

SCIENTIFIC INVESTIGATIONS

Exploring the impact of excessive daytime sleepiness caused by obstructive sleep apnea on patient and partner quality of life: a time trade-off utility study in the UK general public

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Study Objectives: This study aimed to quantify the impact of excessive daytime sleepiness (EDS) on patient and patient's partner health-related quality of life in the form of utility values typically used in health economic evaluations.

Methods: A time trade-off study was conducted in a UK general population sample (representing a societal perspective) to elicit utility values, measured on a 0 to 1 scale, for health states with varying obstructive sleep apnea-associated EDS severity. In a time trade-off study, health states are described, and participants "trade off" time in a specific higher severity state for a shorter amount of time in full health.

Results: Overall, the sample consisted of 104 participants, who were interviewed and took part in the time trade-off exercise to elicit utility values for patient and partner residual EDS health states. The average utility score declined with increasing obstructive sleep apnea-associated EDS severity for both patient (no EDS, 0.926; mild EDS, 0.794; moderate EDS, 0.614; severe EDS, 0.546) and partner (no EDS, 0.955; mild EDS, 0.882; moderate EDS, 0.751; severe EDS, 0.670) health states.

Conclusions: These results demonstrate the high impact that EDS in obstructive sleep apnea is estimated to have on patient and partner health-related quality of life.

Keywords: sleepiness, sleep apnea syndromes, quality of life, health care economics, cost-benefit analysis

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Approximately 9% to 22% of patients with obstructive sleep apnea (OSA) have excessive daytime sleepiness (EDS) and associated impairments in concentration, judgment, and social and work function, despite primary OSA treatment. This study aimed to identify the impact of OSA-associated EDS on the health-related quality of life of patients and their partners.

Study Impact: The study provides utility values for health states of varying OSA-associated EDS severity, in line with changes in Epworth Sleepiness Scale score categories, and demonstrates the high impact of EDS on the health-related quality of life of patients and their partners. These values can also be used in cost-effectiveness analyses of new health care interventions for OSA-associated EDS.

INTRODUCTION

Obstructive sleep apnea (OSA) is a condition in which the walls of the throat relax and narrow during sleep, causing episodes of partial (hypopneas) or complete (apneas) obstruction of the airway, preventing normal breathing, and disrupting sleep.¹ The restricted airflow resulting from apneas and hypopneas can cause loud snoring, noisy or heavy breathing, gasping for air or snorting, and arousal from sleep, which in some cases leads to fatigue during the day.^{1,2} The estimated global prevalence of OSA is 22% for men and 17% for women.³ Excessive daytime sleepiness (EDS), a common symptom of OSA, is present in approximately 1 in 4 patients with OSA.³

People with EDS experience nonrefreshing sleep and, therefore, an urge to sleep despite apparently sufficient hours of sleep at night and regular naps throughout the day. They may

fall asleep at inconvenient times during the day and experience judgement lapses, poor concentration, and inhibited social function,^{1,4} contributing to an overall reduction in health-related quality of life (HRQoL).^{5,6} Sleepiness is a common cause of motor vehicle accidents;⁷ in the United Kingdom, OSA is a "notifiable" medical condition, meaning that patients with a driving license must notify the Driver and Vehicle Licensing Agency of a medical condition that could impact their driving ability.⁸ Patients who do not comply face not having their driving license issued or renewed, which can have a great impact on independent living.

Current treatment in OSA focuses on maintaining the airway during sleep to prevent apneic events and consequent intermittent hypoxia.⁹ Patients often receive a continuous positive airway pressure (CPAP) device to use during sleep. The device maintains the pharyngeal airway pressure above a critical level

to prevent its collapse. CPAP has been demonstrated to both reduce the number of arousals from sleep as early as the first treatment day and reverse daytime symptoms within a short time.^{9–12}

Despite primary treatment with CPAP, EDS still affects an estimated 9–22% of adults with OSA.^{13,14} In these cases, stimulant medicines such as modafinil and armodafinil have shown efficacy in improving vigilance and quality of life (QoL),^{15,16} although neither is licensed in Europe for OSA. Solriamfetol (Jazz Pharmaceuticals Ireland Ltd, Dublin, Ireland) is a licensed treatment for residual EDS associated with OSA. It has been demonstrated to improve wakefulness and self-reported EDS, as well as improving HRQoL for OSA patients and, indirectly, their partners.^{17–20}

Many health technology assessment bodies require evidence of the clinical effectiveness and cost-effectiveness of new treatments to support decisions on public and private health service reimbursement. Often, effectiveness is required to be assessed using patient-reported outcomes to evaluate impact on patient HRQoL. In countries with health technology assessment bodies that use cost-effectiveness evidence to determine value for money and to support health care payers' reimbursement decisions—such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom and the Institute for Clinical and Economic Reviews (ICER) in the United States—HRQoL is evaluated using a specific measure known as utilities.

The utility of different health states (eg, mild, moderate, or severe disease states) that a patient could be experiencing typically is measured on a 0 to 1 scale and represents a value for the HRQoL aspects of each health state. A value of 1 equates to highest HRQoL, whereas 0 is an HRQoL equivalent to death (zero QoL). The utility value for health states of differing severity (and thus differing impacts on QoL) is captured on the 0 to 1 scale using methods that give respondents a choice between the best possible health state (eg, no OSA or EDS) and poorer health states (eg, OSA with EDS) and capture the extent to which the former might be preferred over the latter.

A recognized method for evaluating utility values for different health states is time trade-off (TTO). With this method, participants are asked to “trade off” time in a best health state for a fixed longer time in a poorer health state as a way of eliciting the relative value of the latter. That is, participants might be expected to trade off more life years to avoid a highly severe health state compared with a mildly or moderately severe health state. For example, a participant might be willing to accept only 3 years in the best health state over 10 years in a severe health state—to trade off 7 life years for better HRQoL. The utility of the severe health state in this example would be 0.3 (3 years divided by 10 years). Utility values from TTO studies can be used to quantify the potential HRQoL-impact of conditions such as EDS, as well as the impact on patients' partners, who typically have been neglected in HRQoL studies because of a lack of EDS-specific patient-reported outcomes measures. Given the potential HRQoL impact that EDS has on patients with OSA and their partners, a TTO study from a societal perspective was conducted to estimate the utility impact for patients and partners associated with different severities of residual EDS in OSA.

METHODS

The TTO utility elicitation study presented here is in line with best-practice methods for conducting such utility studies, as reported by Attema et al.²¹

Study design

A cross-sectional TTO study was conducted in the UK general public to elicit utility values for health states relating to different severities of residual EDS associated with OSA. Health states valued by the general public rather than by patients reflects a societal perspective and is the most appropriate approach for making comparisons with other diseases in a publicly funded health service (such as in the United Kingdom), which receives its budget from taxpayers. Obtaining utility values from the general public also avoids patient perspective bias and is the approach recommended by NICE for inclusion of utilities in health technology appraisals.²²

Four health states assessed the HRQoL of patients with residual EDS; another 4 assessed the HRQoL of partners of patients with residual EDS. A study plan was developed with key stages outlined: development of appropriate, validated health state descriptions; design of a web-based TTO tool; a pilot study; and the main utility elicitation interviews. Interview locations were spread over the United Kingdom to capture a broad geographic sample.

Development of EDS health state descriptions

An overview of the health state description development process is shown in **Figure 1**. Four residual EDS severity health states (no EDS, mild EDS, moderate EDS, severe EDS) were developed for both the patient perspective and the partner perspective, yielding a total of 8 health state descriptions. The categorizations were based on the Epworth Sleepiness Scale (ESS). On the ESS, patients are asked to rate how likely they are to fall asleep in 8 different situations. Their ratings, made on a 4-point scale ranging from 0 (“I would never doze”) to 3 (“high chance of dozing”), are aggregated to obtain an overall ESS score between 0 and 24.²³ In the United Kingdom, NICE has categorized ESS as follows: 0–10 represents no EDS; 11–14, mild EDS; 15–18, moderate EDS; and 19–24, severe EDS.²⁴

Content validity was supported by constructing all the health state descriptions with reference to the 5 domains of the EuroQol-5 Dimension (EQ-5D), a generic health status instrument that covers mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with the addition of sleepiness and other disease-specific aspects informed by a targeted literature review of the HRQoL impact of EDS.

The health state descriptions had 2 components: a base component representing the description of a typical patient with OSA using CPAP treatment and a specific component reflecting the impact of residual EDS at different severities. The base description was made constant across all patient and all partner health states to provide context and to enable the utility valuation exercise to focus on the impact of differences in EDS severity rather than on valuing the impact of CPAP treatment. Participants were asked to imagine themselves as a patient with

Figure 1—Overview of development of residual EDS health state descriptions.



EDS = excessive daytime sleepiness, HCP = health care professional.

residual EDS or as a partner of a patient with residual EDS in each of the 4 EDS severity health states.

The draft health state descriptions were reviewed by a UK-based clinical expert sleep physician and were revised accordingly before being posted to a 3-day online bulletin board to elicit feedback from invited patients with OSA and patients' partners. The health states were revised in response to this feedback before being further validated by the expert sleep physician. The health states were piloted with ten general public participants, following which minor revisions were made and a final clinical expert validation performed. **Figure 2** shows one of the residual EDS health state descriptions (the complete set of health state descriptions appears in the **supplemental material**).

Participants, interview schedule, and utility elicitation method

Adults (≥ 18 years old) from the general public were recruited. During the screening process, potential participants answered a demographic questionnaire to ensure selection of a diverse group of participants, representative of the UK population. Participants were excluded if they had participated in market research within the preceding 6 months; if they, their partner, or a close relative had been previously diagnosed with a sleep disorder; or if they, their partner, or a close relative was currently working or previously worked in the pharmaceutical industry, in sleep-related health care, or in market research. All participants provided informed consent to participate.

The study aimed to recruit 120 participants (including 10 pilot interviewees) to achieve a sample size of ≥ 100 responses. The pilot interviews were conducted at a single facility.

All other interviews were conducted between October and December 2019, throughout the United Kingdom: England, Scotland, and Wales.

Participants received a brief introduction to OSA and EDS as background and completed a visual analog scale (VAS) ranging from 0 (death) to 100 (full health) for each of the 8 health states and their own health before completing the main TTO exercise. Interviewers used a web-based tool (e-tool) to administer the questions and exercises, allowing data collection in real time.

The TTO exercise used a sliding time scale of 0 to 10 years, a time frame in line with other recent TTO studies,^{25–27} with participants asked to express a preference between a set time of 10 years with each EDS health state (followed by death) and fewer years with the best imaginable health (followed by death). For the TTO, each participant's point of indifference was determined using a "flip-flop" method: alternating between high and low quantities of time in best imaginable health until a point of indifference (equal preference either way) was reached. Here it involved trading alternating higher and lower numbers of whole years and then, when the participant changed their response from willing to trade to not willing, identifying the number of months between the rejected and accepted years to derive the indifference time point in years and months. This was repeated for each EDS health state, first for the patient health states and then for the partner health states. Patient and partner health states were presented to each participant in a random order selected by the e-tool.

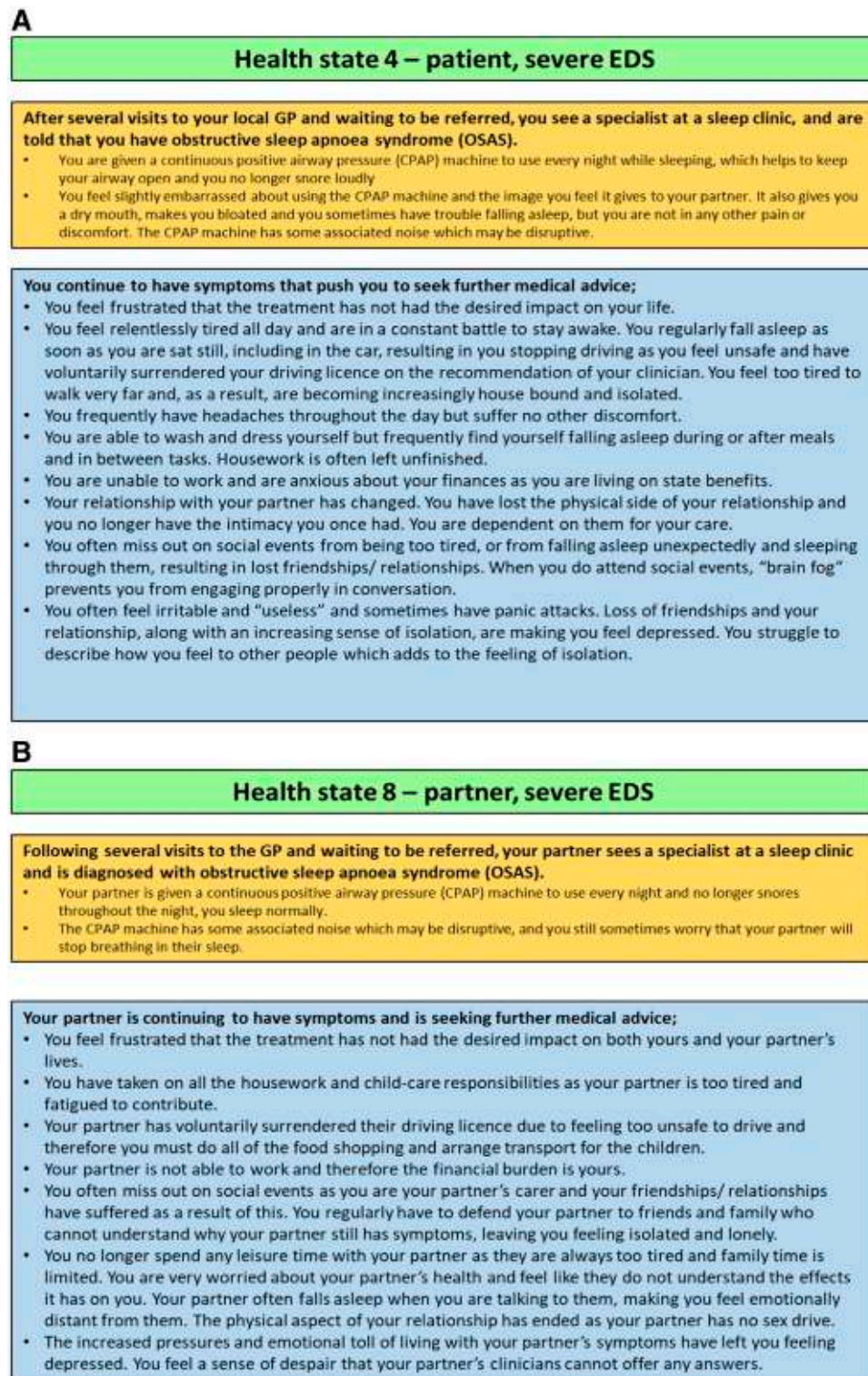
Data validation

For each participant, TTO response sheets were collected in real time on the e-tool, detailing the preference response stated for each health state, and contextual notes were recorded by the interviewer. Given the role of user input with the e-tool, several checks were performed to ensure the validity of the data. All TTO and VAS data were searched for outlier data or illogical responses. Any data queries were resolved by referring to written interviewer notes. This data validation identified participants who failed to understand the task or who were unwilling to complete the TTO.

Statistical analysis

TTO responses were converted to utility values on the 0 to 1 scale by dividing the time stated in the best imaginable health by 10. Mean, standard deviation, and 95% confidence intervals were estimated for each EDS health state TTO value. VAS ratings were on a scale of 0 to 100, with means, standard deviations, and 95% confidence intervals estimated.

Analysis of variance was used to test for differences between the TTO utility values elicited within both patient and partner health states (assuming independence between responses) or between patient–partner utilities for each EDS health state. Following analysis of variance results, post hoc analyses (Tukey honestly significant difference test) were used to determine where the differences in mean utility between health states lie. Relationships between patient and partner health states values were investigated with scatterplots and Pearson correlation coefficients. There were no adjustments made to address the

Figure 2—Example health state descriptions for severe EDS from patient perspective and partner perspective.

Patient perspective (A) and partner perspective (B). Orange box presents base description, which was consistent across all EDS patient and partner health states. Blue box presents health state description specific to severe-EDS patient/partner and was unique within each health state. CPAP = continuous positive airway pressure, EDS = excessive daytime sleepiness, GP = general practitioner.

issue of multiple endpoints analyzed. Therefore, reported *P* values are nominal because statistical significance cannot be claimed, owing to the lack of control for multiplicity.

RESULTS

Characteristics of study sample

Of the 110 participants (excluding pilot interviewees) from whom responses were collected, 104 had their TTO and VAS responses included in the final analysis. Six participants' responses were excluded because the participants showed an unwillingness to trade time for any of the 8 health states. Their reasons included religious beliefs, past medical history (theirs or their partner's), and family values/circumstances. No records were excluded for missing or illogical data, and no imputation of responses was required.

Table 1 summarizes the participants' demographic data. Of the 104 participants, 60 (57.7%) were men. Age ranged from 18 to 80 years; mean (standard deviation) age was 44 (16.41) years. Compared with the older age groups (≥ 65 years), the younger age groups (18–65 years) were slightly overrepresented in the sample. The majority (71.2%) of participants stated they lived in an urban rather than rural area. Three-quarters of participants held a driving license; 78% of these participants stated their license was very important/essential to them. The sample characteristics were broadly generalizable to the UK population: Statistics from the 2011 UK census showed a mean age of 39 years and 49.1% male (slightly lower than in the study sample set).

Utility and VAS results

Utility values declined with increasing EDS health state severity from both patient and partner states. Mean utility scores for patient health states were 0.93 (no EDS), 0.79 (mild EDS), 0.61 (moderate EDS), and 0.55 (severe EDS) (**Table 2**). Differences in patient utility were observed between the no-EDS and mild-EDS health states and between the mild-EDS and moderate-EDS health states, with differences, albeit lower, observed between the moderate-EDS and severe-EDS health states (**Table 2** and **Table 3**).

Estimated mean utility scores for partner health states were 0.96 (no EDS), 0.88 (mild EDS), 0.75 (moderate EDS), and 0.67 (severe EDS) (**Table 2**). The differences were largest between the mild-EDS and moderate-EDS health states (**Table 2** and **Table 3**).

VAS scores showed the same pattern as the mean utility values but were lower for each health state, and the range across health states was larger (**Table 2**).

There was decreasing utility for both patient and partner health states with increasing EDS severity (**Table 2**). Furthermore, lower mean utility values were found for each patient state relative to its corresponding partner state, with 95% confidence intervals not crossing each other for patient–partner state comparisons across all health states other than the no-EDS state (**Figure 3**).

A strong positive correlation, $r(413 \text{ df}) = 0.61$, $P < .001$, of patient and partner utility values was also observed at the

Table 1—Characteristics of study participants.

| Characteristic | Attribute | n (%) |
|---|--------------------------------------|---------------|
| Sex | Male | 60 (57.69) |
| Age, years | Mean (SD) | 43.58 (16.41) |
| | Median (range) | 44.00 (18–80) |
| Age group, years | 18–45 | 58 (55.77) |
| | 46–65 | 34 (32.69) |
| | > 65 | 12 (11.54) |
| Location | Rural | 31 (29.81) |
| | Urban | 73 (71.19) |
| Marital status | Single | 34 (32.69) |
| | Married/cohabiting/civil partnership | 61 (58.66) |
| | Divorced/separated/widowed | 9 (8.65) |
| Education level | Level 1–4 (GCSE/A-Level) | 51 (49.04) |
| | Level 5/6 (undergraduate) | 43 (41.35) |
| | Level 7/8 (masters/PhD) | 10 (9.62) |
| Employment | Full-time | 48 (46.15) |
| | Part-time | 18 (17.31) |
| | Unemployed | 9 (8.65) |
| | Student/retired | 18 (17.31) |
| | Other/preferred not to answer | 11 (10.58) |
| Annual household income | Less than £25,000 | 30 (28.85) |
| | £25,001 to £65,000 | 51 (49.03) |
| | More than £65,001 | 6 (5.77) |
| | Prefer not to say | 17 (16.35) |
| Driving license | Yes | 78 (75.00) |
| | No | 26 (25.00) |
| Driving importance, reported only for participants with a driving license | Not important at all | 5 (6.41) |
| | Slightly important/important | 12 (15.38) |
| | Very important/essential | 61 (78.21) |

GCSE = General Certificate of Secondary Education, PhD = doctor of philosophy, SD = standard deviation.

participant level, which shows that, as patient utility increased or decreased, partner health state utilities tended to increase or decrease in the same direction (**Figure 4**).

DISCUSSION

The impact of residual EDS on the HRQoL of patients with OSA and their partners has not been quantified in studies

Table 2—Utility values and VAS scores for patient and partner health states (n = 104)

| | Utility Values | | VAS Scores | |
|-----------------------|----------------|------|------------|-------|
| | Mean | SD | Mean | SD |
| Patient health states | | | | |
| 1. No EDS | 0.93 | 0.11 | 75.93 | 13.31 |
| 2. Mild EDS | 0.79 | 0.17 | 49.95 | 14.36 |
| 3. Moderate EDS | 0.61 | 0.22 | 36.47 | 13.93 |
| 4. Severe EDS | 0.55 | 0.24 | 27.80 | 11.94 |
| Partner health states | | | | |
| 5. No EDS | 0.96 | 0.08 | 81.85 | 10.85 |
| 6. Mild EDS | 0.88 | 0.13 | 59.79 | 15.36 |
| 7. Moderate EDS | 0.75 | 0.23 | 47.37 | 15.75 |
| 8. Severe EDS | 0.67 | 0.26 | 35.64 | 16.38 |

All values rounded to 2 decimal places. EDS = excessive daytime sleepiness, SD = standard deviation, VAS = visual analog scale.

reported in the literature, and, to our knowledge, no research has been conducted to investigate societal preferences and hence utilities for health states of differing severity in patients with EDS and their partners. This study reports OSA-associated residual EDS utility values obtained using a TTO methodology, as well as the first set of utility values estimated for partners of patients with OSA-associated residual EDS and demonstrates the major impact that moderate to severe OSA-associated EDS is estimated to have on patient and partner HRQoL.

TTO is a method used to derive a utility value that reflects the HRQoL impact of a condition such as residual EDS at different severity levels; the data can be used to generate quality-adjusted life-year outcomes for cost-effectiveness analyses of new treatments.^{21,22,28,29} When a societal perspective is adopted, it is important that TTO general public sample characteristics be representative of the (UK) population in terms of age, education status, other sociodemographic characteristics, and geographic spread to reflect the situation in the United Kingdom, where health care is primarily funded by general

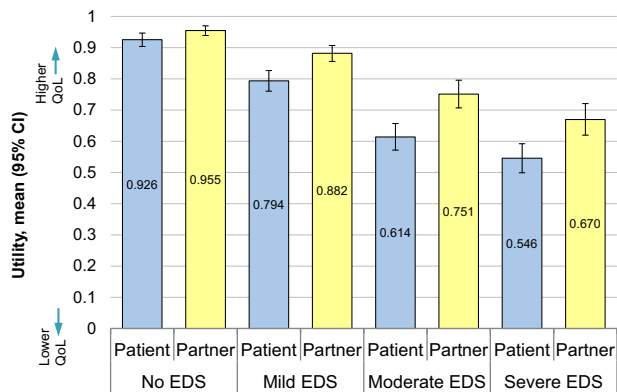
public taxation, and the perspective of the public as taxpayers and potential patients is particularly relevant. The characteristics of this study’s participants appear to be broadly generalizable to the UK adult population, although the average age of participants was 43.58 years, with only 12% greater than 65 years old (compared to approximately 19% in the UK population in 2020³⁰), hence representing a reasonably young sample, which may value health differently than an older population sample. Moderate to severe residual EDS associated with OSA was estimated to have a substantial detrimental impact on the HRQoL of patients and their partners. The estimated utility values for the patient health states demonstrated a notable ($P < .0001$) reduction in HRQoL with each incremental severity category from no EDS (mean utility, 0.926 [equivalent to population norm for HRQoL]) to moderate EDS (mean utility, 0.614). The lowest utility (hence HRQoL) was associated with severe EDS (mean utility, 0.546). In the context of the TTO exercise, this means participants were prepared to trade off an average of 4.5 life years, out of a maximum of 10 years, to avoid

Table 3— P values^a for patient and partner utility differences: Tukey HSD post hoc pairwise analyses across all health states.^b

| | HS1: Patient/ No EDS | HS2: Patient/ Mild EDS | HS3: Patient/ Moderate EDS | HS4: Patient/ Severe EDS | HS5: Partner/ No EDS | HS6: Partner/ Mild EDS | HS7: Partner/ Moderate EDS | HS8: Partner/ Severe EDS |
|-----|-------------------------|---------------------------|-------------------------------|-----------------------------|-------------------------|---------------------------|-------------------------------|-----------------------------|
| HS1 | — | | | | | | | |
| HS2 | < .0001 | — | | | | | | |
| HS3 | < .0001 | < .0001 | — | | | | | |
| HS4 | < .0001 | < .0001 | .1560 | — | | | | |
| HS5 | .9596 | < .0001 | < .0001 | < .0001 | — | | | |
| HS6 | .7075 | .0204 | < .0001 | < .0001 | .1080 | — | | |
| HS7 | < .0001 | .7473 | < .0001 | < .0001 | < .0001 | < .0001 | — | |
| HS8 | < .0001 | < .0001 | .4119 | < .0001 | < .0001 | < .0001 | .0439 | — |

^aThe P values should be considered nominal, as multiplicity adjustment was not performed. ^bTukey HSD post hoc pairwise analyses performed after analysis of variance across all health states for which $P = 2e^{-16}$. EDS = excessive daytime sleepiness, HS = health state, HSD = honestly significant difference.

Figure 3—Comparison of patient and partner health state utility values.



Mean utility value calculated for each EDS health state; error bars are 95% confidence intervals. EDS = excessive daytime sleepiness, QoL = quality of life.

the HRQoL consequences of severe EDS compared with best imaginable health.

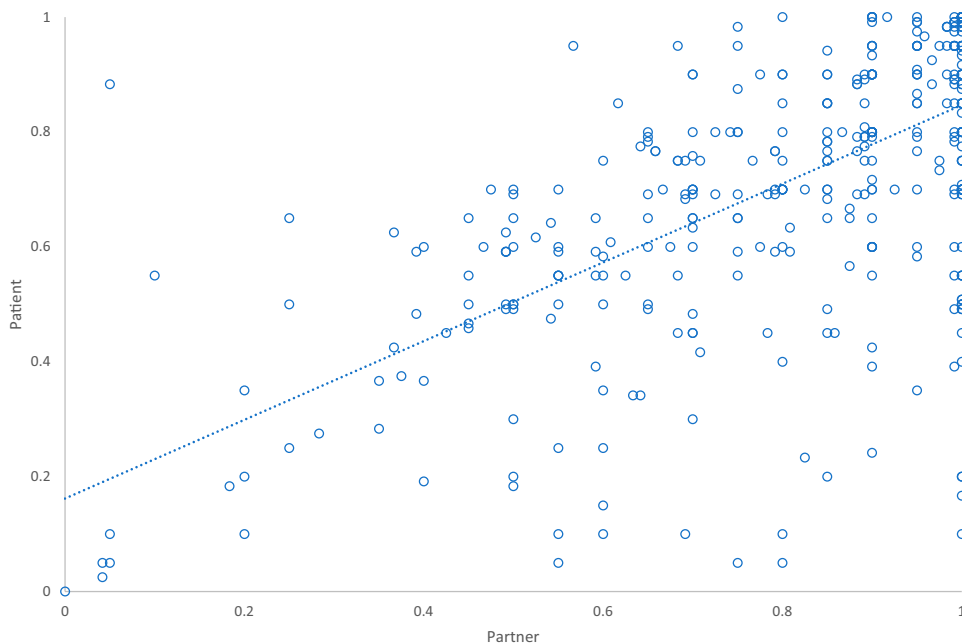
The results for the partner health states demonstrated that the patients' residual EDS had a greater impact on the patients' utility and HRQoL than on the partners'. Nevertheless, the impact on partners was important; mean health state utilities were 0.751 (moderate EDS) and 0.670 (severe EDS) vs 0.955 (no EDS). Notably, there was little effect on partner utility between no EDS and mild EDS. Participants were willing to trade off an

additional 2 life years (moderate EDS) or 2.8 life years (severe EDS) out of 10, compared with no EDS, to avoid the HRQoL impact associated with moderate or severe EDS. There was also a strong, positive correlation between patient and partner estimated utilities. As expected, patient and partner utility values for the no-EDS health state were similar ($P = .9596$), suggesting that a patient with no EDS and a partner with no EDS-related symptoms will have similar utility, validating the differences observed between patients and partners for the other health states.

Results on the 0 to 100 VAS are in line with the TTO utility values, with both patient and partner estimates decreasing with EDS severity.

Although there are no prior TTO studies in EDS, a few studies have investigated the effect of EDS on patient general well-being and HRQoL. Using the Medical Outcomes Survey Short Form 36 to analyze the impact of EDS on general health and functional status, Briones et al.³¹ found significant correlations between ESS scores and several Medical Outcomes Survey Short Form 36 dimensions: general health perceptions ($r, -0.30; P < .001$), energy/fatigue ($r, -0.41; P < .001$), role limitations due to emotional problems ($r, -0.30; P < .001$), and summary well-being ($r, -0.26; P < .005$). Another study, using the 36-Item Short Form Health Survey generic patient-reported outcomes instrument, found that EDS with an ESS score ≥ 11 was significantly associated with problems in physical functioning, physical role, bodily pain, general health, vitality, social functioning, and mental health ($P < .001$).⁵ More recently, Darchia et al.⁶ investigated the effects of sleep disorders in general on HRQoL and found that, although the study sample size was small, participants with ESS scores ≥ 11

Figure 4—Observed utility values for patient vs partner health states.



Pearson correlation coefficient, 0.61 ($P < .001$, nominal).

scored statistically significantly lower on all components of the 12-item version of the Short Form Health Survey. The present study's results are consistent with those in these broader studies.

A study that mapped patient ESS scores to EQ-5D domains found a similar pattern in the relationship between EDS severity and estimated utilities.³² The decline in mapped EQ-5D utilities with increasing EDS severity as measured by ESS scores was lower than with the present study's TTO results, likely because the EQ-5D, a generic utility measure, has less sensitivity to disease-specific changes.

The results from our study show a clear relationship between EDS state severity and utility for both patients and partners when the TTO is performed by a representative sample of the UK general public, hence representing societal values for the HRQoL impact of the health states. Other studies using a similar TTO methodology have been conducted in a representative sample of the UK general public for a range of diseases and conditions, although most of these are in life-threatening and rare diseases. Hence, the mean utility estimates tend to be quite low for such diseases with utilities estimated using TTO methods in a UK general public sample: such as 0.39 for a health state for a patient with chronic lymphocytic leukemia not responding to treatment,³³ or 0.13–0.58 for hereditary angioedema (a potentially life-threatening disorder caused by a genetic defect, which causes painful episodes of swelling) attacks related to the larynx, abdomen, face, and hands.³⁴ The severe EDS state in our study was slightly higher than an estimate of 0.50 for a partial remission state of B-precursor acute lymphoblastic leukemia in a UK general population TTO study.³⁵

There have been very few TTOs in a UK general population sample that have focused on conditions that primarily impact everyday HRQoL. One such study, a TTO exercise conducted in 107 members of the UK general public of health states reflecting varying durations of morning stiffness related to rheumatoid arthritis, produced mean utility estimates of 0.78, 0.61, 0.50, and 0.45 for < 1 hour, 1–2 hours, 2–3 hours, and ~3 hours, respectively.³⁶ Hence, the utility estimates for moderate to severe EDS in our study are similar to the estimates for between 1 and 3 hours of morning stiffness in patients with rheumatoid arthritis using a similar TTO methodology. While there appears to have been no similar TTO studies to compare the partner utilities in our study with, some TTO studies have been conducted for caregiver utilities, eg, a study in osteoarthritis estimated values of 0.85, 0.76, and 0.53 for mild, moderate, and severe osteoarthritis states, respectively,³⁷ the values being similar for the mild-moderate EDS states from the partner perspective.

Despite the studies for other conditions using a similar TTO approach in a representative UK general population, there are caveats in making direct comparisons as there are still differences in study design and population sample characteristics, as well as differences in the underlying conditions, that impact on the absolute values estimated.

Utility analyses are commonly performed as part of health economic evaluations of treatments. Utility values associated with EDS severity health states, such as those generated in this study, can therefore be applied in cost-effectiveness analyses in

sleep medicine to capture and quantify HRQoL improvement as patients move from more to less severe EDS categories with new treatments. When utility estimates are required for more gradual differences in underlying ESS scores (vs EDS severity categories), analyses can be supplemented with regression-based analyses to interpolate utility estimates across the full range of potential ESS scores. The utility values elicited in this study also show the HRQoL impact that OSA-associated residual EDS is estimated to have on partners of patients. This will be an important consideration in future cost-effectiveness studies.

A possible criticism of TTO studies conducted with the general public is the potential for inherent bias regarding health state descriptions and the subsequent utility elicitation process. To support content validity, the present study initially developed its health state descriptions around the EQ-5D, but then revised them based on feedback from patients and partners regarding their experiences with residual EDS (obtained from an interactive bulletin board). This process was followed to ensure coverage of all key general health aspects that affect HRQoL, including domains in which EDS has relatively less impact, such as low or no impact on self-care abilities (eg, washing, dressing), on both patient and partner health states. Despite this, the TTO construct applied to health states categorized according to the ESS is a hypothetical and subjective exercise, hence there is a risk of participants lacking an understanding of the health state descriptions or not understanding, or being willing to engage in, the TTO exercise. This did not appear to be a significant issue in the study but is a potential limitation of all such TTO studies. Conducting the TTO exercise as face-to-face interviews with trained interviewers is likely to have reduced this potential limitation.

The life-year trade-off offered to participants ranged from 0 to 10 years, and utility values were bounded between 0 and 1, meaning states worse than death (negative utility values) were not considered. While this could be considered a limitation, no participants were willing to accept immediate death in best imaginable health (0 year) to avoid 10 years in the most severe EDS health state, suggesting that results were not sensitive to these bounding constraints.

A further potential limitation is the grouping of health states during the interviews. Health states were presented to participants in a random order to avoid bias, but patient and partner states were presented separately to avoid confusing participants. Separate presentation could have influenced the results; switching the order in a sample to present partner health states first could clarify whether this had an impact.

Finally, some participants excluded from the final analysis set appeared not to follow the logic of the TTO exercise to trade off hypothetical life years and refused to fully engage in the exercise. However, such reactions are expected in studies in the general population, and as applicable, appropriate steps were taken to mitigate the impact of these elements to maintain the integrity of the analysis.

Further analyses of respondent data are planned to investigate clustering by respondent. Therefore, due to a lack of multiplicity adjustment, the *P* values reported here should be considered as nominal values.

CONCLUSIONS

The results from this TTO study showed that the utility of both patients and partners declined with increased severity of EDS, highlighting the HRQoL benefits that could result from novel treatment options for residual EDS. This is the first study in which the impact of OSA-associated residual EDS on HRQoL and utility has been estimated for partners of patients with residual EDS.

An important output of this research is that the resulting patient and partner quality of life values, based on using the TTO method in a sleep medicine context, can be directly used in cost-utility analyses of treatments and interventions for OSA-associated residual EDS that have an impact on patient-reported outcomes such as the ESS. The utility values may also be generalizable as proxy HRQoL values in similar sleep conditions associated with EDS, such as narcolepsy. Although the study was conducted in a UK population sample, the results should also be generalizable to populations with similar demographic characteristics (eg, the US population). In the United States and in other European countries, TTO studies are needed in both patients and partners for direct patient valuation and in members of the general public for the societal perspective.

ABBREVIATIONS

CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
EQ-5D, EuroQoL-5 Dimension
ESS, Epworth Sleepiness Scale
HRQoL, health-related quality of life
OSA, obstructive sleep apnea
QoL, quality of life
TTO, time trade-off
VAS, visual analog scale

REFERENCES

- Garbarino S, Scoditti E, Lanteri P, Conte L, Magnavita N, Toraldo DM. Obstructive sleep apnea with or without excessive daytime sleepiness: clinical and experimental data-driven phenotyping. *Front Neurol*. 2018;9:505.
- American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
- Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *J Thorac Dis*. 2015;7(8):1311–1322.
- National Health Service (NHS). Excessive daytime sleepiness (hypersomnia); 2020. <https://www.nhs.uk/conditions/excessive-daytime-sleepiness-hypersomnia/>. Accessed July 8, 2022.
- Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep*. 2001;24(1):96–105.
- Darchia N, Oniani N, Sakhelashvili I, et al. Relationship between sleep disorders and health related quality of life—results from the Georgia SOMNUS study. *Int J Environ Res Public Health*. 2018;15(8):1588.
- Bonsignore MR, Marrone O, Fanfulla F. Sleep apnea, sleepiness, and driving risk. *Sleep Med Clin*. 2019;14(4):431–439.
- UK Government. Obstructive sleep apnoea and driving. <https://www.gov.uk/excessive-sleepiness-and-driving>. Accessed July 14, 2022.
- Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. *Ther Adv Chronic Dis*. 2015;6(5):273–285.
- Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. *Arch Intern Med*. 2003;163(5):565–571.
- British Lung Foundation (BLF). Treatment for OSA; 2019. <https://www.blf.org.uk/support-for-you/obstructive-sleep-apnoea-osa/treatment>. Accessed July 8, 2022.
- National Health Service (NHS). Sleep apnoea. <https://www.nhs.uk/conditions/sleep-apnoea/>; 2019. Accessed December 4, 2019.
- Pépin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: The French multicentre study. *Eur Respir J*. 2009;33(5):1062–1067.
- Gasa M, Tamisier R, Launois SH, et al. Scientific Council of the Sleep Registry of the French Federation of Pneumology-FFP. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res*. 2013;22(4):389–397.
- Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *Sleep*. 2005;28(4):464–471.
- Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther*. 2006;28(5):689–706.
- Sunosi™ (solriamfetol) tablets Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2019.
- Sunosi™ (solriamfetol) tablets Summary of Product Characteristics. Dublin, Ireland: Jazz Pharmaceuticals, Ltd; 2020.
- Weaver TE, Drake CL, Benes H, et al. Effects of solriamfetol on quality-of-life measures from a 12-week phase 3 randomized controlled trial. *Ann Am Thorac Soc*. 2020;17(8):998–1007.
- Schweitzer PK, Rosenberg R, Zammit GK, et al. TONES 3 Study Investigators. TONES 3 Study Investigators. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial. *Am J Respir Crit Care Med*. 2019;199(11):1421–1431.
- Attema AE, Edelaar-Peeters Y, Versteegh MM, Stolk EA. Time trade-off: One methodology, different methods. *Eur J Health Econ*. 2013; 14, S1, Suppl 1:S53–S64.
- National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal; 2013. <https://www.nice.org.uk/process/pmg9/chapter/foreword>. Accessed November 2, 2020.
- Johns M. About the ESS. <https://epworthsleepinessscale.com/about-the-ess/>. Accessed January 26, 2021.
- National Institute for Health and Care Excellence (NICE). Obstructive sleep apnoea syndrome: How should I assess a person with suspected obstructive sleep apnoea syndrome? <https://cks.nice.org.uk/topics/obstructive-sleep-apnoea-syndrome/diagnosis/assessment/>. Accessed August 12, 2020.
- Hall F, de Freitas HM, Kerr C, et al. Estimating utilities/disutilities for high-risk metastatic hormone-sensitive prostate cancer (mHSPC) and treatment-related adverse events. *Qual Life Res*. 2019;28(5):1191–1199.
- Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: A time trade-off study. *Eur J Gastroenterol Hepatol*. 2018;30(2):174–180.
- Jendle J, Sandberg A, Buchs S, Swinburn P, Hadi M, Levin LÅ. A utility valuation study assessing the impact of postprandial glucose control on quality of life of individuals with type 1 or type 2 diabetes. *J Patient Rep Outcomes*. 2017; 2(1):20.
- Brazier J, Longworth L. NICE DSU Technical Support Document 8: An Introduction to the Measurement and Valuation of Health for NICE Submissions; 2011. London: National Institute for Health and Care Excellence (NICE) https://www.ncbi.nlm.nih.gov/books/NBK425820/pdf/Bookshelf_NBK425820.pdf. Accessed July 11, 2022.
- Tolley K. What are health utilities? <https://www.whatseries.co.uk/product/what-are-health-utilities/>. Accessed July 8, 2022.
- Office for National Statistics. UK population. <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020#age-structure-of-the-uk-population>. Accessed July 14, 2022.

31. Briones B, Adams N, Strauss M, et al. Relationship between sleepiness and general health status. *Sleep*. 1996;19(7):583–588.
32. McDaid C, Griffin S, Weatherly H, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. *Health Technol Assess*. 2009;13(4): iii-iv, xi-xiv, 1-119, 143–274.
33. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ*. 2013;14(5):749–759.
34. Lo SH, Lloyd A, Elkhailifa S, Siscic Z, van Nooten FE. Time trade-off utilities for hereditary angioedema health and caregiver states. *Pharmacoecon Open*. 2022; 6(2):231–239.
35. Aristides M, Barlev A, Barber B, Gijssen M, Quinn C. Population preference values for health states in relapsed or refractory B-precursor acute lymphoblastic leukemia in the United Kingdom. *Health Qual Life Outcomes*. 2015;13(1):181.
36. Iqbal I, Dasgupta B, Taylor P, Heron L, Pilling C. Elicitation of health state utilities associated with differing durations of morning stiffness in rheumatoid arthritis. *J Med Econ*. 2012;15(6):1192–1200.
37. Matza LS, Boye KS, Feeny DH, Johnston JA, Bowman L, Jordan JB. Impact of caregiver and parenting status on time trade-off and standard gamble utility scores for health state descriptions. *Health Qual Life Outcomes*. 2014; 12(1):48.

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