

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Sleep and Inflammatory Bowel Disease



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G&H In terms of the connection between sleep and inflammatory bowel disease, does sleep cause the disease or does the disease cause sleep disturbances?

TA This is a challenging question, and we do not yet have the answer. Unraveling this connection relies on understanding sleep physiology, the role of the immune system in sleep, and the different environmental factors involved in the pathogenesis and activity of inflammatory bowel disease (IBD). We do know for certain that sleep is affected by clinically active IBD. Recently, my colleagues and I have also discovered that even if IBD is in clinical remission, sleep may be affected if there is activity at a microscopic or histologic level. It has also been demonstrated that sleep disturbances can affect the immune system. In particular, sleep deprivation can activate proinflammatory cytokines. Therefore, the connection between sleep and IBD appears to work in both directions.

G&H How does IBD affect sleep?

TA IBD symptoms such as abdominal pain and diarrhea can cause fragmented sleep, especially when they occur at night. The onset and total duration of sleep can also be disturbed by these symptoms.

Somewhat less obvious is the understanding that the process of inflammation can produce cytokines that directly alter sleep patterns and can disrupt the stages of sleep. For example, some cytokines are somnogenic (ie, they induce sleep). On the other hand, some cytokines can cause insomnia.

In addition, we can draw from examples of other diseases that disrupt sleep through similar pathways. The classic example is sleeping sickness caused by an infection. Among people infected with HIV, excessive sleepiness is observed even before the onset of AIDS. Similarly, studies have suggested that changes in intestinal permeability during the process of inflammation increase the exposure of bacterial products to macrophages, resulting in the release of somnogenic cytokines. Some cytokines, such as interleukin (IL)-4 and IL-10, can also trigger insomnia.

In my practice, I have seen many patients with active disease complain that they cannot sleep and others complain of somnolence. It is unclear whether these symptoms are connected to specific immune pathways, but it might be possible in the future to predict the involvement of certain immune pathways through sleep disturbances and target therapy accordingly.

G&H How does sleep deprivation affect the immune system?

TA There is good evidence about the connection between sleep deprivation and the activation of the immune system. In experimental models of sleep deprivation, rats with 20 days of sleep loss developed septicemia and died. Another study showed that rats with colitis and sleep deprivation had worsening markers of inflammation, including weight loss and an increase in inflammatory burden, compared with rats that had colitis and were not sleep deprived. Other data suggest that sleep deprivation can activate adhesion molecules and cytokines such as E-selectin, IL-1, IL-6,

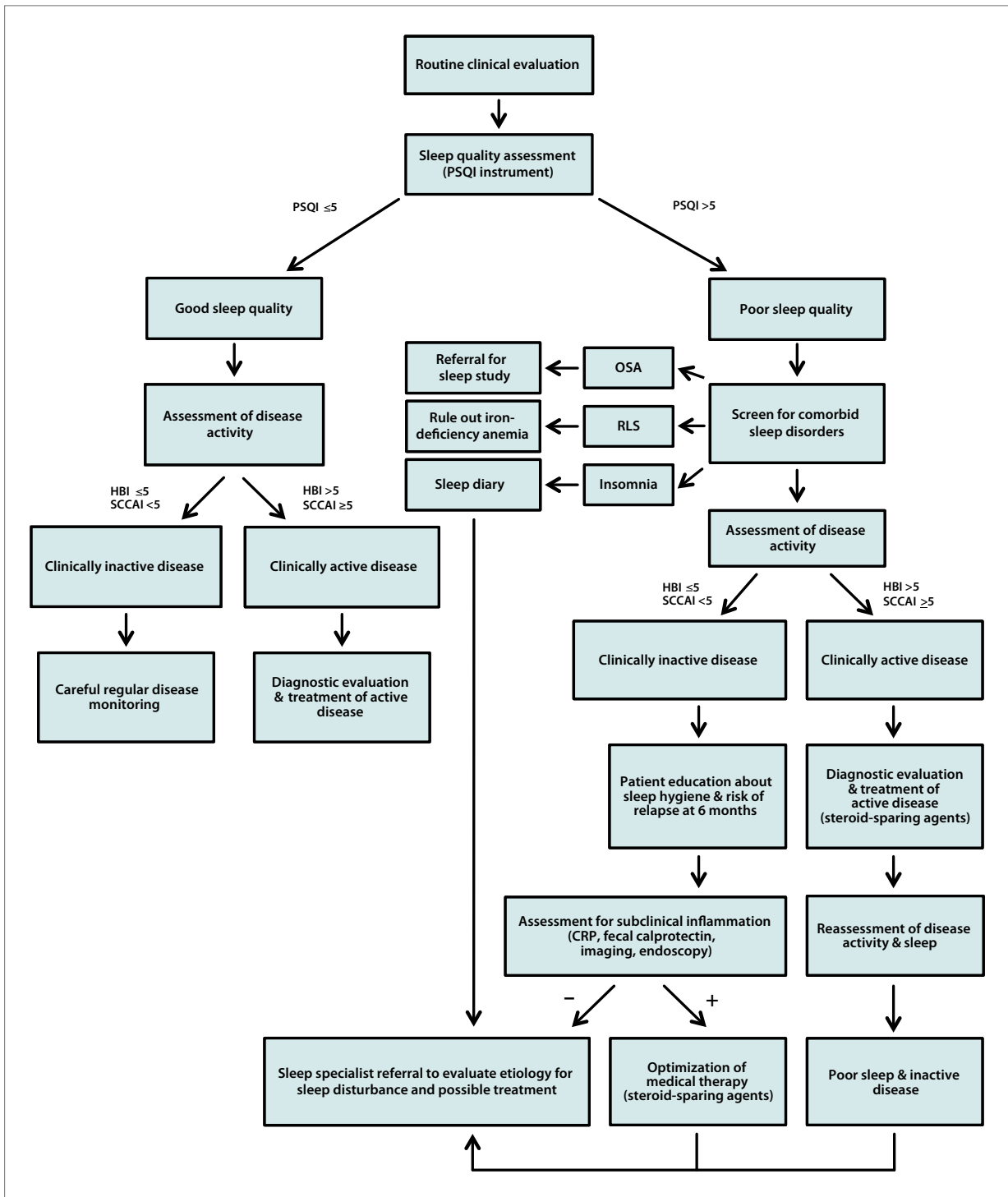


Figure. A proposed algorithm for incorporation of sleep assessment in the management of inflammatory bowel disease.

CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; RLS, restless leg syndrome; SCCAI, Simple Clinical Colitis Activity Index.

Reproduced from Kinnucan JA, Rubin DT, Ali T. Sleep and inflammatory bowel disease: exploring the relationship between sleep disturbances and inflammation. *Gastroenterol Hepatol (NY)*. 2013;9(11):718-727.

and tumor necrosis factor- α , all of which play important roles in the immune pathology related to IBD.

Some data come from research of other diseases. For example, there is evidence that sleep deprivation can activate the immune system of people with rheumatoid arthritis. Other studies suggest that sleep deprivation may predispose individuals to certain infections, including the common cold. Shift workers have been shown to be more prone to colds and upper respiratory tract infections with increased disturbances in day and night shifts at work, suggesting that sleep deprivation can influence the immune system.

In a recent study, my colleagues and I discovered a 3-fold increased risk of IBD relapse in patients with poor sleep. Ananthakrishnan and colleagues also recently looked at the association of sleep duration with IBD. Sleep duration of less than 6 hours per day or more than 9 hours per day was associated with a higher incidence of ulcerative colitis.

G&H Can sleep quality be evaluated for patients with IBD? What could be the practical application of understanding the connection between sleep and IBD?

TA Although we have not yet come to the point where the science can clearly be applied in clinical practice, a great deal of progress has been made. Recently, my colleagues and I proposed an algorithm for evaluating sleep disturbances in clinical practice (Figure). First and foremost is assessing the quality of sleep. This assessment could be performed using a validated questionnaire or simply by asking questions about sleep problems. It may be necessary to rule out other sleep issues, such as obstructive sleep apnea and restless leg syndrome. A patient experiencing sleep problems may be referred to a sleep specialist. Along with this further characterization of sleep quality, disease activity is also assessed.

Patients may have clinically inactive disease but poor sleep. For these patients, we provide education about sleep hygiene and inform them of a possible risk of relapse within the next 6 months, based on studies suggesting that poor sleep quality is associated with a higher risk of relapse, even in clinically inactive disease.

We may also evaluate patients for subclinical inflammation because poor sleep quality has a positive predictive value of approximately 85% for histologic inflammatory activity. Therefore, in these patients, we may measure C-reactive protein or fecal calprotectin levels or perform an endoscopic evaluation.

For patients who have poor quality of sleep and active disease, the disease must be treated with medical therapy. In particular, steroid-sparing agents should be used because of the known association of sleep disturbances

with the use of steroids. Once therapy has started, disease and sleep quality can be reevaluated at a defined interval.

G&H What is sleep hygiene?

TA There are different types of sleep disturbances. Some are conditions that can benefit from therapeutic intervention, such as obstructive sleep apnea. However, sleep habits are also a factor. Sleep deprivation is very common in the United States. Currently, many people spend a lot of time, particularly late at night, watching television and using smartphones and other electronic devices. These devices can have a negative impact on sleep habits.

Sleep hygiene begins with education about good sleep. Sleep has 2 major stages and various substages. These stages are repeated multiple times during sleep. Good-quality sleep depends on fulfilling all of these stages. Typically, people need 7 to 8 hours of uninterrupted sleep in a quiet, dark room. Certain practices need to be adopted in order to have restful sleep because so much immune regulation and so many physiologic processes occur during sleep. Disturbed sleep means a failure to complete all stages of the sleep cycle, which disturbs the physiologic processes that occur during that time.

G&H Do your IBD patients often complain of sleep disturbances?

TA Yes. I have long-term experience with IBD patients complaining about sleep. Gastroenterologists have been relating such experiences to IBD activity on an anecdotal basis until recently, as concrete evidence is starting to emerge about the unique ways in which sleep disturbances can affect the immune system and, thereby, disease activity.

G&H Are patients receptive to the idea that good-quality sleep is part of their treatment?

TA Yes. In addition to my own experiences with patients, I also hear from colleagues that patients tend to complain of disease flares when there are sleep disturbances. Often, an episode of sleep deprivation is connected to a social engagement or life event—for example, moving to a new home or a change in work shift—that ends with an IBD flare. Patients usually understand that their sleep disturbance triggered the disease activity, and they are receptive to the suggestion that improved sleep will help the disease.

G&H Can any other lifestyle changes help patients experiencing sleep disturbances?

TA I often counsel patients about drugs that can negatively affect sleep, such as steroids. I try to wean patients off

steroids because these agents can lead to very serious cycles of sleep-related disturbances. Other substances that can negatively impact sleep include caffeine, alcohol, and certain prescription drugs. I also evaluate patients for depression and anxiety or any concerns that may impact sleep. Assessment of sleep environment, especially background noise, temperature, and light, can also be very helpful.

G&H What are the next steps for research on the connection between sleep and IBD?

TA A larger prospective study is needed to validate and confirm the association between sleep and IBD. Research is also needed to develop a clinical tool to assess sleep. Currently, various patient-reported and self-administered questionnaires are used, but these tools have their own biases and limitations. One of the gold standards for sleep assessment is polysomnography. However, this test can be difficult to use because it requires a sleep laboratory, which is not necessarily reflective of the patient's typical experience. Actigraphy is another objective measure of sleep disturbances; although several commercially available wrist actigraphy watches are available, they need more standardization. A more robust and standardized clinical tool is also needed to measure sleep disturbances, explore the different stages of sleep, and identify the exact sleep disturbances that trigger disease activity. Other important research areas that need to be further explored are disease

monitoring via sleep and the therapeutic implication of sleep in IBD. My colleagues and I are embarking on a study examining how good, restful sleep impacts the immune system and whether such sleep has a positive impact on disease activity and improves IBD. With more data, we can be more specific when making recommendations to patients regarding sleep.

Dr Ali has no relevant conflicts of interest to disclose.

Suggested Reading

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