

Sleep dysfunction, diabetes, and pain: A troublesome triad

Critical to helping patients break the stranglehold of these 3 comorbidities is an understanding of how they interact with one other.

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Sleep dysfunction, diabetes mellitus, and pain are overlapping conditions that clinicians see daily. Consider these statistics: As many as 70% of Americans have complaints about their sleep.¹ Diabetes is a national epidemic; 8% of the US population has it (a 10-fold increase from 1960) and another 25% has prediabetes.² Chronic pain is thought to occur in 15% of the population.³ Research increasingly substantiates the overlap and interaction among these 3 comorbidities.⁴⁻⁶

The increasing incidences of sleep disorders, diabetes, and chronic pain underscore the need to approach these conditions with new insights regarding their interconnectedness. Such knowledge enables us to better understand how a patient's comorbidities influence each other. Understanding these interrelationships will also help physicians and other providers thoroughly assess a patient's clinical profile and develop a comprehensive treat-

ment strategy that will improve outcomes—including quality of life.

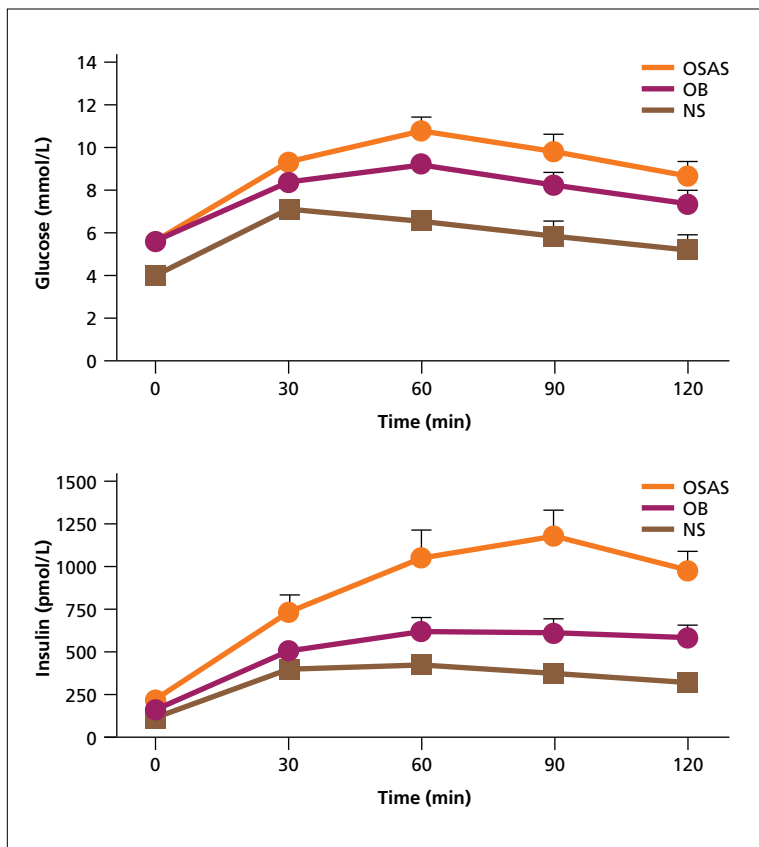


Illustration: Dave Cutler

Disclosure

The author reported no potential conflict of interest relevant to this article.

FIGURE 1: Obstructive sleep apnea independently increases risk of insulin resistance

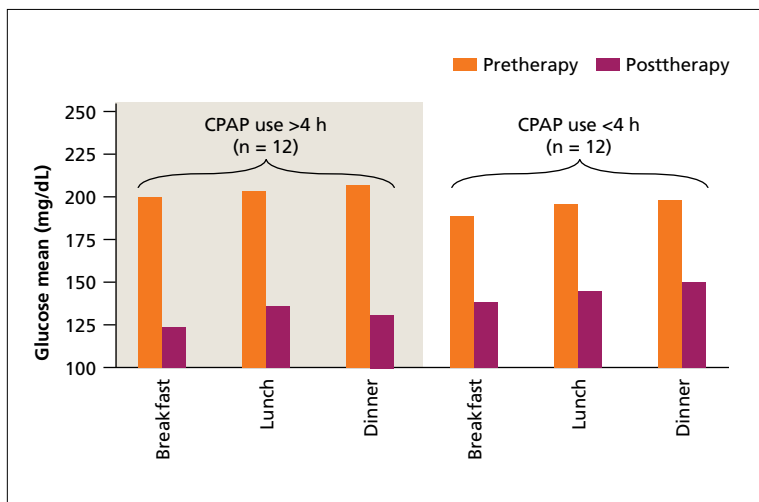


After an oral glucose tolerance test, obese patients with OSA ($n = 30$) exhibited higher serum levels of glucose and insulin than patients with obesity alone ($n = 27$) or normal subjects ($n = 20$) in a study conducted in Italy.

NS, normal subjects; OB, obesity; OSAS, obstructive sleep apnea (syndrome).

Source: Tassone F, et al.¹³

FIGURE 2: CPAP reduces postprandial glucose values



In patients with diabetes and a documented sleep disorder ($n = 25$), CPAP therapy consistently lowered glucose levels after meals, with the recommended duration of >4 hours yielding superior results.

CPAP, continuous positive airway pressure.

Source: Babu AR, et al.¹⁴

Sleep dysfunction and diabetes: An underrecognized association

Diabetes-related nocturia or pain from diabetic peripheral neuropathy (DPN) can worsen sleep or cause sleep loss. We also know that sleep dysfunction increases consumption of sugary foods,⁷ which, in patients with diabetes and prediabetes will lead to worsening control of hemoglobin A1c (HbA1c). Sleep deprivation is also linked with prediabetes. In addition, lack of adequate sleep or fractured sleep is related to weight gain, and weight gain can worsen insulin resistance and glucose intolerance.

Obstructive sleep apnea (OSA)—all too often missed. Fifty percent of men and 20% of women with type 2 diabetes have OSA⁴; 97% of obese patients with diabetes are thought to have OSA.⁸ Despite these staggering numbers, up to 85% of sleep apnea cases go undiagnosed.⁹ Interestingly, OSA may have a causal role in the development of diabetes.¹⁰ Worsening diabetes in patients with OSA has been attributed to such mechanisms as^{11,12}:

- intermittent hypoxia (reduces insulin sensitivity)
- increased sympathetic activity with a rise in norepinephrine (NE) level
- increased hepatic glucose and muscle glycogenolysis
- lipolysis leading to a rise in free fatty acids (insulin resistance)
- a substantial increase in cortisol secretion
- increased glucagon and glucocorticoids
- an adipose leptin increase
- increased levels of interleukin (IL)-6 and tumor necrosis factor (TNF)- α .

Through these mechanisms, OSA is associated with insulin resistance independent of obesity,¹¹ depicted in [FIGURE 1](#).¹³

Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to improve diabetes control and reduce insulin needs ([FIGURE 2](#)).¹⁴ Sleep practitioners should also be aware of the interrelationship of OSA and diabetes, because 30% of patients presenting to a sleep clinic have impaired glucose tolerance or diabetes, of which 40% are undiagnosed.¹⁵ (See page S22 to read how one patient's comorbidities were managed in "Case: Providing pain relief to a patient with diabetes, neuropathic pain, and obstructive sleep apnea.")

The International Diabetes Foundation has recommended that everyone with type 2 diabetes be screened for sleep apnea.¹⁶ This does not mean everyone with type 2 diabetes needs to undergo a formal polysomnography study.

But awareness of the comorbidity of diabetes and OSA should prompt an inquiry about sleepiness, snoring, and witnessed apnea and, if clinically indicated, referral for further testing or treatment.

Diabetes and pain: Focus on glycemic control

Sixty percent to 70% of patients with diabetes have some form of neuropathy, and it is particularly common in patients who have had diabetes for >25 years.⁵ Neuropathy is painful for >30% of patients with diabetes,⁵ but it can also produce tingling and numbness. And some patients with neuropathy are asymptomatic. Diabetic neuropathy can affect every organ system and can occur in various forms.

Causes of DPN are multifactorial and include such metabolic factors as high glucose, high fat, or low insulin; neurovascular factors that result in damage to vessels carrying oxygen and nutrients to the nerves; autoimmune factors that produce neurotoxic inflammation; mechanical injuries, most commonly carpal tunnel syndrome at the wrists and ulnar nerve entrapment at the elbows; and lifestyle factors, such as smoking and alcohol use. Exact mechanisms can vary and are thought to include polyol pathway activation, protein kinase C activation, oxidative stress, poly(ADP-ribose) polymerase activation, alteration in neurotrophic factors, advanced glycation end product formation, and essential fatty acid abnormalities.

Treatment of diabetic neuropathy begins with tight glucose control, which has been shown to slow the progression of DPN. Several medication options are also available (TABLE).¹⁷⁻²² Tricyclic antidepressants, such as amitriptyline, desipramine, and nortriptyline, are inexpensive and effective in reducing the pain of DPN.¹⁷ But they can cause dry mouth, constipation, and sedation.

Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is approved by the US Food and Drug Administration (FDA) for DPN and is usually helpful at 60 mg daily.¹⁸ Nausea occurs in a third of patients. Duloxetine may act by improving neurotransmitter function in the periaqueductal gray matter and descending pain inhibitory pathways.

Anticonvulsants are commonly prescribed for patients with DPN. Carbamazepine was used for many years with success, but it can cause sedation and hyponatremia. Gabapentin, in the so-called gabanoid class, is usually

TABLE
Pharmaceutical and nutraceutical agents used to treat painful diabetic neuropathy¹⁷⁻²²

Agent	Customary dose (maximum)
Tricyclic antidepressants	
Amitriptyline	10 (150) mg at bedtime
Desipramine	25 (150) mg at bedtime
Nortriptyline	25 (150) mg at bedtime
Serotonin norepinephrine reuptake inhibitors	
Duloxetine	60 (120) mg/d
Venlafaxine	37.5 mg/d or bid (225 mg/d)
Anticonvulsants	
Gabapentin	100 (1200) mg tid
Pregabalin	50 (200) mg tid
Opioids/opioid-like substances	
Oxycodone	10 (40) mg bid
Tramadol	100 (400) mg/d
Nutraceuticals	
α -Lipoic acid	100 mg bid
Metanx (vitamin B supplement)	2 capsules daily

taken in a dosage of 100 to 600 mg tid, but clinicians should watch for sedation, edema, and weight gain.¹⁸ Another gabanoid, pregabalin, has a similar adverse effect profile and is FDA approved for DPN; the usual dosage is 50 to 200 mg tid.¹⁹ Pregabalin is an α -2 γ calcium channel blocker and likely mediates its effects through reduction in substance P levels.¹⁹

Opioids such as oxycodone or opioid-like drugs such as tramadol can also be used sparingly. High-potency narcotics are not recommended.

Supplementation with α -lipoic acid 100 mg bid has been shown to reduce diabetic neuropathy deficits.²⁰ Metanx, a vitamin-B–derived supplement, is FDA approved for DPN.²¹

Pain and sleep dysfunction: Ask the right questions

While chronic pain affects 15% of the general population, its prevalence rises to >50% among older adults.³ In chronic pain patients,

CASE**Providing pain relief to a patient with diabetes, neuropathic pain, and obstructive sleep apnea**

A 53-year-old man with diabetes was referred to our neurology department for painful diabetic neuropathy. He is obese and has had type 2 diabetes for 28 years. His feet have been numb for 5 years and painful for >1 year. He says that the pain is worse at night. The patient describes the pain as either burning or electrical, and it significantly interferes with his ability to sleep. Taking gabapentin 600 mg tid has helped reduce the pain substantially, but his weight has increased 50 lb in the last year. His wife says he now snores and stops breathing at night.

Patient history, physical exam findings, lab results

- Medications: Lantus (insulin glargine) 120 units at bedtime; NovoLog (insulin aspart) 20 units tid, plus sliding-scale insulin for meals. Four antihypertension agents—hydrochlorothiazide, atenolol, lisinopril, and nadolol. Gabapentin for diabetic peripheral neuropathy (DPN)
- Blood pressure: 150/92 mm Hg; body mass index: 36
- Nearly absent deep tendon reflexes; absence of vibration stimulation below the knees; diminished pinprick sensation in the feet. Romberg test is positive; tandem gait test is negative. Strength coordination, cranial nerves, and mental status are normal. Epworth Sleepiness Scale is 12 (>10 is pathologic and represents sleepiness)
- Hemoglobin A1c (HbA1c) level is 9.2%.

Initial management plan

The patient underwent a sleep study in which polysomnography revealed severe obstructive sleep apnea, with an apnea-hypopnea index of 69 events per hour. Oxygen desaturation reached a nadir of 78%, and apnea episodes lasted >60 seconds. Continuous positive airway pressure (CPAP) titration showed an optimal pressure of 13 cm, and nightly CPAP therapy was initiated.

We discontinued the patient's gabapentin because of his weight gain and daytime sedation, and prescribed duloxetine 30 mg daily for 2 weeks, then 60 mg daily. We also began α -lipoic acid for DPN.

Follow-up at 1 month

The patient adhered to his CPAP treatment and said he was feeling less sleepy. His Epworth Sleepiness Scale score dropped to 5. His wife said that he no longer snored. His blood pressure dropped to 122/82 mm Hg. The patient reported a number of hypoglycemic episodes, and his primary care physician reduced his Lantus dosage to 80 units at bedtime and his NovoLog boluses to 15 units tid. (Management of obstructive sleep apnea frequently improves diabetes control and increases insulin sensitivity.¹⁴) The duloxetine controlled the patient's DPN. And, with the elimination of gabapentin and treatment of his sleep apnea, his weight dropped by 10 lb.

Follow-up at 3 months

The patient's weight decreased an additional 15 lb without a change in diet. His blood pressure dropped further to 120/78 mm Hg, allowing discontinuation of atenolol and reduction of the nadolol dosage. His HbA1c was 7.8%, and insulin requirements were further reduced. He was sleeping well without snoring and was no longer sleepy during the day. The patient's DPN remained under control with duloxetine.

Patients enter a vicious cycle wherein pain interferes with sleep, and lack of proper sleep worsens pain.

>50% complain of poor or "unrefreshing" sleep, diminished or fragmented sleep, and increased pain.⁶ Consequently, patients enter a vicious cycle wherein pain interferes with sleep, and lack of proper sleep worsens pain. Many chronic pain disorders commonly affect sleep: back pain, headache, facial pain and temporomandibular joint disorder, musculoskeletal pain, fibromyalgia syndrome, and premenstrual dysphoric disorder. Also, many pain medications used for these conditions can fragment sleep.

Investigating patients' sleep and pain connection starts with a thorough history of their sleep patterns. Do they have a sleep dis-

order, such as sleep apnea, restless legs syndrome, insomnia, or hypersomnia? Do they have circadian issues, such as advanced or delayed sleep phase, or do they do shift work? It is now known that, compared with those who work during customary daytime hours, shift workers have higher morbidity and mortality and increased risk of cancer, cardiovascular disease, mental illness, and gastrointestinal disturbances.^{23,24}

How old are their pillows and mattress? Mattresses should probably be replaced at least every 7 to 8 years.²⁵ Modern adjustable mattresses and various memory foams can improve

sleep for patients with chronic musculoskeletal complaints.

Is their sleep environment safe, quiet, clean, and comfortable? Sleep hygiene issues, such as having a computer in the bedroom or sleeping with a TV on, drinking too much caffeine, not having a wind-down ritual, minimizing the need for at least 7 hours of sleep nightly, or obsessing about sleep can all adversely affect sleep. Cognitive-behavioral therapy can usually correct refractive sleep hygiene issues.

Many medications can interfere with sleep, including antidepressants, stimulants, and β -blockers. Sedatives commonly prescribed for insomnia will worsen deep restorative sleep over time.

Lastly, do patients have a routine exercise program or adequate stress-coping mechanisms? Consider all of these issues when addressing chronic pain and sleep complaints. If patients are at risk for sleep-disordered breathing, such as sleep apnea, or complain of hypersomnia, refer them to a sleep specialist for formal sleep testing.

The importance of sleep architecture

Most people need to sleep 7 to 8 hours to feel rested. Some people need more or can do with less sleep, but inadequate (<4 hours) and excessive (>9 hours) sleep have both been associated with increased morbidity and mortality.²⁶

Sleep is a highly regimented and organized series of altered states. Light sleep, stages 1 and 2, constitutes about 50% of sleep and is scattered throughout the night. Deep sleep (stages 3 and 4), which is thought to be restorative for the body and especially important for pain processing, constitutes around 25% of sleep by the fourth decade of life and is clustered only in the first 4 to 5 hours of sleep. People with chronic pain, such as patients with fibromyalgia or the elderly, typically have less than 5% deep sleep.²⁷ What is not clear is whether the lack of deep sleep is the cause or the effect of chronic pain. Most likely the relationship is reciprocal, a negative-feedback loop wherein pain affects sleep and lack of deep sleep affects pain.

Rapid eye movement (REM) sleep, the state associated with dreaming, constitutes approximately 25% of sleep and is clustered in the morning hours. Although the purpose of REM sleep is not entirely clear, it appears to be important for such mental processing as mood stabilization and memory consolidation. Depressed patients usually have more REM periods and

start them earlier in the night, which interferes with deep sleep. Most antidepressants reduce REM sleep.²⁸

Both deep sleep and REM sleep appear to be helpful in "resetting" pain thresholds. In particular, length and quality of deep sleep correlate inversely with pain. The mechanism of interaction between pain and sleep is not clear but may involve 5-HT serotonin receptors, NE release, and substance P neuropeptide regulation.

As mentioned, many pain and sleep medicines can interfere with normal sleep architecture. Because of the connection between deep sleep and pain, investigative approaches have used sodium oxybate, which significantly increases deep sleep. Sodium oxybate is FDA approved for narcolepsy-related hypersomnolence and cataplexy. However, in a study of more than 500 patients with fibromyalgia syndrome and chronic pain, sodium oxybate 4.5 or 6 g taken nightly significantly reduced pain by >30% in most patients and by >50% in nearly half of patients.²⁹ This degree of pain relief is equal to or greater than that provided by the 3 FDA-approved medications for fibromyalgia: pregabalin, duloxetine, and milnacipran.²⁹ Moreover, the added benefit of sodium oxybate for sleep and fatigue shown in the study is not seen with gabapoids or SNRIs.

Adverse effects of sodium oxybate include slower breathing, confusion, depression, edema, dizziness, vomiting, bedwetting, and sleepwalking. Avoid giving sodium oxybate to patients with a history of deep sleep parasomnias, such as sleepwalking or night terrors. Also, patients with heart failure and hypertension are not good candidates for the sodium oxybate because it has a high salt content; the typical dosage contains several grams of sodium.

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