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Gastroenterology for Geriatric Patients (S Katz and A Afzali, Section Editors)

Sleep Disturbances in the Elderly Patient with Inflammatory Bowel Disease

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Abstract

Purpose of review Studies have suggested that sleep and inflammatory bowel disease (IBD) appear to have an important bi-directional relationship, where active disease promotes sleep disruption and poor sleep promotes ongoing and worsening inflammation. In the geriatric population, poor sleep has been linked to increasing morbidity and mortality. The etiologies of poor sleep in the elderly are multifactorial and are understood to be a part of the geriatric syndromes, conditions in the elderly associated with poorer mortality and morbidity. We review the current literature regarding the common sources of sleep disturbances in the geriatric population and, by extension, the growing population of elderly patients with IBD.
Recent findings There is a high prevalence of sleep dysfunction in patients with inflammatory bowel disease, not only in patients in disease remission but also in patients with active disease. Poor sleep has been suggested a potential marker of ongoing subclinical inflammation, and sleep disturbances are linked to poorer outcomes in patients with IBD. Management of inflammation appears to improve fatigue symptoms but is not linked with the elimination of symptoms. Thus, alternative etiologies of poor sleep, especially in the geriatric population, include chronic medical conditions with polypharmacy, co-morbid mood disorders, and primary disorders of sleep.
Summary Sleep disturbances in the elderly patient with IBD are related to multiple etiologies. Poor sleep is linked to both worse disease–specific outcomes and higher morbidity and mortality. Coordination of care with geriatricians, mental health professionals, and sleep specialists is often required to target the appropriate cause. We provide an etiological framework in the assessment of poor sleep in the elderly patient with IBD.

Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic diseases of the gastrointestinal tract that have a relapsing and remitting course. The prevalence of IBD is increasing across the globe, and, as the global population ages, the prevalence of IBD is rising in the elderly. An estimated 10–15% of patients with IBD worldwide are greater than 60 years of age [1].

Moreover, although most persons with IBD are diagnosed between the second and fourth decades of life, a second peak in IBD diagnoses has also been reported in those between the ages of 60 and 70 (citation). A recent study has suggested that nearly 20% of all patients are diagnosed with IBD after the age of 60 [2]. In a large database study from Europe covering the period from 1998 to 2006, roughly 9% of patients with IBD were diagnosed over the age of 60 [3].

Practitioners are increasingly cognizant of the evolving demographics of patients, and, appropriate care must involve an understanding of not only the treatment of bowel disease but also the management of extraintestinal manifestations and associated conditions. Increasingly, disturbed sleep and fatigue are becoming significant factors in the care of patients with IBD. Poor sleep and fatigue have been described not only as extraintestinal manifestations but also as potential mediator of worsening disease course [4, 5].

Changes in sleep patterns along with rising co-morbidity, psychosocial factors, as well as polypharmacy result in a high prevalence of disturbed sleep in the elderly [6]. Data from complied studies have suggested that changes in sleep duration in the elderly have been associated with all-cause and cardiovascular mortality [7]. Thus, sleep disturbance in the elderly should be understood to a part of previously described geriatric syndromes, multifactorial conditions prevalent in the elderly that contribute to significant morbidity and mortality [8].

In assessing the role of fatigue and disturbed sleep in the elderly, a systematic approach must be utilized to assess potential etiologies: active disease, co-morbid psychiatric or medical illness, a primary sleep disorder, or a combination. A working understanding of these potential sources and management strategies will allow practitioners a means to provide complete care for their elderly patients.

In this review, we highlight the interconnected nature of poor sleep in elderly patients with inflammatory bowel disease. Furthermore, we report a potential etiological framework in assessing these patients and discuss potential management strategies (Figs. 1 and 2).

Sleep physiology

Sleep is a dynamic state that cycles through periods of rapid eye movement (REM) sleep and non-REM (NREM) sleep as identified by polysomnography. Most sleep (70–80%) in adults is non-REM, and non-REM sleep is further subdivided into light sleep and slow wave sleep. Non-REM sleep, specifically slow-wave sleep, has been linked to having restorative properties with effects on immunology and inflammation. In contrast, REM sleep is associated with dreaming and learning. The stages of sleep are summarized in Table 1.

Sleep is regulated by a complex interaction of homeostatic pressures, the circadian pacemaker, and environmental factors [9]. The homeostatic pressures, which govern sleep, are often referred to as sleep debt or process S. The circadian regulatory process, in contrast, is termed process C (Table 2).

Process S describes the increasing urge to sleep that occur with time spent awake and the gradual decline in these pressures occur with sleep [10]. The need for sleep is amplified with time spent awake which results in increased sleep time as well as a higher arousal stimulus to awake [11]. In contrast, process C is responsible for the temporal organization of the sleep-wake cycle and cycles over the course of 24 h, dictated by light and melatonin. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, contains a master

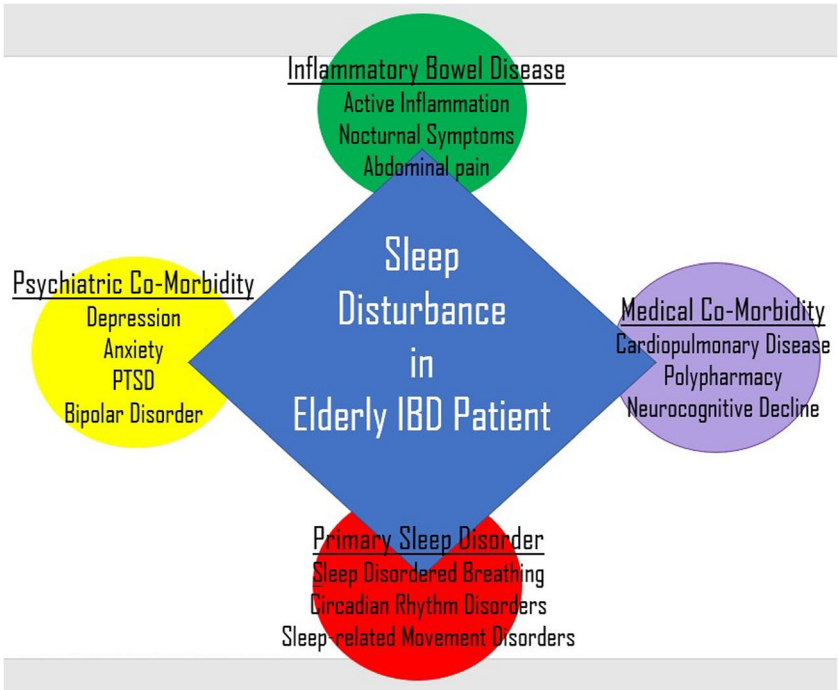

Fig. 1. An etiologic framework for understanding sleep disturbances in the elderly IBD patient.

circadian clock of not only sleep and wakefulness but also other physiologic variables that have a diurnal variation [12].

The counterbalancing forces that promote sleep in process S and the factors that stimulate wakefulness in process C allow for equilibrium that maintains healthy sleep patterns. Dysfunction in sleep can often be traced, as described, directly to biologic or environmental alterations of process C or process S.

Sleep changes in the elderly

There are significant changes in the pattern of sleep in the elderly. These changes are summarized in Table 3. Based on a large meta-analysis of objective sleep parameters, REM and slow-wave sleep tend to decrease in elderly patients, whereas light sleep tends to increase with age. Moreover, total sleep time, sleep efficiency, the amount of time spent asleep while in bed, and the time awake after falling asleep increase [13]. The sleep-wake patterns of older adults also tends to demonstrate increased nocturnal and early morning awakenings with increasing patterns of daytime napping and earlier bedtimes [14, 15].

Older adults show a decline in sleep pressures after sleep deprivation, translating to a decrease desire to sleep compared to the young [16]. Aging does not appear to change the periodicity of the circadian rhythm, which is roughly 24 h [17]. However, older persons do demonstrate a shift in circadian rhythms, namely changes that correspond to earlier bedtimes and nocturnal awakenings [18]. It has been proposed that the cause of decreased sleep pressures occurs due to changes in homeostatic sleep regulation, process S, due to behavioral

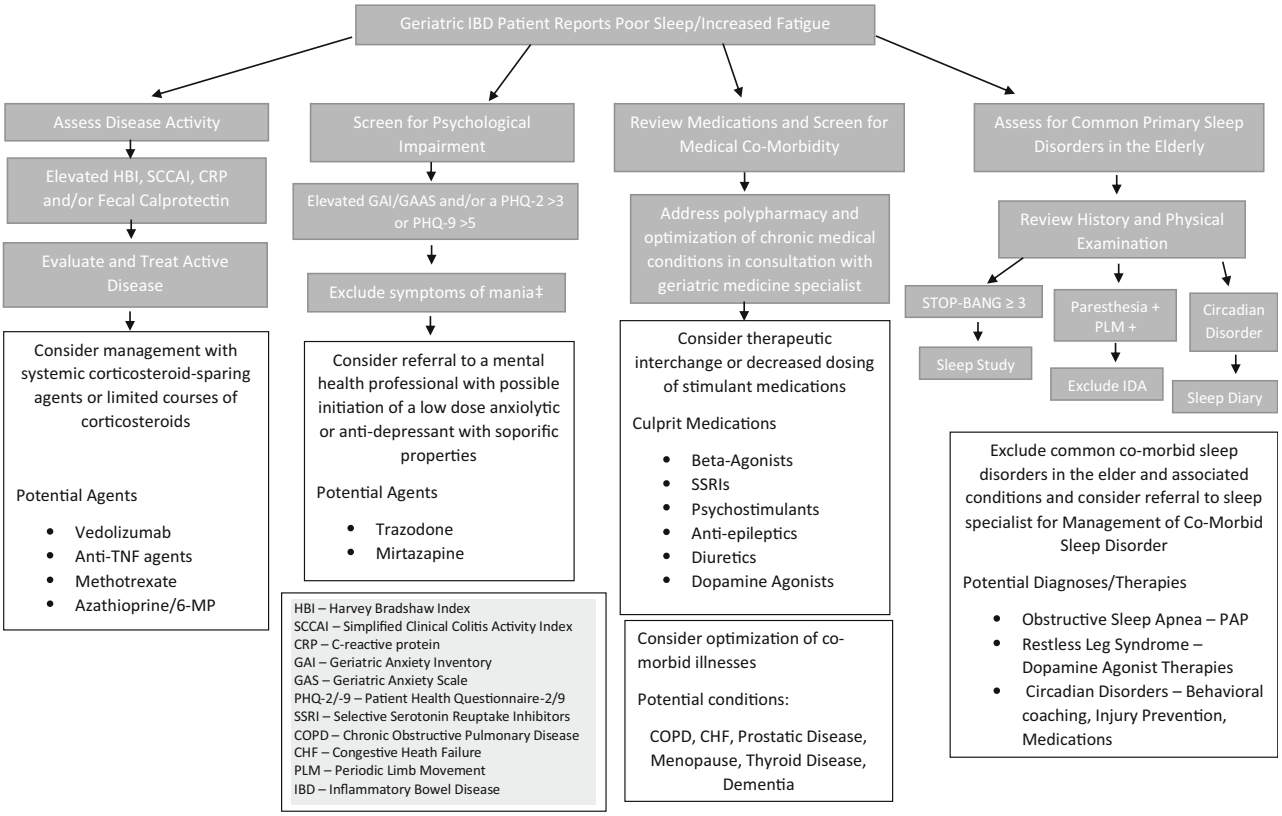

Fig. 2. An algorithm for the proposed assessment and management of sleep disturbance in the geriatric IBD patient. Double dagger: Patient started on an anti-depressant should be screened for symptoms of mania, including distractibility, behavioral indiscretion, grandiosity, flight of ideas, increased activity, pressured speech, and decreased desire/need for sleep. Providers should not provide agents if unable to exclude symptoms.

interactions with an advancement in circadian rhythms [19]. The net effect of these changes results in increased fragmentation of sleep and less restorative sleep in older adults.

Table 1. Stages of sleep. Non-REM sleep: non-rapid eye movement sleep. REM sleep: rapid eye movement sleep

Sleep division	Sleep stage	Characteristic
Non-REM sleep	Stage I	Light sleep
	Stage II	Light sleep
	Stage III	Slow-wave sleep
	Stage IV	Slow-wave sleep
REM sleep	Stage V	Increased brain activity
		Dreaming
		Memory consolidation

Table 2. Sleep regulatory processes

Sleep regulatory process	Modulating factor	Major inputs
Process S	Promotes sleep	Sleep debt, fatigue
Process C	Promotes wakefulness and temporal organization of sleep	Light and melatonin

Sleep and immunology

There is a complex relationship between the immune system and the sleep. Adequate sleep has been found to aid the ability of the immune system to mount a febrile response, and the regulation of temperature is amplified during NREM sleep [20]. Studies have also suggested that specific cytokine profiles promote the lengthening of the NREM phase of sleep [21]. In contrast, sleep deprivation has been linked to the release of IL-1 and TNF-alpha [22]. In summary, NREM sleep appears to be accentuated in inflammatory states, especially in the setting of infections.

In addition to his complex interplay, indirect effects on the immune system are often mediated through circadian variation in the release of growth hormone, prolactin, and endogenous cortisol. Cortisol, particularly, has both direct effects on sleep and promotes changes in serum concentrations of inflammatory cytokines [23]. Moreover, both growth hormone and prolactin have been shown to have pleiotropic effects on the immune system, altering populations of T cells [24].

In net effect, sleep deprivation appears to induce an inflammatory cascade, both directly and through the diurnal variation of release of hormones by the endocrine system. Through these interactions, NREM, or restorative sleep, is accentuated allowing for an immune imbalance in the management of infection and inflammatory states.

Table 3. Common changes in sleep structure and characteristics in the elderly

Sleep changes in elderly
Increased time in light sleep (stages I and II)
Decreased time in slow-wave sleep (stage III and stage IV)
Decreased time in REM sleep
Increased nocturnal and early morning awakenings
Increased diurnal napping
Earlier bedtime
Decrease in total sleep time
Decrease in sleep efficiency

Table 4. Sleep Studies in inflammatory bowel disease subjects utilizing subjective assessments of sleep

Authors	Year	Study type	Patients	Age	Sleep assessment tool	Conclusions
Zimmerman et al. [26]	2003	Case control	56—Age and sex-matched healthy controls 55—IBD 53—IBS	Control—37.5 ± 2.0 years IBS—33.9 ± 1.9 years IBD—33.4 ± 1.7 years	Multisystem Instrument (MSI) 5-Point Likert Score on Sleep Disturbance and Difficulty Falling Asleep	Higher mean sleep disturbance scores in IBD subjects compared to healthy controls ($p <$ 0.004)
Ranjbaran et al. [27]	2007	Case control	15—Health controls 80—IBD 24—IBS	Control—48 ± 4 (19–81) years IBD—40 ± 1.5 (19–67) years IBS—56 ± 2 (36–71) years	PSQI	Poorer subjective sleep quality, increased use of sleep aids, and increased sleep interruption frequency in IBD subjects compared to health controls ($p <$ 0.001) Inverse correlation between IBDQ and PSQI ($r = 0.55$, $p = 0.02$), suggesting that severe disease symptoms related to poorer sleep quality
Graff et al. [5]	2011	Prospective cohort	CD—160 (76 active diseases, 84 inactive diseases) UC—158 (71 active diseases, 87 inactive diseases)	IBD—43 ± 14.06 (19–81) years	PSQI ESS Multidimensional fatigue inventory (MFI)	Significantly higher fatigue, poorer sleep quality, and increased daytime sleepiness in subjects with active CD and UC compared to inactive CD and UC Psychological distress (0.50) and perceived stress ($r = 0.41$) directly correlated with poorer sleep quality Strong negative correlation (– 0.56) between the IBD quality of life and sleep quality
Graff et al. [28]	2013	Prospective cohort	CD—159 UC—153	CD—41.4 ± 14.8 years UC—45.4 ± 14.6 years	PSQI MFI	Poorer sleep quality directly correlated with worsening fatigue scores over time ($r = 0.30$, $p < 0.001$)

Table 4. (Continued)

Authors	Year	Study type	Patients	Age	Sleep assessment tool	Conclusions
						High fatigue scores prevalent in subjects with consistently active or fluctuating disease course
Gingold-Belfer et al. [29]	2014	Prospective cohort	CD—108 (37 active diseases, 71 inactive diseases) Healthy controls—61	Inactive CD—40.31 ± 16.29 years Active CD—45.49 ± 17.82 years Controls—41.77 ± 18.22 years	PSQI	Active disease was associated with significantly lower habitual sleep efficiency, more use of sleep medication, and higher daytime dysfunction ($p < 0.0001$) CDAI directly correlated with poor sleep quality ($r = 0.59$, $p < 0.0001$)
Ali T et al. [4]	2013	Prospective cohort	CD—23 UC—18	37 ± 15.4 years Clinically active: 37 ± 15.5 years Clinically inactive: 38 ± 15.7 years	PSQI	PSQI ≥ 5 present in all 23 (100%) of the patients with clinically active and in 13 (72%) patients with inactive disease (OR, 2.8, 95% CI, 1.8–4.3, $p = 0.007$) All 30 patients with abnormal histology had an abnormal PSQI (OR, 6.0, 95% confidence interval, 2.9–12.5, $p < 0.0001$) Abnormal PSQI (PSQI ≥ 5) highly predictive of subclinical inflammation (PPV 83%)
Ali T et al. [30]	2013	Prospective cohort	CD—24 UC—17	39 ± 16 years	PSQI	Abnormal PSQI (PSQI ≥ 5 associated with clinical relapse at 6 months Significant correlation between baseline PSQI and disease activity at 6 months (CD—$r = 0.56$, UC—$r = 0.54$)
Ananthkrishnan A et al. [31]	2013	Prospective cohort	3173 IBD 2079 CD 1094 UC	SD—45 ± 15 years No SD—45 ± 16 years	PROMS-SD 4a	Impaired sleep is associated with a higher risk of relapse in patients with CD in remission
Wilson R et al. [32]	2015	Prospective cohort	CD—78 UC—53	Age at diagnosis: 25 (18–37) years	PROMIS-SD 8a	High CRP (4.12, 95% CI 1.38–12.29) and depression (1.10, 95% CI 1.05–1.15) associated with poor sleep quality in multivariate regression analysis

Table 4. (Continued)

Authors	Year	Study type	Patients	Age	Sleep assessment tool	Conclusions
						High CRP associated with poor sleep quality independent of nighttime symptoms (OR 3.16, 95% CI 1.01–9.90)
Stevens BW et al. [33••]	2017	Prospective cohort	CD—94 UC—66	Anti-TNF: 33 years Vedolizumab: 37 years	PROMIS-SD 8a	Anxiety independently associated with poor sleep (β 7.14, 95% CI 3.36–10.92) Statistically significant improvement in sleep scores in combined cohort (anti-TNF and Vedolizumab) on therapy (baseline 52.8, week 6 49.8, $p = 0.002$) Significant improvement in sleep quality, depression and anxiety scores with Vedolizumab therapy Patients with active disease and depressive symptoms at follow-up were independent predictors of poor sleep
Michalpoulos G et al. [34••]	2018	Prospective cohort	IBD—90 CD—54 UC—36	IBD—40.5 ± 14.7 years CD—37.3 ± 13.6 years UC—45.4 ± 15.1 years	Greek-PSQI	In CD, the absence of mucosal healing was associated with poor sleep quality (OR 3.62, 95% CI 2.15–5.09)
Sobolewska-Woldarczyk A et al. [35]	2018	Prospective cohort	CD—30 UC—35	CD—38.7 ± 12.5 years UC—42.0 ± 17.8 years	Polish-PSQI	PSQI > 6, 77% sensitive, and 62% specific for recognizing IBD patients in flare Active disease as assessed via clinical scores (CDAI or Partial Mayo) associated with higher PSQI scores: remission 4.78 ± 0.69; mild 5.55 ± 0.58; moderate 9.78 ± 0.63; severe 9.14 ± 0.69; $p < 0.001$)
Sofia MA et al. [36]	2018	Prospective cohort	92—CD	PSQI > 8—41.9 years PSQI ≤ 8—43.9	PSQI	Poor Sleep (PSQI > 8) associated with a higher risk of hospitalization or surgery in multivariate regression model (OR 5.37, 95% CI 1.39–27.54)

Table 4. (Continued)

Authors	Year	Study type	Patients	Age	Sleep assessment tool	Conclusions
Hood MM et al. [37•]	2018	Prospective cohort	47—UC 11—Flaring	42.6 ± 12.4	PSQI	Depression and female sex independently linked to poor sleep quality Sleep quality correlated with IBD-related quality of life
Chrobak AA et al. [38]	2018	Prospective cohort	38—UC 34—CD 57—Control	CD—35.8 ± 13.5 years UC—42.6 ± 15.6 years Controls—41.4 ± 12.5 years	PSQI MFI	CD subjects with a preference for evening chronotype (35.00 vs. 39.64, $p < 0.01$) Evening preference associated with greater symptoms of fatigue in IBD
Zargar A et al. [39]	2019	Prospective cohort	115—IBD 85—UC 39—CD 40—IBD + IBS	38.6 ± 12.2 years	Persian-PSQI	IBS poorly effect both sleep quality and IBD related quality of life in patients with IBD
Chakredo PS et al. [40•]	2019	Retrospective cohort	115—IBD 76—Controls	IBD—41.4 ± 14.81 years Control—34.13 ± 11.96 years	PSQI MEQ MCTQ	Quality of life poorer in IBD patients with a preference for evening or later chronotypes. Social jet lag and sleep debt increased in IBD patients compared to healthy controls Social jet lag and sleep debt associated with fistulizing/structuring CD.

IBD inflammatory bowel disease, *IBS* irritable bowel syndrome, *SD* sleep disturbance, *CD* Crohn's disease, *UC* ulcerative colitis, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *MEQ* Morningness-Eveningness Questionnaire, *MCTQ* Munich Chronotype Questionnaire

Table 5. Sleep studies in inflammatory bowel disease subjects utilizing objective assessment of sleep

Author	Year	Study type	Participants	Age	Sleep assessment tool	Conclusions
Keefer et al. [39]	2006	Case control	16—Inactive IBD 9—IBS 7—Healthy controls	IBD—41.44 ± 12.21 years IBS—52.67 ± 12.12 years Controls—34.00 ± 9.61 years	PSQI ESS Polysomnography	Decreased sleep time in IBD subjects compared to controls ($p < 0.05$) Poorer sleep quality in IBD subjects compared to controls ($p < 0.05$) Lower, but not significant differences in IBD subjects and healthy controls in sleep efficiency, total sleep time. Higher arousal index in IBD subjects compared to controls (difference not significant)
Burgess et al. [42]	2010	Prospective cohort	4—IBD (3 CD, 1 UC) 8—Age, sex-matched healthy controls	22–39 years	Wrist actigraphy	Longer sleep onset latency in IBD subjects compared to controls (23 min vs. 6.32 min, $p < 0.05$) Lower sleep efficiency in IBD subjects compared to controls (78 min vs. 87 min)
van Langenberg et al. [43•]	2015	Prospective cohort	48—CD 30—Healthy control	CD—44 (21–65) years Controls—46 (21–63) years	Wrist actigraphy	Lower sleep efficiency in CD patients compared to healthy controls (94.9% (95% CI 85.6–99.1) vs. 96.2% (95% CI 90.7–99.4), $p = 0.03$)

Table 5. (Continued)

Author	Year	Study type	Participants	Age	Sleep assessment tool	Conclusions
						Greater numbers of awakening overnight in CD subjects compared to health controls (CD 22, range 1–88 vs. healthy controls 11, range 1–35, $p = 0.01$) Greater time spent awake after sleep onset in CD subjects compared to health controls (CD 7 min, range 1–17 min vs. HC 4, range 1–15 min; $p = 0.051$)
Sofia et al. [44]	2018	Prospective cohort	26—CD 12—UC	CD—39.85 (16–63) years UC—40 (18–74) years	Commercially available sleep monitor (FitBit Charge HR)	Sleep fragmentation associated with an increased odds of clinically active disease (1.0004–3.11, $p = 0.023$)
Shitrit et al. [45]	2018	Prospective cohort	34—IBD 27—Matched control	IBD—39.15 ± 15 years Controls—34.6 ± 9.6 years	Polysomnography	IBD patients less REM sleep (23.8% vs. 27.8%, $p = 0.039$) IBD patients with higher percentage of lighter sleep (57.3% vs. 52.25%, $p = 0.057$) Sleep time below 90% oxygen saturation longer in IBD group compared to controls (2.3 vs. 0.17 h, $p = 0.07$)

Table 5. (Continued)

Author	Year	Study type	Participants	Age	Sleep assessment tool	Conclusions
Qazi et al. [46]	2018	Prospective cohort	72—CD 28—Disease remission 22—Mild disease 22—Moderate to severe disease	Disease remission—38 (20–78) years Mild disease—35 (22–62) years Moderate to severe—34 (20–70) years	Wrist actigraphy	Median WASO higher in subjects with moderate to severe disease compared to subjects in disease remission (65.8 min vs. 44.3 min, $p \leq 0.05$) Median sleep efficiency lower in subjects with moderate to severe disease compared to subjects in disease remission (86.6% vs. 89.3%, $p = 0.03$) Severe disease associated independently with fragmented sleep Use of marijuana/opiates linked with poorer sleep efficiency
Paixao DL. Et al. [47]	2019	Case series	20—IBD 7—Active disease 13—Disease remission	NP	Polysomnography PSQI	No difference in home polysomnographic parameters between active and inactive IBD Poor sleep in all patients with IBD as assessed via PSQI

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *IBS* irritable bowel syndrome, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale

Sleep and inflammatory bowel disease

Sleep disruption in inflammatory bowel disease appears to have a bi-directional relationship. From an epidemiological perspective, both hypersomnia and decreased sleep duration have been linked to the development of ulcerative colitis but not Crohn's disease [25]. Several studies have reported disturbed sleep in IBD patients not only because of nocturnal symptoms but also independently related to ongoing inflammation. Additional studies have also suggested poor sleep as being a predictor of subclinical inflammation as well as exacerbations. These studies suggest a potential bi-directional link between circadian disruption and inflammatory colitis and a brief summary is provided with a table (Table 4) providing a more complete review of the literature.

In humans, the authors of the aforementioned study also reported decreased expression of several genes instrumental in regulating circadian rhythm in both the mucosal biopsies as well as the peripheral blood mononuclear blood cells of IBD patients compared to healthy controls [41]. Further clinical studies have also described poor sleep in patients with inflammatory bowel disease compared patients without CD or UC.

A small observational study of age-matched men with IBD and IBS was the first to assess sleep in IBD subjects [26]. The study included 55 subjects with IBD, 23 subjects with UC, and 32 with CD, who were provided with a Multisystem Inventory (MSI), which included an assessment of sleep disturbance graded by severity on a 5-point Likert scale. In comparison to healthy controls, IBD subjects had a significantly higher mean score for sleep SD compared to controls, with the presence of diarrhea being predictive of SD.

An additional survey-based study uses a mail-in questionnaire by Ranjbaran and colleagues using both the Pittsburgh Sleep Quality Index (PSQI) and the IBD quality of life (IBD QoL) questionnaire [27]. The survey included 80 subjects diagnosed with IBD. The results of the survey suggested prolonged sleep latency, increased fragmentation, higher use of sleeping aids, decreased energy, and poor overall sleep quality in comparison to older subjects. There was in inverse correlation between sleep quality and scores of the IBD QoL.

Studies have also suggested poorer sleep quality in subjects with active inflammatory bowel disease compared to subjects in disease remission. In two studies using the Manitoba IBD cohort, subjects with active disease as assessed through clinical indices were found to have poorer sleep compared to subjects in disease remission, and poor sleep indices were have a negative effect on IBD-related quality of life [5]. The same authors were also able to prospectively assess fatigue in subjects over a 2-year period and determined that poor sleep quality was directly related to fatigue in patients in patients with active disease [28]. Additional studies have also demonstrated that in adults, active disease as assessed through the Crohn's Disease Activity Index (CDAI) is directly correlated with an elevated PSQI [29].

Sleep disturbance in IBD patients has also been implicated as risk factor precipitating poor outcomes and as a marker for ongoing inflammation. Ali and colleagues demonstrated that an elevated PSQI was highly predictive of subclinical inflammation assessed on colonoscopy [4, 35]. The authors also demonstrated that IBD patients with an elevated PSQI have a higher risk of

disease exacerbation [30]. Additional evidence demonstrating the role of sleep in predicting relapse was described in the Crohn's and Colitis Partners IBD cohort. The authors demonstrated that an IBD patient in clinical remission but with an elevated score on the PROMIS-SD Short form 4a had a twofold increased risk of disease flare at six months [31]. Additionally, the lack of mucosal healing, even in patients in clinical remission, has been found to associated with poor sleep quality in CD, but not UC.

Interestingly, researchers using the ongoing Prospective Registry for IBD Study at Massachusetts General Hospital (PRISM) have demonstrated that sleep disturbance in IBD is independent of nocturnal symptoms [32]. In a logistic regression analysis, when nocturnal symptoms were included in the logistic regression model, only an elevated CRP was associated with poor sleep.

There are limited data regarding the effect of changes in circadian rhythm and inflammatory disease activity. Recent publications, utilizing questionnaires, suggest that an evening chronotype or a preference for the evening or later points of the day is linked to increased symptoms of fatigue in IBD patients [38]. Another study by Chakredo et al. also assessed circadian misalignment in IBD patients. The authors determined that an evening chronotype was associated with poorer IBD health-related quality of life. The authors also reported that social jet lag, or a preference to sleep later in the night and awaken later in the morning on weekends, and sleep debt were increased in patients with IBD. Moreover, patients with fistulizing disease were found to have increased social jet lag and sleep compared to subjects with uncomplicated CD [40•].

Table 6. Medical co-morbidities associated with sleep disruption

Medical co-morbidities associated with sleep disturbances in the elderly
Congestive heart failure
Acute coronary syndromes
Hypertension
Chronic obstructive pulmonary disorder
Obesity hypoventilation syndromes
Asthma
Diabetes
Hyperthyroidism
Hypothyroidism
Gastroesophageal reflux
Peptic ulcer disease
Irritable bowel syndrome
Benign prostatic hypertrophy
Overactive bladder
Incontinence
Menopause
Alzheimer's disease/neurocognitive decline
Neurocognitive decline
Parkinson's disease
Cerebrovascular disease
Epilepsy

Recent studies have also addressed the role of other co-morbid etiologies in promoting poor sleep and fatigue. A recent study investigated the role of irritable bowel syndrome (IBS) symptoms on IBD quality of life and sleep quality. Despite its limitations, the authors determined that IBS symptoms poorly affect both sleep qualities assessed through the PSQI [39].

Recent studies have also attempted to assess the role of objective sleep patterns as assessed through polysomnography (PSG) and wrist actigraphy in patients with IBD. Although limited and conflicting, the data suggests poorer PSG-related sleep measures in patients with IBD (Table 5). The first study to describe the use of polysomnography and sleep survey in inflammatory bowel disease included 16 subjects with inactive IBD [45]. Subjects with IBD had lower sleep efficiency, decreased total sleep time, increased sleep fragmentation, and overall arousal index compared to healthy controls. An additional study utilizing an ambulatory polysomnographic assessment of sleep in Crohn's patients was described by Shirit and colleagues. The researchers reported that compared to controls, IBD patients had less REM sleep and longer oxygen desaturation periods. Moreover, patients with CD had a lower percentage of REM sleep as well as a higher percentage of lighter sleep [43•].

A larger actigraphy-based study to assess both physical activity and sleep was performed comparing 30 health controls and 49 subjects with Crohn's disease [46]. The study found that subjects with Crohn's disease had significantly higher numbers of nighttime awakenings and time spent awake after sleep onset compared to healthy controls. A more recent study has also suggested that active Crohn's disease as measured through CRP and the Harvey-Bradshaw index was associated with poorer sleep efficiency and more fragmented sleep compared to subjects in disease remission [48•].

There is limited data assessing improvement in sleep quality with the initiation of anti-inflammatory therapy. Nevertheless, a study by Stevens et al. suggested a significant improvement in sleep quality scores in patients treated with anti-TNF and vedolizumab. Additionally, vedolizumab therapy was also associated with improvement in significant changes in depression and anxiety scores [33••].

The compiled evidence suggests an intricate relationship between sleep and IBD. Subjects with inactive IBD appear to have poorer sleep compared to healthy control, and subjects with active disease appear to have poorer sleep compared to subjects in disease remission. Moreover, sleep has been suggested a potential biomarker for poorer outcomes and ongoing inflammation.

Despite the above studies, the literature on assessments of sleep in elderly subjects with IBD is limited and the majority of study subjects were not older in age. Further studies to assess sleep in this population of IBD patients may provide additional evidence on the nature of these SD in the geriatric IBD population.

Sleep and psychological impairment

The co-incident diagnoses of anxiety, depression, or alternative psychiatric disorders can present later in life and effect sleep. Anxiety disorders are the most prevalent disorders in the elderly, and 10% of adults aged 65 years or

older have a manifestation of an anxiety disorder [49]. Rates of late-life depression also have an average prevalence of nearly 13.5% [50]. In patients with sleep complaints, a working understanding on these common disorders can provide practitioners with a means to target therapy or initiate appropriate referrals.

Sleep disturbances are commonly described in patients with unipolar depression and are included in the diagnostic criteria [51]. The majority of older adults, who reported depressive symptoms, also had symptom of insomnia or feelings of lethargy [52]. Sleep disturbance has also been suggested to represent a prodrome of mental illness. Clinicians can screen for unipolar depression with a short two-item questionnaire, the Patient Health Questionnaire 2 (PHQ-2), on symptoms of depressed mood and anhedonia, which has high sensitivity and specificity [53].

Similar to unipolar depression, sleep disturbance features prominently in the diagnosis of anxiety disorders [51]. Sleep complaints are often reported in patients with anxiety disorders, and specifically in older adults, 90% have reported some form of sleep complaint [54, 55]. The converse also appears to be true, as poor sleep has been linked to subsequent development of anxiety disorders [56]. A variety of screening questionnaires exist for the assessment of anxiety, but questionnaires geared to the geriatric population, such as the Geriatric Anxiety Scale or Geriatric Anxiety Inventory, appear to be better suited at screening for anxiety disorders [57].

Bipolar disorders are a rare cause of sleep disturbances in the elderly. Ideally symptoms of mania should be screened for in the elderly population prior to treatment with anti-depressants or anxiolytics. Late-onset schizophrenia, defined as the onset of symptoms after age 44, accounts for 15–20% of all cases of schizophrenia and, although less common than psychoses associated with neurocognitive decline, can represent also represent a therapeutic and diagnostic challenge [58]. Considering the rarer incidence of these disorders, a review of potential secondary causes is warranted and an appropriate referral to a mental health provider is recommended.

Mood disorders, namely depression and anxiety, are common in patients with inflammatory bowel disease and have been shown to affect symptoms perception as well disease course and activity. Additionally, co-incident psychiatric illness has been shown to effect sleep in IBD patients [31, 32]. A recent study by Hood and colleagues utilized a several questionnaires on sleep quality, quality of life, and mental health in 47 patients with UC. Depression was independently associated with poor sleep quality as assessed through the PSQI [37•]. Although performed in pediatric patients, an additional study similarly found sleep disturbances to be prevalent in depressed youth with CD compared to healthy controls [59].

The compiled evidence suggests that screening for mood disorders and psychiatric illness is warranted in all patients with IBD, especially in the situations where patients endorse poor sleep. Moreover, in elderly patients with the sleep disturbances, the exclusion of co-morbid psychiatric illness is essential as these may be the presenting complaints of an underlying psychiatric illness.

Co-morbidity, polypharmacy, and sleep

Chronic conditions and medications for the management of these diseases are prevalent in the elderly. In the National Sleep Foundation 2009 Health and Safety poll, nearly 72% of all respondents reported being diagnosed with a medical condition, 19% reported 2 chronic medical conditions, and 30% reported three or more chronic medical issues [52]. The most common medical diagnoses were hypertension (40%), arthritis (31%), and diabetes (16%). An exclusion of common co-morbid causes of poor sleep and a review of culprit medications is often warranted in elderly patients.

Many of these conditions can contribute to sleep dysfunction. Notably, hypertension, diabetes, and heart disease are known to promote sleep-disordered breathing [60, 61]. Sleep-related movement disorders are also prevalent in the setting of hypertension, arthritis, depression, and diabetes [62]. Lastly, frequent nocturia, either as a result of a medical condition such as prostatic disease or in the setting of medications, can promote sleep disruption.

Dementia and neurocognitive decline are also increasingly prevalent in the elderly. The global prevalence is 5–7% in patients aged 60 or older [63]. Prevalence appears to increase with age to nearly 37.4% in patients aged 90 or older [64]. Neurocognitive decline can promote disruptive sleep through development of symptoms of both psychiatric impairment and through associations with conditions that disrupt sleep. Moreover, impairment in cognitive function has also been linked poor sleep parameters as assessed via polysomnography independent of co-morbidity [65]. A summary of the medical co-morbidities associated with sleep disturbance is provided in Table 6.

Polypharmacy or multiple medication use is common in the elderly population, with the median number of prescription medication in older adults doubling from 2 to 4 between 1988 and 2010 [66]. Many medications, including beta-agonists, anti-depressants, and anti-convulsants, have been linked to promoting insomnia and disturbed sleep. Corticosteroids, often prescribed in IBD, have been linked with poor sleep [67]. In IBD patients, vedolizumab has been linked to the improvement in clinical scores of depression and sleep quality, and anti-TNF therapies have been shown to improve sleep quality not only in IBD but also in other chronic inflammatory conditions [33••, 68, 69]. A review of culprit medications that can promote poor sleep should be performed in IBD patients, and the use of agents, which disrupt sleep, should be limited.

Primary sleep disorders

Senescence results in an increased prevalence of several primary sleep disorders which should be assessed in patients with IBD who describe sleep disturbances. Sleep-disordered breathing, namely sleep apnea, should be excluded in patients. Periodic limb movement disorders, namely restless leg syndrome, also rise in prevalence not only in the aged but also in patients with IBD. Lastly, specific circadian rhythm disorders and dream-directed behaviors should also be considered in older patients. A summary of the common sleep disorders in the geriatric population are provided in Table 7.

Table 7. Common Primary Sleep Disorders in the Elderly

Primary Sleep Disorder Class	Sleep Disorder	Clinical Features
Sleep Disordered Breathing	CSA	Cessation of breathing while sleeping in the absence of airway obstruction
	OSA	Intermittent Airway obstruction/Snoring
Sleep Related Movement Disorder	RLS	Paresthesia
		Urge at moving Lower Extremities during Inactivity
	PLMS	Inadvertent cyclical leg kicking promoting nocturnal arousal
Circadian Rhythm Disorder	Advanced Sleep Phase Syndrome	Exaggerated earlier onset of sleep
		Early Morning Awakenings
	REM Behavior Disorder	Acting out dream-like behaviors
		Dream recollection with awakening

CSA: Central Sleep Apnea, OSA: Obstructive Sleep Apnea. RLS: Restless Leg Syndrome. PLMS: Periodic Leg Movement in Sleep

Relevant, common sleep-disordered breathing in the elderly include central sleep apnea and obstructive sleep apnea (OSA). Central sleep apnea occurs without evidence of airway obstruction and results from increased sensitivity of chemoreceptors related to cardiac or pulmonary pathology. Cheynes-Stokes respiration is form of central sleep apnea where patients oscillate between periods of apnea or hypopnea and hyperventilation. Evidence of Cheynes-Stokes respiration in patients should warrant screening cardiac and cerebrovascular diseases [70, 71].

OSA, in contrast, occurs in the setting of intermittent airway obstruction with resultant hypoxemia and hypercarbia leading to disturbed sleep. Aging is an important risk factor for the development of OSA and has been linked to increased mortality [72, 73]. Thus, it is important to screen for OSA in this population, and a simple questionnaire incorporating four subjective and objective criteria can be used to predict the presence of OSA. A score of ≥ 3 as the cutoff to predict any OSA was 83.9% using this questionnaire [74].

Sleep-related movement disorders include restless leg syndrome (RLS) and periodic limb movement in sleep (PLMS). RLS is a sleep-related movement disorder associated with an uncomfortable urge to move the legs during periods of inactivity. PLMS is characterized by cyclical leg kicking in patients while asleep which often leads to arousal. Both RLS and PLMS are common in the elderly [62, 75, 76]. Both RLS and PLMS are often associated with secondary causes, namely iron deficiency. Moreover, RLS in common in the IBD population, and IBD patients with RLS have a higher rate of SD [77•]. A thorough history assessing for the discomforting sensations, paresthesia, or periodic movements is warranted in assessing fatigue in elderly patients with IBD.

Although a range of circadian rhythm disorders have been described, two important circadian rhythm disorders in the elderly are advanced sleep phase syndrome and REM behavior disorder. Advanced sleep phase disorder is described as an exaggerated earlier onset of sleep, beyond what is reported with normal aging, with subsequent early morning awakening. REM behavior disorder is an uncoupling of muscle atonia during REM sleep, resulting in SD due

to patients acting out dream associated behaviors [78]. REM behavior disorder tends to occur in elderly men often in the setting of neurodegenerative disease [79]. A careful history and evaluation can often implicate these circadian issues, allowing for a proper referral to a sleep specialist for evaluation.

Conclusion

There appears to be a bi-directional relationship in sleep and IBD, where inflammation not only promotes poor sleep but sleep disturbances also provoke further inflammation. In inflammatory bowel disease, the majority of the studies investigating poor sleep do not include elderly patients; however, overwhelming evidence suggests that patients with IBD have poorer sleep than patients without IBD, both in inactive and active states of disease. Moreover, poor sleep may function as a marker of ongoing inflammation as well as future poor outcomes.

There is evidence to suggest that by targeting inflammation in patients with IBD, patients may experience improvement in other downstream factors, including mood symptoms or primary sleep disturbances. In clinical practice, many patients continue to experience symptoms of fatigue despite the initiation of a biologic [34••]. This suggests that sleep complaints and fatigue, by extension, appear to be multifactorial.

In the elderly, a variety of factors appear to play a role in the development of sleep disturbances and fatigue, and the management of a single factor may unmask the contribution of other components promoting poor sleep. Sleep complaints are prevalent in the elderly and are associated with adverse outcomes. A framework for the assessment of poor sleep can be used to understand likely causes and initiate therapy of referral to appropriate providers.

Compliance with Ethical Standards

Conflict of Interest
Taha Qazi declares that he has no conflict of interest. Francis A. Farraye declares that he has no conflict of interest

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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