

Original Research**Nighttime Symptom Burden in Chronic Obstructive Pulmonary Disease: A Qualitative Study**

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Abbreviations: ADLs: Activities of daily living; BA: Bachelor of Arts; BSc: Bachelor of Science; CASIS: COPD and Asthma Sleep Impact Scale; CAT: COPD Assessment Test; COD: Confirmation of Diagnosis; COPD: Chronic obstructive pulmonary disease; CPAP: Continuous positive airway pressure; FRAIL: Fatigue, Resistance, Ambulation, Illnesses, Loss of weight; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GR: Group; HCl:

Hydrochloride; ICS: Inhaled corticosteroid; ICF: Informed consent form; IRB: Institutional Review Board; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; MD: Doctor of Medicine; PhD: Doctor of Philosophy; PRO: Patient-reported outcome; Q1: First quartile; Q3: Third quartile; SD: Standard deviation; SMT: Symptom Management Theory; US: United States; USD: United States dollars;

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Abstract

RATIONALE: Nighttime symptoms are clinically important but understudied in chronic obstructive pulmonary disease (COPD). This study explored patients' perceptions of nighttime symptoms, their effects on daily life, and symptom-management strategies.

METHODS: Thirty U.S. adults with COPD and moderate-to-high symptom burden (COPD Assessment Test score ≥ 10), without hospitalization or emergency department visits for severe exacerbation during the previous year, participated in semi-structured interviews. All participants received single-inhaler dual or triple maintenance therapy and completed the 7-item COPD and Asthma Sleep Impact Scal. Interviews were transcribed verbatim and thematically analyzed using the Symptom Management Theory framework.

RESULTS: Participants (median age 63; 60% female; 90% White) reported a high burden of nighttime symptoms and sleep disruption (87% severely impacted based on CASIS). Participants described a pronounced nighttime symptom experience, most frequently shortness of breath, mucus/phlegm production, coughing, and difficulty staying asleep or frequent awakenings. A range of symptom management strategies was reported, including behavioral adaptations (routines, avoidance of technology, sleep hygiene), pharmacological management (antidepressants, sleep medications, rescue inhalers), and complementary and integrative approaches (meditation, acupuncture, relaxation techniques). Nighttime symptom outcomes extended beyond sleep disruption. Participants reported significant daytime consequences, including fatigue and impaired concentration. These effects contributed to activity avoidance and limitations in social participation.

CONCLUSIONS: Among symptomatic patients receiving single-inhaler dual or triple maintenance therapy, nighttime COPD symptoms were commonly reported and were associated with substantial physical, emotional, and functional impacts. The findings support further consideration of nighttime symptoms in clinical assessment and individualized COPD management.

Introduction

Chronic obstructive pulmonary disease (COPD), the fifth leading cause of death in 2023,² imposes a substantial population burden in the United States, with an estimated 11 million individuals affected.¹ COPD is often associated with significant symptom burden, including ongoing dyspnea, chronic cough, mucus production, dry mouth, fatigue, pain, depression, and anxiety.^{3,4} Symptoms have been reported as most problematic in the morning and have an impact on daily activities.⁵

Nighttime symptoms (including early morning symptoms) are a clinically significant yet understudied aspect of COPD.⁶⁻⁸ COPD nighttime symptoms involve a complex interaction of perception, management behaviors, and consequent outcomes. Nighttime symptoms contribute to poor sleep quality, which can include difficulty falling asleep, frequent awakenings, and insomnia. One study estimated the prevalence of poor subjective sleep quality to be 55% in patients with moderate to severe COPD.⁹ Poor sleep quality in turn worsens COPD burden, including daytime fatigue, reduced physical/mental functioning, and diminished quality of life.⁹⁻

¹⁶ As such, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends assessing symptoms, including sleep disturbance and insomnia, at each routine COPD visit.¹⁷

To inform clinical practice and improve patient outcomes, it is essential to understand nighttime symptom experience, the burden of nighttime symptoms in patients with COPD, and strategies for managing nighttime symptoms. Inhaled triple therapy (inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA)) is a recommended maintenance treatment for patients with a history of COPD exacerbations. In clinical trials, triple therapy has been shown to improve lung function, reduce exacerbations, and enhance quality of

life compared with LAMA alone, LABA/LAMA, or ICS/LABA.¹⁷⁻²¹ With COPD symptoms often persisting despite medical management,³ the extended therapeutic coverage of twice-daily therapies including the second peak in lung function with the evening dose may offer improved control of nighttime symptoms. The purpose of this study was to investigate how patients on single-inhaler dual or triple therapy and once-daily or twice-daily dosing perceive and manage nighttime symptoms associated with COPD.

Materials and Methods

Methodology

The University of California, San Francisco Symptom Management Theory (SMT)²² served as the theoretical framework for this study. The SMT is essential for understanding individuals' symptom experiences, which comprise three components that interact simultaneously: symptom experience, management strategies, and outcomes. Symptom experience includes the individual perception and evaluation of the symptom. Symptom management strategies are techniques aimed at preventing or mitigating the symptom experience, and symptom outcomes are the result of these strategies and experiences. While symptom experience was the primary focus of our study, we also examined the relational factors associated with symptom management strategies and outcomes.

Semi-structured interviews (see supplementary materials for the interview guide) used open-ended questions to explore several key topics, including the following: the frequency and severity of nighttime symptoms (including early morning symptoms), impact of symptoms on daily life and sleep, coping techniques and strategies used for symptoms, potential perceived burden or benefit associated with taking a second daily dose of medication (if applicable),

perception and efficacy of evening dosing in nighttime symptom alleviation and the use of rescue medication before going to bed at night.

Sociodemographic and clinical data, including current medication use, CAT²³, CASIS¹², and questions to assess frailty status (using the FRAIL framework²⁴) were collected. Four investigators experienced in qualitative research conducted the interviews, with only the participant and the interviewer present. Interviews were conducted between March 11th and May 7th, 2025. The interviews lasted approximately 60 minutes. Participants were compensated with USD 125 for their time. All interviews were audio recorded through Zoom, transcribed verbatim and de-identified to remove personally identifiable information.

Study Population

Thirty U.S. adults with a physician-confirmed diagnosis of COPD participated in this study. All participants reported moderate or high symptom burden (CAT score ≥ 10)²³, with no severe exacerbations resulting in hospitalizations or emergency department visits in the past year. A CAT score of ≥ 10 was required to ensure that participants had a clinically meaningful COPD symptom burden and were able to provide relevant experiential insight into the effects and management of nighttime symptoms. There were 10 patients in each of the following groups: single-inhaler once-daily triple therapy (“GR1”), single-inhaler twice-daily triple therapy (“GR2”), and single-inhaler dual maintenance therapy (“GR3”).

To qualify, patients needed to reside in the U.S., have a confirmed diagnosis of COPD, be on single-inhaler triple therapy or on single-inhaler dual therapy as their maintenance treatment, and have at least two fills of their COPD maintenance therapy (or evidence of use for 60 days). Exclusion criteria included multi-inhaler (“open”) maintenance therapy, taking ensifentrine

nebulizer as maintenance therapy for COPD, taking a biologic treatment for COPD, having a diagnosis of lung cancer, asthma or interstitial lung disease, or a history of lung transplant. The study was designed to examine experiences among patients receiving single-inhaler maintenance therapy, including experiences associated with once- versus twice-daily dosing. Patients receiving open triple therapy were therefore excluded to avoid conflating dosing experiences with the burden of managing multiple inhalers. Patients receiving single bronchodilator therapy were excluded because the study focused on patients with persistent symptom burden despite dual or triple maintenance therapy. Patients receiving ensifentrine were excluded to maintain a sample receiving established inhaled dual or triple maintenance regimens.

Patients unable to complete the interview due to language difficulties or cognitive impairment, as well as those with a lack of reliable internet access, were also excluded from the study.

Participants were recruited primarily through a recruiter's panel of nurse navigators and other nurses working in pulmonary and primary care settings. Recruitment also took place through a patient advocacy group (Pillar Patient Advocates).

Analysis

Interviews were analyzed by three researchers using a hybrid coding approach that began with deductive codes informed by the interview guide while remaining open to inductive codes that emerged during analysis. When new codes emerged from the interviews, they were added to the coding framework as part of the inductive process. Following the development of the preliminary coding dictionary, the research team prepared the first two transcripts for coding. An agreement of 84% was established, after which an intercoder agreement assessment was conducted using dual coding and reconciliation; minor coding discrepancies were discussed and resolved through consensus. The coders subsequently proceeded independently using the finalized coding

dictionary. The analysis software used was Atlas.ti version 25, with code frequency tabulated in R version 4.3.

Results

A total of 2,126 patients were invited to participate in the qualitative interviews. Of these, 406 patients completed the screening process, with 349 excluded. Fifty-seven patients met eligibility criteria and consented to participate. Thirty-five patients were scheduled for interviews, of whom 30 participated and completed the interview (Figure 1).

Patient characteristics

Participants had a median age of 63 years; 60% were female, and 90% were White. Education varied, with nearly half having some college or university experience (47%). Insurance coverage varied, with the majority insured by Medicare (60%). Two-thirds of participants were receiving single-inhaler triple therapy, split evenly between fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate (33% each). The remaining participants were receiving single-inhaler dual maintenance therapy, most commonly fluticasone propionate/salmeterol (13%), followed by tiotropium bromide & olodaterol (10%), budesonide/formoterol (6.7%), and fluticasone furoate/vilanterol (3.3%).

Detailed sociodemographic and clinical characteristics are presented in Table 1. The majority (87%) were severely impacted by nighttime symptoms and sleep disruption, as measured with CASIS. Based on established thresholds, severe sleep impairment was defined as a total CASIS score of ≥ 30 . Participants differed in COPD severity, with most reporting high (21-30) or very high (31-40) impact on the CAT PRO (73%).

Qualitative Findings

Thematic analysis of the 30 interviews revealed three key themes aligned with the three components of the SMT: a high nighttime symptom burden, wide-ranging outcomes from nighttime symptoms, and various symptom management strategies.

Table 2 presents a structured summary of participant quotes organized according to the three primary components of the SMT, highlighting the movement from perception and evaluation of symptoms to concrete management behaviors and finally to the physical, emotional, and functional consequences reported by participants. The following sections describe the main findings, organized by key dimensions of the SMT.

Main Findings - Nighttime Symptom Experience

The most frequently reported nighttime symptoms, as shown in Figure 2, were shortness of breath (80%), mucus/phlegm production (80%), coughing (77%), and difficulty staying asleep or experiencing frequent awakenings (77%). Wheezing, sweating or night sweats, and snoring were each reported by 60% of participants.

- **P15_GR2:** *"I'm up and I'm just coughing, but I'm not really producing anything to spit out and it just makes sleeping very difficult because it's like I'm struggling with my breathing"*
- **P12_GR3:** *"Yeah, hard for me to get a lot of sleep because I, you know, whenever I'm wheezing and I keep coughing and not getting any sleep."*

When asked about the top three most bothersome symptoms, participants most often identified difficulty staying asleep or frequent awakenings (40%), followed by shortness of breath (33%), mucus/phlegm production (33%), and coughing (33%). Wheezing and sweating or night sweats

were less frequently ranked among the top three most bothersome, and snoring was not identified as a top concern by any participant.

- **P26_GR2:** *“Well, I would say the wakefulness is more bothersome because it makes my day... I mean, I don't want to have no energy to do nothing through the day.”*
- **P19_GR1:** *“I think it's staying asleep. Falling asleep is not always an issue because I'm so exhausted from getting up from the night before that I can't really. You know, I'm kind of tired, so I will fall asleep.”*

Main Findings - Nighttime Symptoms Outcomes

Nighttime symptoms were reported to have wide-ranging impacts (see Figure 3). Physical impacts were the most frequently reported consequence of nighttime symptoms. Nearly all participants (93%) reported experiencing physical effects, and these were most often mentioned spontaneously (80%) without probing.

- **P06_GR2:** *“It affects me because if I'm doing housework, running the vacuum cleaner, I've got to take a break. I'll do one room and I'm like, I've got to sit down for a minute. It slows me down. Just like to make a bed, it takes my breath. It's just I get really winded.”*
- **P23_GR3:** *“When I'm up in the night and I have broken sleep, I have a terrible breathing day. Because I think my body's tired and it takes more of an impact on me. So if I sleep well, I feel better during the day. If I don't, then a lot of times I have to take a nap during the day because I'm so tired.”*
- **P59_GR1:** *“The fatigue. And it kind of all runs together because I don't think if I wasn't so fatigued, I wouldn't be so snappy.”*

Emotional (77%), reduced sleep quality (77%), cognitive (63%), and social impacts (60%) were also frequently reported. Emotional impacts were evenly split between spontaneous and probed reporting, while cognitive and social impacts were more commonly identified following probing.

Anxiety was the most frequently reported emotional impact, affecting 78% of participants who described emotional consequences.

- **P03_GR2:** “...when I get the anxiety or anxious feeling, that's bothersome, because I feel like I'm lost. Okay. And anxiety, is it at nighttime as well? Well, it starts in the afternoon.
- **P12_GR3:** “When I'm having a hard time breathing or whatever, you know, it kind of gets you get a lot of anxiety, hoping you can keep on you know, to the night and get by through everything and stuff and everything”
- **P12_GR3:** I was struggling to breathe. I was having to write things on paper for my wife, because I couldn't even talk.”

When participants ranked the most bothersome impacts, physical impacts were selected most often, identified by 50% of participants. Reduced sleep quality and social impacts were both ranked among the top three most bothersome (30% each), and emotional impacts were reported as the most bothersome by 27% of the participants.

Main Findings – Nighttime Symptom Management Strategies

Participants reported a combination of behavioral adaptations, complementary and integrative approaches, and pharmacological symptom management strategies (Table 3).

To manage sleep disruptions, participants most commonly relied on consistent sleep routines (33%), sleep hygiene, and relaxation techniques such as meditation or breathing exercises (33%).

- **P14_GR2:** "I just stick to a routine. I go to bed at a certain time."
- **P15_GR2:** "I do acupuncture every single Monday, and that gives me one hour a week to relax and reset and just get grounded. And during that hour of acupuncture, I listen to this meditation, a Deepak Chopra, something the acupuncturist puts on me...So on those nights when I have difficulty falling back to sleep, when I wake up in the middle of the night, what I do in my head is I start listening to the chakras."
- **P35_GR3:** “For the sleep, and then, I'll listen to YouTube. I listen to frequencies, like the 528, 423 frequency, the theta waves, binaural beats, delta waves. Anything that'll make me sleep.”

- **P03_GR2:** *"Most of the time, I can talk myself out of it. I don't know if that makes sense, but I'm like, relax, relax, relax, relax. And I, like, meditate myself out of it."*

Around one-third (30%) used non-COPD medications, mainly antidepressants, to support sleep.

- **P10_GR3:** *"With the sleeping, the amitriptyline. That is what I totally give all credit to that. Because I guarantee if I didn't pay, if I wouldn't take it, it would be bad. It would be like 18 hours up, and the other hours very, very, very restless."*
- **P16_GR3:** *"I just got a dosage of hydroxyzine, increased to 50 milligrams because the 25 milligrams wasn't working. They also got me on melatonin as well."*
- **P40_GR1:** *"I'm on medication for my mental health and he's trying to help my sleeping"*

Inhaler device use was common: 83% reported using rescue inhalers at night, with more than half describing them as very effective, and some (37%) used them preventatively before bedtime.

- **P23_GR3:** *"Sometimes I use it before I go to bed. I'm not very good at keeping track of when the last time it is, I used it. ...I'll do it, so that I don't wake up in the night all winded. Because if I don't use it, I definitely have exacerbations."*
- **P15_GR2:** *"I find I need it more at night, for example, when I had to walk up the sixth flight of stairs, y... Like, I feel like I need it, but I don't want to get up...at night, when I'm laying there, and then I, I guess I said earlier, I think everything just kind of settles, and then it comes up at night."*
- **P31_GR3:** *"I think I notice symptoms more at night, and also just because I know it'll probably help me sleep a little better."*

Additional management strategies included nebulizer use (47%), oxygen therapy (20%), and CPAP machines (10%).

Table 4 summarizes participant experiences with twice-daily maintenance therapy among those with existing and/or prior exposure to a second daily dose (80%). Participants described a number of perceived benefits from the second daily dose, including improved symptom control (25%), better sleep (21%), and prolonged effectiveness (21%). Smaller proportions (13%)

reported feeling no noticeable changes, and some participants described challenges, such as difficulty remembering the second dose or disruptions to daily routines (38%).

- **P09_GR1:** *“Yes [the second dose provides additional relief] because I’ll cough more without it. [The twice-daily] totally helped with my coughing that is what made my coughing manageable. So if I don’t do that nighttime dose, I wake up crappy in the morning, and I’m sluggish, and I don’t know. It does something. I’m better if I do two doses.”*
- **P57_GR1:** *“I don’t get exacerbations. And to me that’s very important because I don’t want to go back to the hospital. I don’t like being in the hospital, so controlling exasperations is very important to me.”*
- **P35_GR3:** *“[The twice-daily] gets you through the day and night.”*

Discussion

This study provides in-depth insights into the nighttime symptom experiences of symptomatic patients with COPD receiving single-inhaler dual or triple maintenance therapy. The findings suggest that nighttime symptoms represent a considerable burden to these patients and may impact daily functioning and quality of life. The SMT²² provided the guiding conceptual framework for interpreting these findings, situating nighttime symptoms within the dynamic relationship between symptom experience, management strategies, and outcomes.

Nighttime symptoms in this study encompassed evening, night, and early morning manifestations, most participants reporting CASIS scores indicative of considerable nighttime symptom burden and sleep disruption. These findings align with prior studies, including the ASSESS study, which similarly demonstrated high nighttime symptom burden among patients with COPD.¹⁶ Participant narratives emphasized that symptoms were often perceived as more severe at night, using descriptions such as distressing, persistent, and difficult to control.

Dyspnea, cough and mucus production disrupted sleep and were physically and emotionally taxing.

Consistent with prior evidence, nocturnal symptoms were perceived to contribute to frequent awakenings, difficulty initiating and maintaining sleep, and reliance on rescue or nebulized medications during the night.⁹⁻¹⁵ Within the SMT framework, findings reflect a heightened symptom experience beyond physical symptoms, including emotional responses such as anxiety or fear related to breathlessness. Nearly all participants reported physical consequences of nighttime symptoms, and four in five reported reduced sleep quality, consistent with prior literature showing pervasive daytime fatigue and impaired functioning^{9,11,12,15,25}. Emotional and psychological consequences were commonly reported and appeared clinically meaningful, with patients describing nocturnal anxiety, panic related to breathlessness, and anxiety attacks, further diminishing quality of life across physical, social, and emotional domains.^{9,15,26} Difficulty staying asleep or frequent awakenings emerged as the most bothersome nighttime symptom, while physical impacts were most often identified as the most burdensome consequence, suggesting that disrupted sleep may be one pathway through which nighttime symptoms affect daytime functioning.

Within the SMT framework, the findings suggest that nighttime symptom burden and inadequate symptom control extend beyond nocturnal discomfort to influence functional outcomes and daily behaviors. Activity avoidance emerged as a salient symptom outcome, with participants describing reduced participation in social activities, household tasks, and physical exertion. Such avoidance may contribute to progressive physical deconditioning and reduced independence, reinforcing a cyclical relationship between symptom burden and functional limitation in COPD.

Participants described a wide range of symptom management and coping strategies aimed at mitigating symptoms and improving sleep. Behavioral adaptations, such as structured sleep routines and a controlled sleep environment (e.g., adjusting sleep positioning, lighting, and temperature), were commonly reported and have been described in prior research as beneficial for improving sleep quality and symptom relief.²⁷⁻²⁹ These strategies reflect the adaptive efforts and active patient engagement in symptom self-management.

Pharmacological management was also frequently employed. Approximately one-third of participants reported using antidepressant medications to aid sleep, with some also using supplements like melatonin, both of which have been shown to have potential effects on sleep latency or sleep quality.³⁰ Notably, limited prior research has examined real-world sleep management strategies among individuals with COPD, particularly from the patient perspective. The present findings, therefore, add insights into how patients combine prescribed treatments with self-initiated strategies to manage nighttime symptoms in COPD.

The findings of the current study suggest that participants used a comprehensive and individualized approach to sleep management, which integrates behavioral, complementary and integrative approaches, and pharmacological strategies. Participants described actively balancing clinician-directed treatment plans with self-management behaviors and taking an active role in their sleep management. Clinicians may wish to consider that patients often engage in substantial self-management efforts alongside prescribed therapies to address nighttime symptoms.

Inhaler use was commonly mentioned as a symptom management strategy; one-third of individuals used rescue inhalers preventively at night, while others relied on maintenance therapy, particularly twice-daily regimens, which some participants perceived to be beneficial for nighttime symptom control and sleep outcomes. These observations are consistent with prior

studies suggesting that extended-dosing regimens may contribute to nighttime symptom control.^{31,32}

Despite longstanding recognition of nighttime symptom burden, the GOLD report, as of the 2025 edition, still lacks explicit recommendations for managing sleep disturbance or nighttime COPD symptoms. Findings from this study support further consideration of nighttime symptoms in clinical care and may help inform future guideline development and recommendations to address the full 24-hour symptom experience in COPD.

Limitations

The sample size and homogeneous composition of the sample impose constraints on the generalizability and transferability of findings. Although efforts were made to ensure an equal number of participants within the three groups, the limited number of participants per group does not allow for group-specific conclusions. Another limitation is that it was not always possible to distinguish whether impacts, such as reduced sleep quality or emotional effects, were primarily driven by nighttime symptoms or the overall burden of disease and treatment. This may have influenced the accuracy of data on nighttime-specific experiences. The eligibility criteria may also limit the transferability of the findings. Requiring a CAT score of ≥ 10 and current single-inhaler dual or triple maintenance therapy selected a symptomatic population with persistent burden despite maintenance treatment. Consequently, the nighttime symptoms and associated impacts reported may be more pronounced than those experienced by people with lower CAT scores, milder COPD, or different treatment profiles. The findings are most applicable to symptomatic patients receiving single-inhaler dual or triple therapy. The exclusion of open triple therapy means that the findings may not reflect the treatment burden associated with managing multiple inhalers. The findings may also have limited applicability to patients receiving single-

bronchodilator regimens or newer maintenance options such as ensifentrine. Detailed exacerbation history was not collected beyond confirming the absence of a severe exacerbation resulting in hospitalization or an emergency-department visit during the previous 12 months. The relationship between prior exacerbation burden and the reported nighttime experiences therefore could not be assessed.

Conclusions

This study suggests that nighttime symptoms represent a substantial burden in COPD among symptomatic patients receiving single-inhaler dual or triple maintenance therapy. Patients described persistent nighttime symptom distress and relied on a combination of pharmacological, complementary and integrative approaches to manage nighttime symptoms, indicating both adaptive self-management and areas where additional support may be needed. These findings highlight the potential value of more systematic assessment of nighttime symptoms, comprehensive and early patient education, and integration of multidisciplinary care to support COPD management across the full 24-hour cycle. Clinicians may wish to consider nighttime symptoms as part of COPD care and tailor management discussions to individual symptom patterns, treatment needs, and dosing schedules where clinically appropriate.

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Ethics approval and informed consent

The study protocol was reviewed and approved as exempt by the Pearl Institutional Review Board (IRB) before study procedures commenced. The study adhered to all applicable local regulations and good research practices. Each participant was provided with an informed consent form (ICF) prior to the interview.

Consent for publication

Not applicable. All data are reported in anonymized and aggregated form.

Data availability

No data are available. Data not available as no consent was sought from patients to allow sharing of data with third parties.

Declaration of interest

Hayley Germack, Meredith Bell, Norbert Feigler, Randy Legg are employees of AstraZeneca Pharmaceuticals LP and hold AstraZeneca stock.

Gerard Criner has received grants/contracts and consulting fees from AstraZeneca, GSK, Chiesi, Boehringer Ingelheim, Pulmonx and Apreo. He has also received consulting fees from Intuitive and Uniquity. He is part of an Advisory Board for Chiesi and Sanofi Regeneron.

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Dorsa Khazaei, Karen Winkler, and Tommi Tervonen are employees of Kielo Research, which received fees from AstraZeneca related to this work. Tommi Tervonen holds stock in Kielo Research.

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Tables

Table 1: Sociodemographic characteristics, CAT and CASIS

Characteristic	Total sample (N = 30)
Age, median (Q1, Q3)	63 (57, 66)
Gender¹	
Female	18 (60)
Male	12 (40)
Education¹	
Elementary/primary school	1 (3.3)
Middle school/junior high school	3 (10)
High school	4 (13)
Some college/university	14 (47)
College/university (BA, BSc)	5 (17)
Postgrad. degree (Masters, MD, PhD)	3 (10)
Ethnicity¹	
White	27 (90)
Black or African American	3 (10)
Insurance¹	
Medicare	18 (60)
Medicaid	7 (23)
Employer-provided insurance	7 (23)
Self-provided insurance	2 (6.7)
Veteran Affairs/Military healthcare	1 (3.3)
Current maintenance treatment¹	
Fluticasone propionate/salmeterol	4 (13)
Tiotropium bromide & olodaterol	3 (10)
Budesonide/formoterol	2 (6.7)
Fluticasone furoate/vilanterol	1 (3.3)
Fluticasone furoate/umeclidinium/vilanterol	10 (33)
Budesonide/glycopyrrolate/formoterol fumarate	10 (33)
CAT category¹	
Medium impact (10-20)	8 (27)
High impact (21-30)	18 (60)
Very high impact (31-40)	4 (13)
CASIS category¹	
Less severe sleep impairment (<30)	4 (13)
Severe sleep impairment (≥30)	26 (87)

¹ n (%)

Table 2. Participant quotes framed within the Symptom Management Theory.

Dimension	Sub-Domain	Participant Quotes
Symptom Experience	Perception	P15_GR2: “Basically, I go to bed and I wake up a lot in the middle of the night and I just feel, I guess maybe it's the dripping of whatever into my lung and I feel like a lump and I just cough a lot. I'm up and I'm just coughing, but I'm not really producing anything to spit out and it just makes sleeping very difficult because it's like I'm struggling with my breathing”
	Evaluation	P20_GR3: “And just generally at night, my symptoms do seem to be worse. I've got this my lungs hurt a little bit, not extremely bad, but they do hurt. And I've got this, I don't know, shortness of breath feeling in them.” P12_GR3: “...whenever I'm having a hard time breathing or whatever, you know, it kind of gets you get a lot of anxiety because you know you're just, you know, hoping you can keep on you know, to the night...”
	Response	P22_GR3: “...the feeling of restlessness, so an inability to relax. Do you have those at all? Yeah, no, that's a 10 right there.” P12_GR3: “Yeah, hard for me to get a lot of sleep because I, you know, whenever I'm wheezing and I keep coughing and not getting any sleep. So it's like sometimes I sleep two or three hours. Then I get up and then come back and sleep another hour or two and get up like stuff like that. Sometimes it's just off and on. Sleep like 3 or 4 segments. Instead of sleeping all the way through the night.”
Symptom Management Strategies	Behavioral Adaptations (Routines, Sleep Hygiene)	P09_GR1: “I'm very regimented to manage this disease.” P14_GR2: “I just stick to a routine. I go to bed at a certain time.” P15_GR2: “I don't use my phone at night, I use during the day...” P15_GR2: “I do external things like I don't use my phone and I'll turn off the TV, because so these distractions interrupt with sleep. So I, you know, keep a dark room and, you know, I keep the, you know, a little cooler. And so in addition to my sleeping medicines, you know, I've adopted other practices, like, you know, no technology and stuff to help.”
	Pharmacological Management	P10_GR3: “With the sleeping, the amitriptyline. That is what I totally give all credit to that. Because I guarantee if I didn't pay, if I wouldn't take it, it would be bad. It would be like 18 hours up, and the other hours very, very, very restless.” P16_GR3: “I just got a dosage of hydroxyzine, increased to 50 milligrams because the 25 milligrams wasn't working.” P09_GR1: “I start out with the rescue inhaler and then I have a long acting Breztri after that and I have my medicine that I take for my anxiety and depression...I take, some anxiety meds because sometimes they don't work. Especially if I start coughing and it won't go away, that's like. It's very, you know, scary.”
	Complementary and Integrative Approaches	P26_GR2: “It is very difficult to fall asleep...like depending with the pillows and trying to get comfortable. And then I have coughing and it's like, “Oh my God, I'm not going to fall asleep.” I use sleep

		meditation, sleep hypnosis to help me fall asleep, so it does help..." P09_GR1: "I have 10 supplements you know, to try to maintain my energy. I drink electrolytes all day long because I've noticed how much the energy had, my energy has been affected, so I have an electrolyte drink that I drink that I'm hoping helps me with my energy" P19_GR1: "I take supplements to help me fall back asleep. I don't like to take a sleeping pill. So I take a, you know, like stuff with melatonin in it. And sometimes it works, sometimes, sometimes it doesn't." P03_GR2: "I do acupuncture every single Monday, and that gives me one hour a week to relax and reset and just get grounded. And during that hour of acupuncture, I listen to this meditation, a Deepak Chopra, something the acupuncturist puts on me...So on those nights when I have difficulty falling back to sleep, when I wake up in the middle of the night, what I do in my head is I start listening to the chakras."
Symptom Outcomes	Activity Avoidance	P09_GR1: "I can't get up in the morning and go somewhere. I have to plan my day around my symptoms. There's no getting up in the morning and going and of course then if I'm having a flare up then I don't get to do things maybe I planned it's very disruptive to life." P62_GR1: "sometimes, depending on the day, I might not take a trip because of that. I'm like, "Oh, y'all going to be walking all fast, I'm not going to go." So sometimes it does hold you back." P03_GR2: "if I wanted to go to the movies, I couldn't do it. I'd be coughing. So I feel like I'm interrupting everybody. So the coughing is my biggest one that bothers me."
	Daytime effects	P22_GR3: I can't sleep and it affects my whole during the daytime and I'm not focused." P23_GR3: "When I'm up in the night and I have broken sleep, I have a terrible breathing day. Because I think my body's tired and it takes more of an impact on me. So if I sleep well, I feel better during the day. If I don't, then a lot of times I have to take a nap during the day because I'm so tired."
	Life/ADLs	P19_GR1: "I have a lot of clients that I help and there are times where I just can't concentrate or think good. It's not as good as it used to be." P06_GR2: "...if I'm doing housework, running the vacuum cleaner, I've got to take a break. I'll do one room and I'm like, I've got to sit down for a minute. It slows me down. Just like to make a bed, it takes my breath. It's just I get really winded."

Table 3: Strategies for dealing with sleep disruption

Strategy, n (%)	Total sample (N = 30)
Coping mechanisms	
Sticking to a sleeping routine	10 (33)
Stress-management/relaxations techniques	10 (33)
Taking antidepressant medications	9 (30)
Drinking liquid before bed	3 (10)
Having a distraction, such as TV or reading, before bed	4 (13)
Medications such as painkillers or muscle relaxants	3 (10)
Pre-emptying cough technique before going to bed	2 (7)
Reducing media or TV consumption before bed	2 (7)
Avoid caffeine	1 (3)
Sleep environment	
Change pillow/bed/body position (e.g., head elevated)	9 (30)
Light	7 (23)
Temperature	6 (20)
Humidity	5 (17)
Reduce noise	1 (3)
Sleep supplements	
Magnesium	4 (13)
Tylenol PM ¹	4 (13)
Melatonin	2 (7)
Electrolyte drink	1 (3)
Valerian	1 (3)
Other medical management methods for nighttime symptoms	
COPD medication or nebulizer	14 (47)
Oxygen therapy	6 (20)
CPAP machine	3 (10)
Preventive rescue inhaler use to help with sleep	11 (37)

¹ Nighttime Pain Reliever & Sleep Aid (acetaminophen & diphenhydramine HCl)

Table 4: Experience with twice-daily therapy

Aspects of the second dose, n (%)	Patients with twice-daily therapy experience (N = 24)
Positive	
Better COPD symptom control	6 (25)
Works well with patients' schedules	6 (25)
Better nighttime symptom/sleep management	5 (21)
Prolonged effectiveness	5 (21)
Easy to remember	4 (17)
Neutral	
No difference was noticed with the second dose	3 (13)
Negative	
Difficulties with remembering/disruption to daily activities	9 (38)

Figures

Figure 1: Participant dispositions.

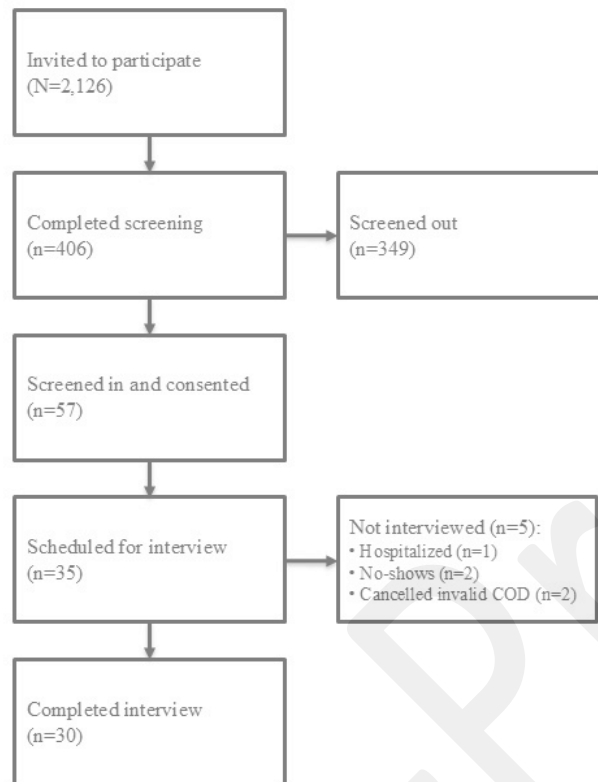
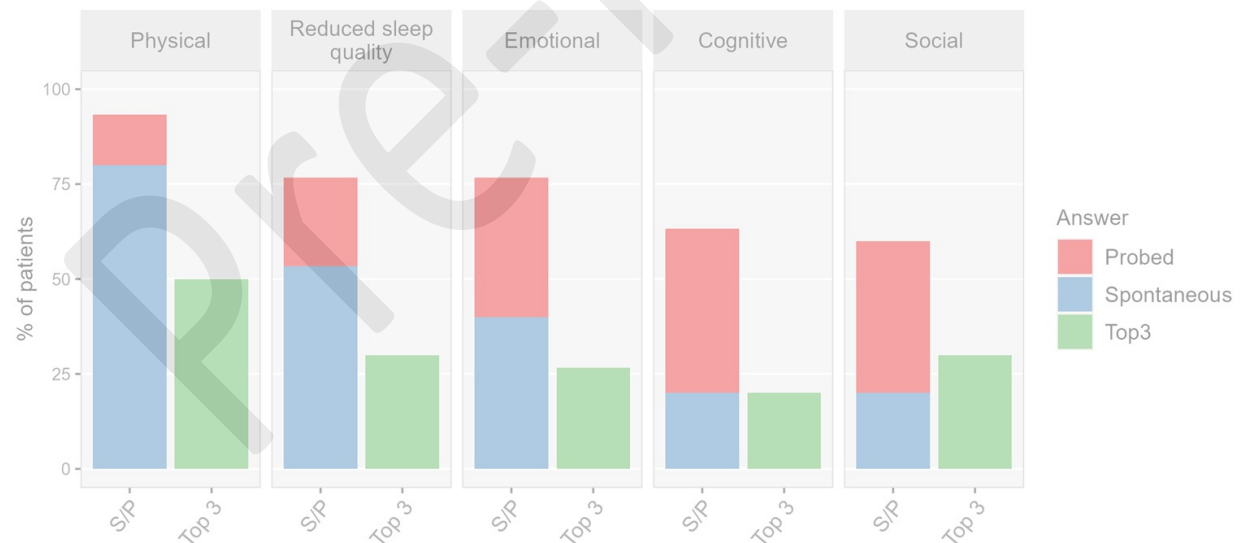


Figure 2: Frequently reported nighttime symptoms.



Figure 3: Frequently reported impacts of nighttime symptoms.



Online Supplement

KR2402 INTERVIEW GUIDE AND SURVEY QUESTIONS

a. Instructions to Interviewer

The purpose of this interview is to understand patients' perceptions of nighttime symptoms associated with COPD, their impact on sleep, and preferences and experiences with different treatment regimens and devices. The interview will last approximately 60 minutes. You may adapt the guide based on the flow of the conversation and responses from the participant.

Patients may discuss ways to cope with COPD symptoms in the evening and early morning. For example, they may take additional rescue medication to preemptively treat nighttime symptoms. All such ways of coping with the disease in the evening or early morning may relate to nighttime symptoms. If reported by the patient, the interviewer should probe further how the symptoms relate to their symptoms at night and how this is associated with the frequency of their maintenance medication (once / twice daily).

b. Introduction [5 min]

Thank you for taking the time to speak with me today. My name is [Interviewer's name]. I am a [Role] with Kielo Research.

The purpose of this interview is **to get your experiences with COPD nighttime symptoms, impacts and treatment**. We are interested in your impressions, experiences, and opinions to understand what matters to patients like you. There are no right or wrong answers; we are interested in your personal experiences and opinions.

1. Do you still want to take part in this interview? [If yes, continue; if no, terminate call]

This interview will be audio-recorded to ensure we capture everything you say. This recording will be kept confidential, and your name will not be linked with your responses.

2. Do I have your permission to audio-record the interview? [If yes, proceed with the interview; if no, inform the patient they must be recorded to participate]

i. Discussion Rules

Before we begin, let me suggest some things to make our discussion more productive.

- My role here is to ask questions and to listen. I'll also summarise the information you've said at times to ensure I understand you correctly. I'll ask questions to obtain your feedback, and I'll move the discussion from one question to the next to keep us on track so that we can finish within the time we have.
- Please speak loudly. We're audio-recording the session because we don't want to miss any of your comments.
- I will not use your name during the interview after the recording starts.
- There are just a few other things that I want to let you know.
- I am not a medical doctor. I am a research professional. My background is in conducting various types of research, so I am not qualified to give out medical advice.
- I want to remind you that you are a volunteer in this study, so you can skip any question you do not want to answer or stop the interview at any time. All your responses will be kept confidential.

Do you have any questions before we begin?

I'm going to start the recording.

[Start the Recorder]

This is study KR2402, qualitative interviews, with participant ID [Participant's ID]. Today's date is [Date].

1. Do I have your permission to record our interview?

[If no, please thank the participant and terminate the interview here]

2. Can you confirm that you have read the informed consent, and do you have any other questions you would like us to discuss?

[If needed, share the screen with the consent language on it and read it to the participant or let the participant read it]

3. After having read the consent form, do you agree to participate in this study?

[If no, please thank the participant and terminate the interview here]

c. Part 1: Diagnosis and Nighttime Symptoms [10 min]

i. Diagnosis

1. Can you tell me about when you were first diagnosed with COPD?
2. What symptoms led you to see a doctor?
3. How was your diagnosis explained to you?

ii. Nighttime Symptoms

1. Can you describe the current nighttime symptoms you experience as part of your COPD?

[Let patients describe their symptoms and mark them down (table 1) with S (spontaneous). Then, probe them for symptoms they have not described. Mark any symptoms they now confirm having experienced with P (probed).]

2. How frequently do these symptoms occur?
 - Occasionally (or rarely)
 - Sometimes (a few times per week)
 - Frequently (most days)
 - Always/constantly (or every day)
3. Can you describe the timing of your nighttime symptoms? For example, are they typically worse while you are trying to fall asleep or do your symptoms affect your sleep and cause you to wake up through the night?
4. Do you experience symptoms in the early morning when you are starting to wake up?

Probe: If any, which one is worse in the morning

5. Can you describe the severity of these symptoms on a typical night? (On a scale of 0 to 10, where 0 means not at all and 10 means extremely severe)

[Write down the frequency and severity score (table 1).]

6. Which of these symptoms are the 3 most bothersome for you today? Why?

[Mark down the 3 most bothersome symptoms in the table below]

Table 1 . Nighttime symptoms

Symptoms	Experienced	Frequency	Symptom severity score	3 most bothersome
	[S/P or No]		[0-10]	[X]
Shortness of breath/Difficulty breathing				
Persistent Coughing				
Chest pain or tightness				
General pain				
M Wheezing				
Snoring				
Choking				
Mucus/phlegm production				

Difficulty falling asleep				
Difficulty staying asleep/Frequent awakenings				
Prolonged wakefulness				
Sweating/ night sweats				
Anxiety/ panic attacks at night				
Restlessness/ inability to relax				
Other:				

d. Part 2: Impact on Sleep [10 min]

1. Can you describe what impact do these nighttime symptoms have had on your everyday life?

[Let patients describe their impacts and mark them down (table 2) in the corresponding categories with S (spontaneous). Then, probe them for impacts in categories they have not described. Mark any category of impacts they now confirm having experienced with P (probed).]

Follow up with a question about early morning symptoms impacting their everyday life

2. How frequently do these impacts occur?
3. How severe are these impacts (On a scale of 0 to 10, where 0 means not at all and 10 means extremely severe)?

[Write down the frequency and severity score (Table 2), note severity separately for evening and morning]

4. Which of these impacts are the 3 most bothersome for you today? Why?

[Mark down the 3 most bothersome impacts in Table below.]

Table 2. Nighttime symptom impacts

Impacts	Experienced [S/P or No]	Frequency	Impact severity score [0-10]	3 most bothersome [X]
Reduced sleep quality				
Cognitive (Examples: concentration/focus, alertness, memory)				
Physical: (Examples: Daytime fatigue, exercising, household chores, running errands)				
Activities of self-care: (Examples: bathing, dressing, grooming, eating, toileting, transferring)				
Emotional: (Examples: anxiety, depression, sadness, frustration, embarrassment, guilt, fear of dying, de-motivation/impaired coping)				
Social: (Examples: reduced participation in leisure activities and hobbies, interaction with others or attendance to social gatherings or activities, social or cultural stigma)				
Relations/Intimacy (Examples: relationship with a partner, dating others, close relationships)				
Engaging in unhealthy behaviours (Examples: watching TV to avoid sleeping, snacking)				
Work/Studies				
Increased exacerbations (like hospital/doctor visit)				
Difficulty to manage comorbidities				
Financial impact				
Other:				

5. [If not mentioned:] On a typical night, how many hours of sleep do you get ? Do you feel rested in the morning? How many times do you wake up during the night?
6. Are you using any sleep management strategies to make you sleep better? E.g. sticking to a sleep routing, avoiding naps during the day, reducing media consumption before bedtime
7. What about your sleep environment, have you made any changes to your sleep environment to help you to sleep better?
8. Do you take medication or dietary supplements to help you sleep?

e. **Part 3: Managing Around-the-Clock Symptoms [5 min]**

1. How do you manage your COPD nighttime symptoms throughout the night or early morning?

[Probe: Behavior changes, rescue medication use, or other strategies.]

- a. Are there any specific strategies or treatments you rely on more during the night compared to the day?
- b. What do you find helpful in your symptom relief?

If clarification needed for rescue medicine:

*A **rescue medication** is a fast-acting inhaler that helps quickly relieve sudden breathing problems. It works by relaxing the muscles around the airways, making it easier to breathe. These are used **only when needed**, not for daily control (maintenance).*

2. How often do you use rescue medication to manage your COPD symptoms?

- b. Is the frequency of rescue medication use different during the day versus the night? If so, why?
 - c. Do you feel your rescue medication is effective in alleviating your symptoms, particularly during the night? Why or why not?
 - d. Do you ever take rescue medication before going to bed? If so, why? [Probe: is it to prevent nighttime symptoms]
- 3. Do you feel your current treatment regimen adequately addresses your nighttime and daytime symptoms? Why or why not?
 - 4. In your opinion, what changes would improve your sleep quality while managing your COPD symptoms?

a. Part 4: Preferences for Once- vs. Twice-Daily Therapy [10 min]

- 1. Have you used both once-daily and twice-daily COPD therapies? If so, can you describe your experiences with each?
[Probe: Ease of use, effectiveness, side effects, convenience]
- 2. If applicable: Do you notice differences in how these therapies impact your nighttime symptoms?

[For twice-daily therapies:]

- a. What do you find valuable about the second daily dose?
 - b. Does the second dose provide additional relief or benefits in your nighttime comfort or sleep?
- 3. If applicable: How does the dosing schedule (once-daily or twice-daily) fit into your daily routine?
 - 4. If applicable: Have you faced any challenges incorporating the therapy into your schedule?
[Probe: Have you ever forgotten to take a dose?]
 - 5. [If applicable, for participants who have switched from dual to triple therapy:] How has this transition impacted your preferences for dosing schedules?
 - a. Did switching treatments change how you feel about once-daily or twice-daily therapies?

6. If you were to choose a therapy, which dosing schedule would you prefer, and why?

b. Part 5: Experiences with Inhaler Devices [10 min]

1. What type of inhaler are you currently using?

- [Probe:] Is it a metered dose, dry powder, or soft mist inhaler?

[If participant needs more information, these inhaler types are:

1. Metered dose inhaler: Puffs dose of medicine when you press on it. Medicine is held in a pressurized canister.
2. Dry powder inhaler: Delivers powder medicine when you inhale.
3. Soft mist: Sprays dose of medicine when you press on it. Medicine comes in a liquid format and is turned into a fine mist when you spray]

2. Can you describe your experience with your current inhaler device?

[Probe: Ease of use, effectiveness, maintenance requirements, side effects.]

3. Have you used other types of inhalers in the past? How did your experience with those compare to your current device?

4. Does the type of inhaler device impact how well you feel your symptoms are managed? If so, how do you measure that? How do you know you're feeling better?

5. What improvements, if any, would you like to see in your inhaler device?

c. Closing [10 min]

We would now like to complete a questionnaire on you and your current health status. Thank you for your valuable insights so far.

[Complete the online questionnaire (next section) with the participant.]

SHORT QUESTIONNAIRE ON SOCIODEMOGRAPHIC AND CLINICAL INFORMATION

Moderator to enter participant ID [_____]

1. What best describes the area you live in? [implement as radio buttons]
 - Urban
 - Suburban
 - Rural
2. What was your total household income before taxes during the past 12 months? [implement as radio buttons]
 - Less than \$25,000
 - \$25,000 to \$34,999
 - \$35,000 to \$49,999
 - \$50,000 to \$74,999
 - \$75,000 to \$99,999
 - \$100,000 to \$149,999
 - \$150,000 or more
 - Don't know or prefer not to answer
3. How would you describe your race or ethnicity? (you can choose multiple options) [implement as checkboxes]
 - White
 - Black or African American
 - American Indian or Alaska Native
 - Asian
 - Native Hawaiian or Other Pacific Islander
 - Hispanic

- Other
- 4. What best describes your marital status? [implement as radio buttons]
 - Married
 - Separated/divorced
 - Widowed
 - Living with partner
 - Single
- 5. What best describes your employment status? [implement as radio buttons]
 - Employed, full-time
 - Employed, part-time
 - Self-employed
 - Voluntary work
 - Home maker
 - Retired
 - Student
 - Unemployed
 - On sick leave
- 6. What is the highest level of education you have completed? [implement options as radio buttons]
 - Elementary/primary school
 - Middle school/ junior high school
 - High school
 - Some college/ university

- College/university (BA, BSc)
 - Postgraduate degree (Masters, MD, PhD)
7. What type of health insurance do you have? (select all that apply) [implement options as check boxes]
- Employer-provided insurance
 - Self-provided insurance
 - Veterans Affairs / Military healthcare
 - Medicare
 - Medicaid
 - None (uninsured)
8. How long ago were you diagnosed with COPD? [implement as radio buttons]
- Less than 1 year
 - 1–5 years
 - 6–10 years
 - More than 10 years
9. What is your current smoking status? [implement as radio buttons]
- Never smoked
 - Current smoker
 - Former smoker
10. [Only ask if answer to 7. is 'Current smoker' or 'Former smoker']
- What is the total number of years you have smoked in your lifetime? Do not include the times when you were smoke free.
- Less than 5 years
 - 6-9 years
 - 10-19 years
 - 20 years or more

11. What rescue medications do you use for your COPD symptoms?

(Please select the medication you take to treat symptoms when they get too bad or worsen unexpectedly) [implement as check boxes]

- ☐ Ventolin or other inhaler
- ☐ Nebulizer
- ☐ Other (Specify: _____)

12. How often do you use your rescue medication for COPD symptoms? [Implement as radio buttons]

- ☐ Daily
- ☐ 3-6 days per week
- ☐ 1-2 days per week
- ☐ 0 days per week

13. What time of day you typically use your rescue medication for COPD symptoms (check all that apply)? [Implement as check boxes]

- ☐ Morning
- ☐ Afternoon
- ☐ Evening
- ☐ Night

14. Has a doctor ever told you that you have one of the following conditions? Check all that you have been diagnosed with [implement as checkboxes]

- ☐ Hypertension
- ☐ Diabetes (type 1 or type 2)
- ☐ Cancer (other than a minor skin cancer)
- ☐ Heart attack
- ☐ Heart failure
- ☐ Angina

- Arthritis
 - Stroke
 - Kidney disease
 - Sleep apnea
 - Depression
 - Anxiety
15. Have you used a continuous positive airway pressure (CPAP) machine to help with breathing while you sleep?
- Yes, currently using
 - Yes, have used in the past but not currently using
 - No, never used
16. How much of the time during the past 4 weeks did you feel tired? [implement as radio buttons]
- All of the time
 - Most of the time
 - Some of the time
 - A little of the time
 - None of the time
17. By yourself and not using aids, do you have any difficulty walking up 10 steps without resting? [implement as radio buttons]
- Yes
 - No
18. By yourself and not using aids, do you have any difficulty walking several hundred yards? [implement as radio buttons]
- Yes
 - No

19. How much do you weigh with your clothes on but without shoes?

___ KG [allow only numbers between 30 and 300]

or

___ LBS [allow only numbers between 60 and 600]

[Allow only one of these to be filled]

20. One year ago, how much did you weigh with your clothes on but without shoes?

___ KG [allow only numbers between 30 and 300]

___ LBS

[Present only the unit answered in the previous question]

CASIS

For each question below, please check ☐ the response that best represents how you feel. When answering the questions, please think about the impact of breathing problems/COPD/asthma on your sleep during the past week, even if the past week was unusually good or unusually bad.

[implement as radio button group per row]

During the past week, how often did you:	Never	Rarely	Sometimes	Often	Very Often
1. have a bad night's sleep?	☐	☐	☐	☐	☐
2. have problems staying awake during the day?	☐	☐	☐	☐	☐
3. have trouble falling asleep?	☐	☐	☐	☐	☐
4. wake up at night with breathing problems (shortness of breath, coughing, chest tightness, etc.)?	☐	☐	☐	☐	☐

5. wake up during the night and have trouble falling back asleep?	☐	☐	☐	☐	☐
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Please think about the impact of your breathing problems during the past week, and check ☒ the response that best represents how you feel.

[implement as radio button group per row]

During the past week, how often did you:	Never	Rarely	Sometimes	Often	Very Often
6. have a good night's sleep?	☐	☐	☐	☐	☐
7. wake up feeling rested?	☐	☐	☐	☐	☐