Gastroesophageal Reflux Disease and Sleep Disorders: A Wake-Up Call for Physicians and Their Patients

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Sleep’s implications to the physiology and pathogenesis of a number of diseases have been ignored until recently. With the evolution of studies conducted in sleep laboratories, the relationship between various gastrointestinal diseases, in particular gastroesophageal reflux disease (GERD), and sleep disorders is being recognized. This article discusses the personal and societal impact of GERD-related sleep disorders, including quality of life issues and work and leisure impairment. A review of intervention studies indicates that GERD-related sleep disorders respond effectively to acid-suppressive medical therapy. Clinicians are advised to take a proactive stance in evaluating patients with GERD for unrecognized sleep disorders and ascertaining whether patients with sleep disorders have GERD symptoms as well.

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Sleep is a phenomenon experienced by virtually all mammalian species and is associated with remarkable behavioral as well as physiologic changes. It is a reversible state of behavior and responsiveness that is associated with revitalization and alertness. Restful sleep occupies the heart of a person’s physical and emotional well-being, and simply missing a few hours reminds us of this fact. A sleep disorder can affect every area of a person’s life, causing fatigue, excessive daytime sleepiness, irritability, depression, anxiety, lack of concentration, and lost productivity.
Sleep's implications to the physiology and pathogenesis of a number of diseases have been ignored until recently. With the evolution of sleep laboratories, the relationship between sleep and various gastrointestinal diseases, in particular gastroesophageal reflux disease (GERD), is being recognized. It seems intuitive that daytime activities or events may affect sleep and that consequent sleep dysfunction may in turn affect daytime function.

Although there is considerable agreement that GERD affects sleep, a gap in the knowledge of the scope of this association remains. This review will serve to 1) further develop an awareness of the prevalence of this association, 2) define and clarify the relationship with GERD and sleep disorders, 3) develop an awareness of the implications of GERD-related sleep disorders, and 4) examine the effects of treatment for GERD-related sleep disorders.

**Sleep Disorders**

The clinical definition of a sleep disorder is a disruptive pattern of sleep that may include difficulty falling or staying asleep, falling asleep at inappropriate times, excessive total sleep time, or abnormal behaviors associated with sleep. Over 100 different sleeping/waking disorders have been identified and each one has a different causation. Studies reveal that over 40 million Americans suffer from a sleep disorder, with the majority receiving little or no treatment.

**Consequences of Sleep Disorders**

More than half of American adults say they sleep badly most nights, and nearly 1 in 5 complain of feeling tired or fatigued every day, according to a National Sleep Foundation (NSF) nationwide poll of 1506 respondents over 18 years of age. Half of employed adults reported showing up late for work—or missing work—because they overslept, did not feel rested in the morning, went to bed too late, or slept poorly. Many also reported being error prone on the job.

Intimacy is also affected by sleep disorders. One fourth said they have sex less often or have lost interest in sex because they felt too sleepy. One third said their partner’s snoring, kicking, frequent awakenings, or other sleep problems caused them to lose nearly an hour of slumber every night. About one fourth sleep in a separate bed or room, or use earplugs or an eye mask to help foster sleep.

Sleep dysfunction–related psychiatric diagnoses were also frequently reported in the NSF poll. Eighteen percent of survey respondents reported a diagnosis of sleep dysfunction-related depression, and 12% said they had been diagnosed with associated anxiety disorders.

Sleep dysfunction had a considerable effect on driving capabilities. Sixty percent reported that they had driven while drowsy, and 37% reported nodding off at the wheel. About 4% had an accident or near miss because of dozing. According to the National Safety Foundation, drowsy driving causes at least 1550 fatalities in the United States each year.

Overweight or obesity was reported in 70% of respondents in the NSF poll. Obese respondents were more apt than those of average weight to sleep less than 6 hours on weekdays, have a higher risk of developing sleep-related breathing disorders, feel sleepy in the daytime at least 3 days a week, and report troubled intimate relationships.

Obese patients showed a near inverse linear relationship between weight and reported sleep time.
increase in duration and the last third of the night is typically dominated by REM sleep.\textsuperscript{12,13}

Physiologically compared to the waking state, NREM sleep involves a general slowing of the autonomic functions (eg, heart rate, blood pressure, and metabolic rate). In contrast, REM sleep is characterized by marked physiologic changes in regulation with lowered core body temperature and changes in the mechanisms that normally regulate oxygen, carbon dioxide, and acid-base balance.

Also, a unique skeletal muscle paralysis invoked during REM is thought to preclude acting out physical events in a dream. “Restful sleep” depends not only on orderly progression through the REM stage, but passing through the NREM stages as well.

### Measures of Sleep Disturbance

Standard sleep studies involve extensive measures of physiologic testing. This includes a sleep laboratory study that incorporates electroencephalography, electro-oculography, electromyography, and respiratory and cardiac monitoring. Although an accurate diagnostic tool for sleep disturbance and related physiologic consequences, this type of monitoring has some obvious limitations for wider use for all suspected sleep disorders. Such factors as cost, availability, and first night adaptation to a strange setting have led many investigators to consider other outpatient assessment tools to diagnose potential sleep dysfunction.

Objective assessment of sleep quality has been measured by using an actigraphy watch. Worn on the wrist for 48 hours, this device monitors motion to differentiate sleep from wakeful states. The wrist actigraphy activity record provides measurements of sleep efficiency, immobility time percentage, and total activity. A digitally integrated recording of wrist activity has previously been reported to be a reliable indicator of sleep and wakeful states.\textsuperscript{14,15}

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item validated questionnaire completed as an outpatient assessment of the previous month period. This questionnaire is not disease specific and has been validated in multiple languages. Items are grouped into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

Each component score is weighted on a 0 to 3 scale, with 3 representing the worst effect, then totalled to yield a global PSQI score that can range from 0 to 21. Patients with a global score of > 5 are considered to have poor sleep quality.\textsuperscript{16} PSQI has become one of the most commonly used assessments in sleep research and has been shown to be a valuable tool in defining sleep disorders and assessing responses to interventional measures.\textsuperscript{17}

Rather than diagnose sleep dysfunction, the work productivity and activity impairment (WPAI) questionnaire is used to assess impact of work missed due to GERD-related sleep disturbance. This validated, self-administered outpatient questionnaire evaluates hours of work missed and the degree (0-10 scale) of impact on work productivity.\textsuperscript{18}

### Prevalence of GERD and Sleep Disorders

Overall, GERD affects as many as 40% of adults in economically developed countries. Heartburn and other GERD-related symptoms experienced during the night commonly cause sleep disturbances, including arousal from sleep, increased wakefulness, and overall poor sleep quality.\textsuperscript{2,3} Furthermore, greater heartburn severity has also been found to be associated with more reported sleeping difficulties.\textsuperscript{19,20}

The impact of nocturnal heartburn was particularly evident in a recent Gallup poll survey of patients in the United States with GERD. Sixty-nine percent of patients responded that they “experienced GERD symptoms when lying down to sleep at night”; 54% responded that they were “awakened at night by GERD symptoms”; and 29% responded that they were “awakened at night by coughing or choking because of fluid or an acidic or bitter taste or food in the throat.” In addition, impairment in next day function was reported by 40% of respondents.\textsuperscript{5}

A recent multinational survey of almost 2000 people with GERD in the United States and Europe found that approximately 50% had trouble sleeping, which affected work, productivity, and leisure activity.\textsuperscript{19} In people with GERD-related sleep disturbance, work productivity was reduced by 15% and leisure activity impaired by 22%.

A significant number of patients were not receiving appropriate therapy for GERD and suffered detrimental impacts on sleep and work productivity.
Health-related quality of life (QOL) is also more impaired in patients with nighttime symptoms of GERD compared to healthy control subjects or patients with GERD and no nighttime symptoms. In addition, heartburn severity and nighttime heartburn are associated with reduced work productivity, particularly when nighttime heartburn interferes with sleep. Thus the negative effect of nocturnal GERD on QOL and work productivity is likely due to an adverse effect on sleep.

**Reflux Patterns and Sleep**

It is well established that gastro-esophageal reflux (GER) events occur more commonly during the day, particularly in the postprandial state. Immediately following a meal, GER is a normal physiologic response to gastric distension that precipitates transient lower esophageal relaxations. In the waking state, the occurrence of acid reflux prompts swallowing to clear the refluxed acid. Bicarbonate-laden saliva helps to clear the acid refluxate by stimulating esophageal peristalsis, which initiates volume clearance. Buffering of the swallowed bolus also occurs. Acid clearance from the esophagus is further increased by upright posture and the beneficial effect of gravity.

GER can occur at night, typically during NREM sleep stages and rarely in REM sleep. The most frequent occurrence of reflux after sleep onset takes place during episodes of transient arousal in the early stages of sleep.

When GER occurs during sleep there is a considerable risk for prolonged esophageal contact with refluxate. Acid clearance from the esophagus is impaired by several factors. First, the mechanical advantage of gravity is lost in the recumbent position. Second, the production of saliva is dramatically reduced during sleep. Saliva contains protective components for the esophageal mucosa—namely bicarbonate, mucus, and epidermal growth factor. Third, heartburn is a sensation that requires a wakeful state. If asleep, the patient is unable to recognize heartburn and cannot swallow a saliva bolus. As a result, acid contact time with the esophageal mucosa is prolonged during sleep-related reflux.

Although nocturnal acid reflux can precipitate awakening, a swallow response, however, does not always occur. Acid reflux may also stimulate a physiologic response, inducing a secondary stimulus of esophageal motility that facilitates acid clearance via a peristaltic response. This secondary acid clearance mechanism does not require the patient to awaken. A sensory arousal occurs that can stimulate a physiologic response but not a cognitive awakening. Sleep then can be disrupted either by the direct awakening due to GER or a sleep cycle dysfunction precipitated by the GER-induced sensory event that promotes the secondary acid clearance responses.

Sleep also promotes changes in the proximal migration of a reflux episode, likely due to impaired arousal responses. This may in turn allow for gastric refluxate contact with the tracheobronchial tree as well as naso- and oropharyngeal-structures. The absence of a robust arousal response may further incur a greater acid contact time with the mucosa of these structures. The significant injury or symptomatic consequences of this proximal acid reflux exposure are readily apparent in patients who present with the supra-esophageal consequences of GERD.

**Insomnia**

Insomnia, the most common sleeping disorder, is a symptom or condition of heterogeneous origin that affects 25% of the population on an occasional basis and 10% as a chronic problem. Everyone experiences occasional sleepless nights for various reasons, but chronic insomnia means that the brain is not getting enough rest on a consistent basis, which can lead to greater problems. Insomnia includes any combination of difficulty with falling asleep, staying asleep, intermittent wakefulness, and early-morning awakening.

Although many medical conditions may be implicated, only recently has GERD been identified as a causal association with insomnia. Bixler and colleagues studied 1741 adults who reported having risk factors for sleep-related breathing disorders, and found a significant relationship between GERD and excessive daytime sleepiness and insomnia. Leodolter and colleagues reported that in a 5-year study involving 6215 patients with GERD, 60% of patients noted difficulty falling asleep or staying asleep.

In a US study of patients with GERD, 69% responded that they “experienced GERD symptoms when they lay down to sleep at night”; 54% responded that they were “awakened at night by GERD symptoms”; and 29% responded they were “awakened by coughing or choking because of fluid or an acid or bitter taste, or food in the throat.” In a Gallup survey of patients with heartburn, 79% reported nighttime heartburn, and of those, 75% had symptoms that affected their sleep. Forty percent believed that nighttime heartburn impaired their ability to function the next day.

In a recent multinational survey of patients with GERD, 50% (of 1523 respondents) reported that GERD symptoms had awakened them from sleep during the night, and they remained awake for 70 minutes on the average. Chand and colleagues reported that in a study of erosive esophagitis, 89% had abnormal PSQI scores.
Clearly, insomnia signals the need for careful and systematic diagnostic inquiry. Primary medical, psychiatric, and other causes of insomnia should be identified and treated accordingly. Pharmacotherapeutic approaches to insomnia use agents that further decrease nocturnal sensory and cognitive function. If GERD is occurring and is not appropriately treated, the use of sleep hypnotics may put patients at risk for further acid contact damage to the esophageal mucosa.

**Sleep Apnea**

Studies have suggested that there may be a causal relationship between obstructive sleep apnea syndrome (OSAS) and GERD. A plausible hypothesis is that OSAS causes or exacerbates GERD. The large negative intrathoracic pressures generated during apneic events may draw gastric contents into the esophagus, particularly during arousals and movements that accompany respiratory instability. An auxiliary hypothesis is that even small amounts of refluxed material might lead to swallowing with subsequent reduction in lower esophageal sphincter pressure and larger amounts of reflux.3

The most recent data reported on over 1100 patients, however, suggest that OSAS and symptoms of GERD are not related.27 In addition, Graf and colleagues did not find a relationship between severity of OSAS and GERD as documented by pH probe.28 In a study of 228 patients, using a validated GERD questionnaire and polysomnography, Morse and colleagues did not establish a relationship between OSAS and GERD.29

Finally, in another study involving 135 patients that used both polysomnography and a validated GERD questionnaire, the authors stated that their data “failed to show a causal link between GERD and OSA.”30 Thus 4 different studies of approximately 1387 patients using 3 different validated questionnaires have not found a correlation between OSAS and GERD.

**GERD-Related Sleep Intervention Studies**

Extremely limited data are available about GERD-related sleep interventions, including only 1 prospective randomized controlled study. Orr and colleagues reported that a study using rabeprazole failed to demonstrate any improvement in sleep variables—sleep efficiency, sleep onset latency, sleep architecture (measured by polysomnographic measures), or number of arousals per hour.31 However, in regard to subjective sleep data, sleep quality was improved significantly for the individuals treated with rabeprazole 20 mg qam compared to placebo. In that study there was no outcome for intervention based on the PSQI, as it was given at the initial visit only.

Chand and colleagues reported a pilot study intervention trial involving reflux esophagitis patients who had no known sleep disorder.3 In this open-label trial involving consecutive patients presenting without therapy who had endoscopically confirmed erosive esophagitis, 89% of patients had abnormal PSQI at baseline. After 4 weeks of treatment with esomeprazole 40 mg qam, 72% had improved PSQI scores and 49% had normalized their scores (Figure 1).

The ProGERD intervention study involving 6215 GERD patients reported that at baseline 37% and 49% of patients with insomnia also have GERD and it is not appropriately treated, the use of sleep hypnotics may put them at risk for further acid contact damage to the esophageal mucosa.

Figure 1. In a study of gastroesophageal reflux disease patients without known sleep disorders, sleep scores improved almost 50% after a 4-week treatment with open-label esomeprazole (40 mg qam). P = .008 vs baseline. Symptom scores were assessed by Pittsburgh Sleep Quality Index and GI symptom rating scale. Data from Chand N et al.3
of patients reported impairment in falling asleep or staying asleep. After 2 weeks of standardized therapy with esomeprazole 40 mg qam sleep dysfunction was significantly improved (Figure 2).

Only 1 published prospective randomized, controlled study provides information about therapy for GERD-related sleep interventions. This recently published study compared esomeprazole 20 or 40 mg taken orally qd versus placebo in patients with symptomatic moderate to severe nighttime heartburn and GERD-related sleep disturbance. The PSQI assessed sleep dysfunction in response to therapy.

There was a significant (P < .0001) difference in resolution of GERD-related sleep disturbances after 4 weeks of therapy with esomeprazole compared to baseline for the 40 mg group (83.2% vs 73.7%) and 20 mg group (84.1% vs 73.2%) than in those who received placebo (61.5% vs 41.2%).

Both esomeprazole groups had fewer days with GERD-related sleep dysfunction (Figure 3) as well as greater PSQI global score changes from baseline (P < .0001) versus placebo (Figure 4).

Other Consequences: Leisure and Work Impairment
It is intuitive that someone who does not sleep well at night is less likely to function optimally the following day. In a multinational survey, Liker and colleagues recently reported on the effects of GERD-related sleep disturbance on leisure and work productivity. Respondents who experienced sleep disturbance were absent from work for an estimated 30 minutes the week before the interview compared to only 6 minutes for those who slept uninterrupted.

The respondents whose sleep was disturbed also had a significantly higher proportion of work productivity lost due to GERD symptoms compared to those GERD patients without sleep disturbance (8% vs 15%; P < .01). Similarly, patients with sleep disturbance also reported a 12% higher rate of leisure time lost (22% vs 10%; P < .01) compared to GERD patients without sleep disturbance.

Johnson and colleagues in their prospective randomized control trial with esomeprazole versus placebo, also reported on work productivity effects as a measure of treatment response of GERD-related sleep dysfunction. This trial is the only controlled trial evaluating GERD-related sleep dysfunction in which work productivity was assessed.
Using WPAI as a validated measure, the authors demonstrated a highly significant improvement (P < .0001) in work hours saved per week per patient compared to baseline (esomeprazole 40 mg, 11.0 vs 11.6 hours; esomeprazole 20 mg, 11.8 vs 12.3 hours; placebo, 6.1 vs 6.2 hours). The outcome is illustrated in Figure 5.

Using an average total employee compensation cost of $24.59 from the US Bureau of Labor Statistics, the cost of hours saved per patient per week was $286 and $301 in the esomeprazole 40 mg and 20 mg groups, respectively. This represents a cost savings of approximately $131 and $148 per week per patient, respectively, compared to placebo. Analyzed differently, for a month of therapy, the return on investment (ROI) for a dollar spent on proton pump inhibitor (PPI) therapy resulted in approximately $4.30 in improved work productivity.

**Conclusion**

Gastroesophageal reflux disease and sleep disorders are extremely prevalent conditions, and it seems intuitive that there must be some overlap between the two. The overlap, however, is larger than should occur by chance, suggesting some element of causality. It is becoming apparent that GERD is causal for sleep dysfunction in a large number of patients. Sleep disorders may in fact be one of the most prevalent of the extraesophageal complications of GERD and often goes unrecognized. With this in mind, the “Castell iceberg” model for extraesophageal GERD may need to be revised (Figure 6).

In addition, physicians need to be more proactive in evaluating GERD patients for unrecognized sleep disorders. Similarly, patients with sleep disorders should be carefully questioned about GERD symptoms. Physicians evaluating the treatment response for GERD need to ask questions about nighttime symptoms as well as next day function.

The recent literature has indicated that sleep disturbance due to GERD is a treatable condition that is responsive to effective, acid-suppressive medical therapy. Sleep disturbance has a significantly negative effect on QOL and affects leisure activity and work productivity. Effective therapy for GERD-related sleep disorders leads to significant financial return based on improved work productivity.

Treatment strategies that maximize outcomes are investments that can be actually justified by a business model, one that employers and insurance...
companies need to understand. It is becoming apparent that the implications of GERD are far greater than the perception that this as a "lifestyle disease" with just a "little bit of heartburn."

References
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Main Points
- With the evolution of studies conducted in sleep laboratories, the relationship between sleep and various gastrointestinal diseases, in particular gastroesophageal reflux disease (GERD), is being recognized.
- Studies reveal that over 40 million Americans suffer from a sleep disorder, with the majority receiving little or no treatment. Sleep disorders can negatively affect quality of life issues, and have a major impact on work productivity, leisure, and intimacy.
- Studies have recently identified GERD as having a causal association with insomnia. Careful and systematic diagnostic inquiry is advised. If treated with sleep hypnotics, patients with insomnia who also have GERD may be at risk for further acid contact damage to the esophageal mucosa.
- Although studies have suggested a causal relationship between obstructive sleep apnea syndrome (OSA) and GERD, to date 4 different studies have not determined a correlation between the two.
- Despite limited data on GERD-related sleep intervention studies and the existence of only 1 prospective randomized controlled study, sleep disturbance due to GERD appears to be a treatable condition that is responsive to effective, acid-suppressive medical therapy.
- From a diagnostic standpoint, sleep disorders may be one of the most prevalent of the extraesophageal complications of GERD that often goes unrecognized. Physicians are advised to be more proactive in evaluating GERD patients for unrecognized sleep disorders and should carefully question patients with sleep disorders about GERD symptoms.


