. COMISA patients show prolonged cortical arousal time and heart rate recovery time compared with OSA patients alone, suggesting insomnia has a synergistic effect on cortical activation and sympathetic activation in COMISA [31]. Cognitive behavioral therapy for insomnia (CBT-I) is first-line treatment for chronic insomnia and has clear efficacy in improving insomnia symptoms in COMISA while modestly reducing OSA severity, partially explaining that respiratory events in COMISA are associated with unstable sleep [26, 32]. Further research is needed to confirm the exact pathophysiological mechanisms of COMISA.

5. Clinical Manifestations

5.1 Typical Symptoms

- Sleep onset difficulty (SL $>$ 30 min), sleep maintenance difficulty ($\geq$ 2 awakenings per night), early awakening, poor sleep quality, and/or reduced TST (typically $<$ 6.5 h), with poor sleep perception.

- Patients report awakening from sleep due to choking or gasping, and witnesses report snoring, breathing interruptions, or mouth breathing during sleep, along with increased nocturia.

- Daytime dysfunction 主要包括: (1) fatigue, lack of energy, or general discomfort; (2) poor concentration or memory decline; (3) irritability; (4) daytime sleepiness; (5) behavioral problems (e.g., hyperactivity, impulsivity, or aggression); (6) increased errors and accidents; (7) anxiety about sleep, excessive concern about adverse effects of poor sleep, or dissatisfaction with sleep quality; and (8) functional impairment in social, family, occupational, or academic domains.

5.2 Multi-system Manifestations

Both insomnia and OSA are associated with multi-system diseases, and current research supports that COMISA is more prone to comorbidities across multiple systems, including:
(1) **Cardiovascular diseases**: hypertension, ischemic heart disease, arrhythmias, and valvular heart disease [4, 14, 33-34];
(2) **Endocrine system**: insulin resistance, glucose metabolism abnormalities, type 2 diabetes [35], lipid metabolism abnormalities [36-37], metabolic syndrome [38];
(3) **Respiratory system**: chronic obstructive pulmonary disease [39-40];
(4) **Genitourinary system**: nocturia [41-43], erectile dysfunction [44];
(5) **Digestive system**: gastroesophageal reflux [45];
(6) **Neurological and psychiatric systems**: cognitive impairment [46-47], mood disorders [48], restless legs symptoms [49], cerebrovascular disease [33, 39], and epileptic seizures [50-51].

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6. Assessment Methods

6.1 History Taking

6.1.1 Clinical Interview Clinicians should conduct detailed interviews with patients and family members, combined with questionnaire assessments and sleep diaries, to collect comprehensive history including specific sleep patterns, somatic and psychiatric symptoms, medication and substance use history, personal history, and family history.

Insomnia characteristics: Assess presence of sleep onset difficulty, frequent awakenings, difficulty returning to sleep, and early awakening, including precipitating factors, duration, and frequency.

Sleep-related breathing symptoms: Snoring, choking awakenings, breathing interruptions, mouth breathing, dry mouth, and morning headaches.

Sleep schedule: Bedtime, wake time, sleep onset time, wake-up time, eating and exercise patterns.

Other sleep-related symptoms: Nocturia frequency, enuresis, limb movements, abnormal behaviors, and altered consciousness.

Daytime functional impact: (1) Fatigue, low energy, or physical discomfort; (2) poor concentration or memory; (3) irritability; (4) daytime sleepiness; (5) behavioral problems; (6) increased errors/accidents; (7) anxiety about sleep; and (8) functional impairment.

Factors affecting sleep quality/quantity: (1) Somatic diseases (neurological, cardiovascular, respiratory, digestive, endocrine, skin pruritus, chronic pain); (2) psychiatric disorders (mood, anxiety, cognitive, other mental disorders); (3) medication/substance use history (antidepressants, stimulants, analgesics, sedatives, theophylline, steroids, alcohol, other psychoactive substances); (4) special periods (pregnancy, menstruation, lactation, perimenopause, major life events); (5) family history.

6.1.2 Physical Examination Routine physical examination includes: height, weight, BMI calculation, blood pressure, heart rate; examination of lips, eyelids, nail bed color; craniofacial morphology; nasal, oral, and pharyngeal examination; cardiopulmonary examination. For overweight patients (BMI $\geq$ 25 kg/m^2), neck, chest, abdominal, and hip circumference should also be measured.

6.2 Scale Assessment

Select self-rated or clinician-rated scales based on patient needs:
(1) Pittsburgh Sleep Quality Index for sleep quality;
(2) Insomnia Severity Index for insomnia severity;
(3) Stop-bang, Berlin questionnaire, and Epworth Sleepiness Scale (ESS) for sleep apnea risk;
(4) Anxiety scales: Generalized Anxiety Disorder scale, State-Trait Anxiety Inventory, Zung Self-Rating Anxiety Scale, Hamilton Anxiety Scale;
(5) Depression scales: Patient Health Questionnaire-9, Zung Self-Rating Depression Scale, Hamilton Depression Scale;
(6) Daytime function impact: ESS and Fatigue Severity Scale;
(7) Sleep-related cognitions: Dysfunctional Beliefs and Attitudes about Sleep questionnaire;
(8) Chronotype: Morningness-Eveningness Questionnaire;
(9) Sleep function outcomes: Sleep Apnea Quality of Life Index and SF-36.

6.3 Other Assessments

6.3.1 Polysomnography (PSG) PSG is the gold standard for diagnosing OSA and assessing sleep architecture. Studies show that compared with insomnia alone, COMISA patients have more significant N3 reduction, more pronounced N1 increase, greater WASO and arousal index increases, higher apnea-hypopnea index (AHI), and lower oxygen saturation. Compared with OSA alone, COMISA patients have prolonged sleep latency, longer WASO, lower SE, shorter TST, relatively reduced REM sleep, greater mismatch between subjective and objective sleep duration, relatively lower AHI, and higher minimum oxygen saturation. The mismatch between subjective and objective sleep time is more pronounced in COMISA [53]. PSG can also identify other sleep disorders such as periodic limb movements and parasomnias, and can be used for clinical efficacy evaluation. Sleep staging and event scoring should follow the latest *AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* [54]. For severely ill patients or when overnight PSG cannot be performed, split-night PSG can identify obstructive respiratory events but affects assessment of overall sleep quality.

6.3.2 Out-of-Center Sleep Testing (OCST) OCST, also called portable or home sleep monitoring, is suitable for: (1) patients with mobility issues or safety concerns; (2) lack of PSG facilities or urgent clinical situations; (3) high suspicion of OSA without complex comorbidities; (4) when PSG is not used and does not affect diagnosis of coexisting sleep disorders. OCST is generally not used for severe cardiopulmonary disease, neuromuscular disease, opioid use, or suspected severe sleep disorders. Note that some OCST devices lack EEG, chin EMG, and EOG monitoring, and can only assess respiratory events.

6.3.3 Actigraphy Actigraphy helps differentiate circadian rhythm sleep-wake disorders and assess treatment efficacy for insomnia symptoms.

6.3.4 Other Auxiliary Examinations Laboratory tests can assess factors affecting COMISA and comorbidities: blood routine, liver/kidney function, electrolytes, thyroid function, lipids, glucose; brain MRI, cephalometric analysis, nasopharyngeal endoscopy, Müller maneuver, upper airway 3D CT, upper airway MRI, esophageal pressure measurement, and drug-induced sleep endoscopy.

[**Recommendations**]
- Screen all patients with insomnia complaints for OSA-related symptoms (1A).
- If COMISA is suspected, perform PSG to assess sleep architecture and OSA severity (2A).
- If PSG is unavailable, consider OCST (2C).
- If OCST does not confirm OSA but clinical suspicion for COMISA remains high, repeat PSG assessment is recommended (2C).
- Do not use scales alone to diagnose COMISA (1A).
- For patients with suspected OSA, assess insomnia symptoms, questionnaires,

and sleep diaries to consider COMISA possibility (1A).
- For insomnia patients, record sleep diary at initial assessment (1C).
- Use ESS to assess daytime sleepiness when COMISA is suspected (1C).
- Evaluate for related conditions (thyroid dysfunction, acromegaly, ENT/dental diseases) when COMISA is suspected (1B).
- Assess for comorbid sleep disorders when COMISA is suspected (1C).
- When diagnosing COMISA, identify and diagnose other comorbidities and symptoms (1B).

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7. Diagnostic Criteria for COMISA

See Table 3 . Diagnosis requires meeting criteria A-H simultaneously.

Table 3. Diagnostic Criteria for Co-morbid Insomnia and Sleep Apnea

A. Presence of one or more abnormal sleep symptoms (self-reported or observed by caregivers): (1) difficulty falling asleep; (2) difficulty maintaining sleep; (3) early awakening.

B. Presence of one abnormal breathing symptom during sleep: witness reports of snoring, breathing interruptions, or mouth breathing; or awakening due to choking or gasping.

C. Presence of one or more daytime symptoms related to COMISA (self-reported or caregiver-reported): (1) fatigue, low energy, or general discomfort; (2) poor concentration or memory; (3) irritability; (4) daytime sleepiness; (5) behavioral problems; (6) increased errors/accidents; (7) anxiety about sleep; (8) functional impairment.

D. PSG or OCST shows predominantly obstructive respiratory events (including obstructive apnea, mixed apnea, hypopnea, and respiratory effort-related arousals) $\geq$ 5 events/hour.

E. Sleep symptoms and daytime symptoms cannot be explained solely by inadequate sleep opportunity or inappropriate sleep environment.

F. Sleep symptoms and daytime symptoms occur $\geq$ 3 nights/week.

G. Sleep symptoms and daytime symptoms persist for $\geq$ 3 months.

H. Not better explained by another sleep disorder.

Note: Although PSG shows respiratory event-related arousals, if other features are present···

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8. Differential Diagnosis

(1) Circadian Rhythm Sleep-Wake Disorders: Different types include advanced sleep-wake phase disorder (early sleep and awakening), delayed sleep-wake phase disorder (difficulty falling asleep and waking), non-24-hour sleep-wake rhythm disorder (cyclic pattern of sleep difficulty, reversal, early sleep, normal pattern), and irregular sleep-wake rhythm disorder ($ $3 irregular sleep periods daily). These require differentiation from COMISA' s sleep onset difficulty, frequent awakenings, early awakening, and daytime sleepiness. Specific sleep-wake patterns can be identified through clinical interview, sleep diary, and actigraphy.

(2) Obesity Hypoventilation Syndrome: Defined as obesity (BMI $>$ 30 kg/m^2) with elevated awake arterial CO_2 partial pressure [$PaCO_2 > 45$ mmHg (1 mmHg = 0.133 kPa)], often with marked daytime sleepiness. Snoring may not be a primary feature. These patients often have severe OSA and may experience subjective insomnia, allowing comorbid diagnosis.

(3) Restless Legs Syndrome: Patients experience sleep onset difficulty due to leg discomfort and frequent awakenings due to periodic limb movements, with daytime sleepiness requiring differentiation from COMISA. Periodic limb movements occur after sleep onset with characteristic PSG features unrelated to respiratory events. Respiratory event-related leg movements often resolve with NPPV treatment. Detailed history and PSG can differentiate.

(4) Panic Disorder: Nocturnal panic attacks can cause gasping/choking sensations with fear and severe dread, similar to OSA symptoms. However, PSG in nocturnal panic typically shows awakenings from N2 sleep without characteristic OSA changes. Patients may have difficulty falling asleep due to fear of attacks, and some have daytime panic history.

(5) Medication/Substance-Induced Insomnia or Respiratory Events: Substance use and withdrawal (including medications) can cause insomnia or respiratory events. Detailed history usually identifies the causative agent, and follow-up shows improvement after discontinuation.

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9. Treatment

9.1 Overall Goals and Intervention Strategies

Overall Goals: (1) Improve sleep quality and/or increase effective sleep time, reduce respiratory events, and improve nocturnal oxygen saturation; (2) Restore social function and improve quality of life; (3) Reduce risks of comorbid somatic and psychiatric conditions; (4) Minimize adverse effects of interventions.

Intervention Strategy: Single-modality treatment has limited efficacy. Individualized combined therapy is recommended. Insomnia-targeted interventions

include psychological therapy, pharmacotherapy, physical therapy, and traditional Chinese medicine. Psychological therapy includes sleep hygiene education and CBT-I, which effectively improve insomnia. Short-term pharmacotherapy has proven efficacy but requires consideration of risks in COMISA (increased respiratory events, hypoxia, long-term adverse effects, addiction). Physical therapies (light therapy, transcranial magnetic/electrical stimulation, diet, aromatherapy, massage, homeopathy) lack large-scale controlled studies and are optional adjuncts [52]. Traditional Chinese medicine has a long history but requires modern evidence [52].

OSA-targeted interventions include psychological therapy, lifestyle modification, myofunctional therapy, weight loss, positional therapy, NPPV, oral appliances, surgery, and pharmacotherapy. Psychological therapy, weight loss, positional therapy, and lifestyle changes are foundational. NPPV significantly improves respiratory events and hypoxemia but may worsen insomnia and has suboptimal adherence, requiring combination with health education, CBT-I, motivational interviewing, and enhanced follow-up. Oral appliances are effective for mild-moderate COMISA patients with craniofacial abnormalities. Surgical options (hypoglossal nerve stimulation, maxillofacial surgery, weight loss surgery) require strict indications. No drugs have proven efficacy for improving nocturnal respiratory events or hypoxia in adult OSA, though some improve daytime sleepiness with addiction risks.

9.2 Psychological and Behavioral Treatment

Psychological and behavioral treatments modify cognition, enhance self-efficacy, improve sleep quality, and increase treatment motivation and adherence.

9.2.1 Cognitive Behavioral Therapy for Insomnia (CBT-I) CBT-I is first-line treatment for chronic insomnia, effective for COMISA insomnia symptoms and modestly reducing OSA severity [26, 32]. CBT-I components include sleep hygiene education [56-57], relaxation therapy [57], stimulus control [58], sleep restriction [52, 57-59], cognitive therapy [52, 60], biofeedback [57, 60], paradoxical intention [58, 61], intensive sleep retraining [60], and mindfulness meditation [58, 62]. Different CBT-I methods are effective for COMISA insomnia, though specific implementation varies across studies [57-58, 63]. CBT-I improves NPPV adherence in COMISA [64]. However, stimulus control and sleep restriction may increase daytime sleepiness risk and require monitoring [60]. Sleep hygiene education should follow general insomnia rules [52] plus COMISA-specific content: (1) weight control through diet and exercise; (2) side-sleeping and head elevation; (3) adherence to NPPV or oral appliance therapy when prescribed. Good sleep hygiene is essential but insufficient alone.

9.2.2 Motivational Interviewing (MI) MI is a theory-driven, person-centered approach that elicits personal motivation for change, establishes goals, and promotes commitment. It improves adherence to initial NPPV therapy

[65], increases exercise [66], and combined with CBT improves anxiety [67]. MI content includes discussing NPPV benefits/risks, setting treatment goals, identifying facilitators/barriers, and promoting goal achievement. While no studies have examined MI combined with CBT-I specifically, MI increases community exercise levels and may enhance behavioral intervention effects in CBT-I.

9.2.3 Myofunctional Therapy Myofunctional therapy combines oropharyngeal exercises (oral and throat exercises) that improve respiratory function during sleep in OSA patients. These include isotonic and isometric exercises for oral, pharyngeal, and upper airway muscles involved in speaking, breathing, blowing, sucking, chewing, and swallowing, reducing AHI, improving sleep quality, and decreasing daytime sleepiness [68].

9.2.4 Exercise Exercise increases sleep drive, reduces weight, and improves OSA. Combined aerobic and resistance training is more effective than aerobic exercise alone for reducing AHI [69-70]. Exercise improves subjective sleep quality, reduces insomnia severity, and decreases daytime sleepiness [71-72]. It also improves fatigue levels [73]. Direct studies on exercise for COMISA are lacking.

[**Recommendations**]
(1) CBT-I is recommended as initial treatment for COMISA (1A).
(2) Health education and sleep hygiene should be combined with other treatments, not used alone (1C).
(3) For COMISA patients with excessive daytime sleepiness (EDS), use caution with stimulus control and sleep restriction as they may worsen EDS and accident risk; monitor EDS closely (2A).
(4) Use MI before NPPV to improve adherence (2A).
(5) Consider combining CBT-I with MI to enhance behavioral intervention initiation and maintenance (2D).
(6) Myofunctional therapy may be used as adjunctive treatment to improve respiratory events, sleep quality, and daytime sleepiness (2D).
(7) Exercise training is recommended for COMISA: 4-5 sessions/week of aerobic exercise, 60 min/session, for at least 8-12 weeks, with long-term maintenance advised (2D).

9.3 Pharmacotherapy

Pharmacotherapy targets insomnia and daytime sleepiness symptoms. No drugs have proven efficacy for reducing respiratory events or improving nocturnal hypoxia in COMISA [74-75].

9.3.1 Pharmacotherapy for Insomnia Symptoms Balance benefits and risks, considering effects on respiratory events, oxygen saturation, comorbidities, drug availability, cost, patient preference, adherence, prior response, and adverse

effects. Note that some sedating medications are contraindicated in sleep apnea; medication labels should be reviewed carefully.

9.3.1.1 Benzodiazepine Receptor Agonists (BZRAs)

BZRAs include benzodiazepines (BZDs) and non-benzodiazepines (NBZDs). BZDs are non-selective GABA-A receptor agonists with sedative, hypnotic, anxiolytic, muscle relaxant, and anticonvulsant effects. NBZDs are selective $ $1 subunit agonists with primarily hypnotic effects.

- **BZDs**: Improve insomnia but sedation and muscle relaxation may induce/worsen OSA and acute respiratory failure risk [76]. Contraindicated in hepatic/renal impairment, myasthenia gravis, and severe ventilatory dysfunction.

- **NBZDs**: Zolpidem, eszopiclone, and zopiclone have rapid onset for sleep onset and maintenance difficulties. Zaleplon' s short half-life suits only sleep onset difficulty. NBZDs have similar efficacy to BZDs but lower next-day residual effects and dependence risk. Short-term NBZD use at recommended doses improves objective sleep quality in OSA without worsening respiratory events, suggesting COMISA patients may benefit for insomnia symptoms and pressure titration success [77-78]. Eszopiclone improves NPPV adherence, but zolpidem and zaleplon need further study [79].

[**Recommendations**]
(1) Short-term eszopiclone may be used for COMISA insomnia and to improve NPPV titration success and adherence (2C).
(2) BZDs are not recommended for COMISA (1A).
(3) Zolpidem and zaleplon are not recommended for COMISA (2C).

9.3.1.2 Melatonin and Melatonin Receptor Agonists (MRAs)

Melatonin regulates sleep-wake cycles but is ineffective for chronic adult insomnia [80]. Prolonged-release melatonin shortens sleep latency and improves SE, with better effects in insomnia patients >55 years [81]. Ramelteon, an MT1/MT2 agonist, shortens sleep latency, improves SE and TST, and is approved for long-term insomnia treatment without dependence or withdrawal. Studies show ramelteon during NPPV does not affect AHI, ESS scores, or mean oxygen saturation while improving NPPV adherence without serious adverse effects [82-83].

Agomelatine is both an MRA and 5-HT2C antagonist with antidepressant and hypnotic effects, improving depression-related insomnia by shortening sleep latency and increasing sleep continuity. A randomized single-blind study in mild-to-severe OSA showed agomelatine increased TST, improved SE, and reduced awakenings without affecting other sleep parameters or respiration [84].

[**Recommendations**]
(1) Melatonin is not recommended for COMISA insomnia (1B).
(2) Short-term prolonged-release melatonin may be used for COMISA insomnia

in patients >55 years (2C).
(3) Ramelteon may be used for COMISA insomnia (2C).
(4) Agomelatine may be used for COMISA insomnia (2C).

9.3.1.3 Orexin Receptor Antagonists (ORAs)

Suvorexant, lemborexant, and daridorexant are approved for adult insomnia (sleep onset and maintenance) in the US and Europe [85-86]. ORAs reduce sleep latency, decrease WASO, and increase TST and SE with better tolerability than NBZDs, MRAs, and placebo [87]. Adverse effects include increased daytime sleepiness, parasomnias, fatigue, dry mouth [88], pharyngitis, and headache [89].

Studies show suvorexant alone or combined with zolpidem does not increase AHI [90]. Lemborexant in mild OSA showed no AHI increase or oxygen desaturation after single and 8-day use [91], with similar results in moderate-severe OSA [92]. Daridorexant in mild-moderate OSA also showed no AHI or oxygen saturation changes while improving sleep parameters [93]. Current evidence suggests ORAs improve COMISA insomnia without affecting respiratory events.

[**Recommendation**] Short-term ORAs may be used for COMISA insomnia (2C).

9.3.1.4 Antidepressants with Sedative-Hypnotic Effects

Some antidepressants have H1 and 5-HT2C antagonism, reducing arousal threshold and improving upper airway muscle tone, potentially effective in COMISA with anxiety/depression. However, evidence comes from small studies in depression, insomnia, or OSA patients, with low reliability.

- **Tricyclics**: Low-dose doxepin (3-6 mg/d) improves subjective sleep quality, SE, and TST without affecting sleep latency, with good tolerance and no withdrawal. Observational studies show doxepin improves NPPV adherence [94].

- **Trazodone**: Low-dose trazodone (25-150 mg/d) has sedative-hypnotic effects, increases N3 sleep, and treats chronic insomnia and hypnotic discontinuation rebound. Preliminary studies show trazodone increases arousal threshold [96], reduces AHI [97], and improves post-stroke OSA severity [98], alone or combined with atomoxetine, and improves NPPV adherence [60].

- **Mirtazapine**: Low-dose mirtazapine (3.75-15.00 mg/d) has minimal effect on sleep latency, increases N3 sleep, but is not used alone for insomnia. Mirtazapine (4.5-50 mg/d) does not improve AHI and may increase weight and worsen OSA [75, 99], though it may improve NPPV adherence [94]. It also increases restless legs and periodic limb movements [100]. No studies evaluate mirtazapine specifically for COMISA.

[**Recommendations**]

(1) Short-term doxepin may be used for COMISA insomnia and to improve NPPV adherence (2C, 2D).
(2) Trazodone may be used for COMISA insomnia (2B) and to improve NPPV adherence (2D).
(3) Long-term mirtazapine alone is not recommended for COMISA insomnia (2D); short-term use may improve NPPV adherence (2D).

9.3.2 Pharmacotherapy for Daytime Sleepiness Studies on daytime sleepiness medications come from OSA patients, lacking COMISA-specific research. These drugs' main adverse effect is insomnia, and whether they worsen COMISA insomnia is unclear. COMISA patients with marked daytime sleepiness may receive appropriate medications (e.g., pitolisant [101-102], modafinil/armodafinil [103], solriamfetol [102, 104]) after adequate NPPV and other sleep improvements, with monitoring for insomnia adverse effects.

9.3.3 Pharmacotherapy to Reduce AHI Preliminary studies suggest some agents (tramazoline, semaglutide, liraglutide, spironolactone/furosemide, acetazolamide, dronabinol, zonisamide, phentermine, spironolactone, ondansetron/fluoxetine) may reduce AHI compared with placebo, but no drugs are currently recommended to reduce AHI due to insufficient evidence [75].

9.4 NPPV Therapy

NPPV is an effective OSA treatment [105-106], including CPAP, APAP, and BPAP. Mode selection for COMISA follows OSA guidelines [107-108]. NPPV can improve subjective sleep quality, sleep perception, TST, and SE while reducing WASO in some COMISA patients [109]. However, COMISA patients are less likely to initiate NPPV, use it fewer hours per night, and have poorer long-term adherence [28]. COMISA patients should undergo pressure titration and mode selection under professional guidance, with insomnia-improving strategies to enhance titration success and adherence.

Relative contraindications for NPPV: (1) pulmonary bullae on imaging; (2) pneumothorax or mediastinal emphysema; (3) marked hypotension (<90/60 mmHg); (4) unstable acute myocardial infarction; (5) CSF leak, head trauma, or intracranial air; (6) uncontrolled acute otitis media, rhinitis, sinusitis; (7) glaucoma [55].

[**Recommendations**]
(1) Use laboratory CPAP or home APAP for pressure titration in COMISA without significant complications (1A).
(2) Continue CPAP or APAP for COMISA treatment (1A).
(3) Use BPAP for CPAP/APAP-intolerant patients, those requiring pressures >15 cmH_2O, or with alveolar hypoventilation (COPD, neuromuscular disease, obesity hypoventilation) (1B).
(4) Modified pressure modes may be used for adherence-difficult or CPAP-intolerant patients (2D).

(5) Use nasal mask as first choice if no patient preference (1A); heated humidification is recommended to reduce adverse effects (1A). Split-night studies are acceptable emergencies for patients with severe OSA or prolonged apneas causing severe hypoxia; however, do not use split-night titration results directly for treatment. Repeat full-night titration is recommended if optimal pressure cannot be determined or adherence is poor (1C).
(6) For COMISA patients who cannot accept NPPV, consider non-NPPV treatments to reduce OSA severity and nocturnal hypoxia (1C).

9.5 Oral Appliance Therapy

Oral appliances protrude and stabilize the mandible during sleep to maintain airway patency. Studies in OSA show oral appliances reduce respiratory events and hypoxemia, improve sleep architecture and daytime sleepiness, with better tolerance and adherence than NPPV, though less effective on respiratory events [110].

[**Recommendations**]
(1) Oral appliances are recommended for COMISA patients unwilling or unable to tolerate NPPV with AHI/RDI/REI 5-15 events/h (1B).
(2) Use PSG to titrate oral appliances and confirm efficacy (2C).

9.6 Hypoglossal Nerve Stimulation

Hypoglossal nerve stimulation uses an electrode on the distal hypoglossal nerve that discharges during inspiration to protrude the tongue and enlarge the retroglossal airway. It reduces respiratory events, improves oxygen saturation, decreases daytime sleepiness, and improves sleep and quality of life [111-113]. Retrospective studies show similar adherence in COMISA and OSA patients, with greater insomnia and daytime sleepiness improvement in COMISA patients with moderate-severe insomnia [114], though another study found shorter usage time in COMISA vs. OSA [115].

[**Recommendation**] Hypoglossal nerve stimulation may be used for moderate-severe COMISA patients who are NPPV-intolerant or unresponsive (2D).

9.7 Surgical Treatment

Surgical options include bariatric surgery for obesity [116-117] and upper airway surgeries (nasal, tonsil/adenoid, uvulopalatopharyngoplasty, soft palate implants, tongue base/hyoid surgery, maxillary/mandibular advancement) to reduce AHI and improve nocturnal hypoxia [118]. Referral and procedure selection should be based on specific patient problems, following OSA surgical studies [119]; direct COMISA evidence is lacking.

[**Recommendations**]
(1) Refer COMISA patients with BMI $\geq$ 37.5 kg/m^2 without contraindications for bariatric surgery evaluation (1A).

(2) Refer COMISA patients not accepting NPPV with BMI < 40 kg/m^2 for surgical consultation (1A).
(3) Refer COMISA patients with BMI ≥ 35 kg/m^2 who are NPPV-intolerant or non-accepting for bariatric surgery evaluation (1A).
(4) Refer COMISA patients with BMI < 40 kg/m^2 and persistent NPPV intolerance due to adverse effects to sleep surgeons to discuss surgical options (2A).
(5) Use NPPV as initial treatment for COMISA with upper airway abnormalities, then consider surgical referral (2A).

9.8 Weight Loss

Behavioral, pharmacological, and surgical weight loss reduce OSA severity and improve quality of life [116-117]. Current evidence comes from OSA management; direct COMISA studies are lacking.

[Recommendations]
(1) Overweight/obese COMISA patients should receive comprehensive lifestyle intervention including low-calorie diet, exercise, and behavioral counseling (1C).
(2) Low-calorie diet and exercise are recommended as foundational management (2C).
(3) For COMISA patients with BMI ≥ 27 kg/m^2 without cardiovascular disease who fail lifestyle modification, consider weight loss medications (2D).
(4) For COMISA patients with BMI ≥ 37.5 kg/m^2 who fail lifestyle intervention, consider bariatric surgery evaluation if no contraindications (2D).

9.9 Other Treatments

Light therapy, transcranial magnetic stimulation, transcranial electrical stimulation, and traditional Chinese medicine/acupuncture have some efficacy for insomnia [52], but effects on OSA are unknown.

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10. Summary

Based on the above evidence and recommendations, individualized diagnostic and treatment plans should be selected according to COMISA patient characteristics (Figure 1 [Figure 1: see original paper]).

Figure 1. Diagnostic and Treatment Flowchart for Comorbid Insomnia and Sleep Apnea
[Figure 1: see original paper]

Note: OSA = obstructive sleep apnea, ESS = Epworth Sleepiness Scale, STOP-BANG = OSA risk screening tool, PSQI = Pittsburgh Sleep Quality Index, ISI = Insomnia Severity Index, PSG = polysomnography, OCST = out-of-center sleep testing, AHI = apnea-hypopnea index, RDI = respiratory disturbance index, REI = respiratory event index, COMISA = comorbid insomnia and

sleep apnea, CBT-I = cognitive behavioral therapy for insomnia, NBZDs = non-benzodiazepine drugs, NPPV = noninvasive positive pressure ventilation.

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References: [1] through [119] as cited throughout the guideline.

Note: Figure translations are in progress. See original paper for figures.