Sleep-wake patterns in patients with cirrhosis: all you need to know on a single sheet

A simple sleep questionnaire for clinical use

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Abbreviations:

PSQI: Pittsburgh Sleep Quality Index; ROC: Receiving Operator Characteristic curve;

STSQS: Sleep Timing and Sleep Quality Screening questionnaire

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Background/Aims: Sleep-wake abnormalities are common in patients with cirrhosis but their evaluation is time consuming and laborious. The aim of this study was to assess the validity of a simple Sleep Timing and Sleep Quality Screening questionnaire (STSQS) against an established sleep questionnaire and daily sleep diaries.

Methods: The study population comprised 87 patients with cirrhosis and 19 healthy volunteers. All participants completed the STSQS (*sleep quality* score range 1-9) and the Pittsburgh Sleep Quality Index (PSQI; total score range: 0-21; scores >5 identify ‘poor’ sleepers); a subgroup of 35 patients and 12 healthy volunteers also kept daily sleep diaries for 2 weeks.

Results: Patients slept significantly less well than the healthy volunteers (total PSQI score: 8.4 ± 4.9 vs. 4.6 ± 2.5 , $p < 0.01$; STSQS *sleep quality* score: 4.8 ± 2.1 vs. 3.6 ± 1.4 , $p = 0.02$). Significant correlations were observed between the STSQS *sleep quality* score and the PSQI total score (healthy volunteers: $R = 0.75$, $p < 0.01$; patients: $R = 0.74$, $p < 0.01$). STSQS *sleep quality* thresholds were identified, which separated individuals classified as ‘poor’/‘good’ sleepers on the basis of the PSQI (healthy volunteers: STSQS *sleep quality* >4: sensitivity 75%, specificity 93%; patients: STSQS *sleep quality* >3: sensitivity 83%, specificity 70%). The STSQS provided estimates of habitual sleep timing variables which did not significantly differ from the average data recorded in the sleep diaries, although more variability was observed in the patients.

Conclusions: The STSQS provides acceptable estimates of *sleep quality* and *sleep timing* and could be used to identify patients with cirrhosis whose sleep behaviour might require further assessment.

1. Introduction

Approximately two-thirds of patients with cirrhosis report sleep-wake abnormalities [1-3], manifest as disturbed night sleep, delayed sleep habits and excessive day-time sleepiness [1,3]. These abnormalities are known to significantly affect quality of life [4]. Nevertheless, specific enquiry about sleep behaviour is rarely included in the clinical assessment of patients with cirrhosis, most likely reflecting the fact that the currently available sleep-wake evaluation tools are time consuming and laborious to use.

Subjective sleep disturbance is usually assessed using retrospective questionnaires and sleep diaries [5]. However, difficulties can arise in their use in the elderly and the infirm, who often require assistance in interpreting and answering long strings of questions - over 150 for the most comprehensive questionnaires [6] - and in collecting repeat diary data in an organised and accurate fashion. In addition, both questionnaires and diaries take time to review and to score. Objective assessment techniques such as polysomnography or actigraphy are utilised as second-line investigations and only in 10-25% of patients with sleep-wake disturbance, even in specialists centres [5].

Several sleep centres, for example the Centre for Chronobiology of the University of Surrey, have developed simplified questionnaires or semi-structured interviews, for use as a prelude to a more formal assessment of sleep behaviour [5]. The Sleep Timing and Sleep Quality Screening questionnaire (STSQS) [7] is one such tool and, if validated in patients with cirrhosis, would allow their sleep problems to be formally documented and then, perhaps, better addressed.

The aim of this study was to validate the STSQS against a standard sleep quality questionnaire and a set of daily sleep diaries in patients with cirrhosis and in age-matched healthy volunteers.

1. Patients and Methods

1.1 Study Subjects

The patient population comprised 87 individuals (51 men: 36 women) of mean (range) age 58 (34-80) years, with biopsy-proven cirrhosis. The aetiology of the liver disease was determined on the basis of clinical, laboratory, radiological and histological variables (alcohol-related: 66 [76%] patients, alcohol plus hepatitis C: six [7%], non-alcohol related: 15 [17%]). The functional severity of the liver injury was assessed using Pugh's modification of the Child's grading system [8] (Child's class A: 59 [68%] patients; B: 16 [18%], C: 12 [14%]). Patients were excluded from the study if they were under 20 or over 80 years of age, could not speak English or comply with the study procedures, had misused alcohol in the preceding six months, had severe overt hepatic encephalopathy, a history of insulin-dependent diabetes mellitus, significant head injury, cardio-vascular/cerebro-vascular disease, arterial hypertension or significant psychiatric co-morbidity, or were taking neuroactive drugs or drugs known to affect sleep.

The reference population comprised 19 healthy volunteers (12 men: 7 women) of mean age 53 (32-85) years. None had a history, clinical or laboratory evidence of alcohol misuse, chronic liver disease or neurological/psychiatric disturbances; none drank alcohol in excess of 20 g/day or took prescription medications.

1.2 Sleep wake profile

All subjects were asked to complete:

- The STSQS [7] (Figure 1). This questionnaire provides a simple, overall assessment of *sleep quality* rated on a 1 to 9 analogue scale (1 = best, 9 = worst sleep ever) and allows collection of information on habitual *sleep timing* (bed-time, sleep latency, night awakenings, wake-up and get-up time). No attempt is made to differentiate week from

week-end days or to account for atypical nights. [The STSQS takes 1-2 min to complete with no additional time needed for scoring.](#)

- The Pittsburgh Sleep Quality index (PSQI) questionnaire [9]. This validated tool is used to assess sleep quality and sleep disturbances over the preceding month, and to differentiate ‘good’ from ‘poor sleepers’ [9,10]. Questionnaire responses to 19 questions are used to generate seven components, each of which is scored from zero to three, where three represents the negative extreme. These component scores are then summated to provide the total PSQI score (range: 0-21); scores of >5 identify ‘poor sleepers’ [9,10]. [The PSQI takes approximately 10 min to complete and 5 min to score.](#)

A subgroup of 35 patients (mean age, 56 [39 - 80] yr) and 12 healthy controls (58 [32 - 84] yr) were also asked to keep individual sleep diaries for 15 consecutive days, recording *bed-time*, *the time they started trying to sleep*, *sleep onset time*, *night awakenings*, *wake-up* and *get-up times* and the *number of naps* taken during the following day [7]. [Each sleep diary takes the patient 3-5 minutes/day to complete and a set of 15 diaries takes the clinician 10-15 min to process.](#)

The *sleep quality* information obtained from the STSQS analogue scale was compared to the PSQI total score, while the *sleep timing* parameters obtained from the STSQS were compared with corresponding data from the sleep diaries, averaged over the 2-week collection period.

1.3 Statistical Analysis

The distributions of variables were tested for normality using the Shapiro-Wilk’s W test. Differences between normally/non-normally distributed variables were examined by the Student’s t/Mann-Whitney U test. Categorized indices were compared by the Pearson’s χ^2 . Correlations between variables were tested using the Spearman’s R. Receiving operator characteristic (ROC) curves were used to define an SQSTS sleep quality threshold equivalent

to that available for the total PSQI score (PSQI >5: 'poor sleepers'). The agreement between estimates of habitual *sleep timing* obtained from the STSQS and from the sleep diaries were assessed using Bland and Altman plots [11]. Analyses were undertaken using the Statistica version 6.0 (StatSoft, Inc., Tulsa, OK, USA) and MedCalc® version 9.5.2.0 (MedCalc Software, Mariakerke, Belgium) packages. Data are expressed, unless otherwise stipulated, as mean $\pm$ 1SD.

1.4 Ethics

The protocol was approved by the Royal Free Hampstead NHS Trust Ethics Committee. All participating subjects provided written, informed consent. The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European) guidelines.

2. Results

2.1 Sleep quality

PSQI data were obtained from 19 (100%) of the healthy volunteers and 81 (93%) of the patients with cirrhosis, while STSQS *sleep quality* data were obtained from 18 (95%) of the healthy volunteers and 87 (100%) of the patients.

The patients slept significantly less well than the healthy volunteers (PSQI total score: 8.4 ± 4.9 vs. 4.6 ± 2.5 , $p < 0.01$; PSQI total score > 5 : 67% vs. 21%; $\chi^2 = 13.1$, $p < 0.001$; STSQS *sleep quality* score: 4.8 ± 2.1 vs. 3.6 ± 1.4 , $p = 0.02$).

Significant correlations were observed between the STSQS *sleep quality* score and the total PSQI score in both the healthy volunteers and the patients with cirrhosis ($R = 0.75$, $p < 0.01$; $R = 0.74$, $p < 0.01$, respectively). Individuals classified as ‘poor sleepers’ (PSQI total score > 5) had significantly higher STSQS *sleep quality* scores than their counterparts classified as ‘good’ sleepers (PSQI total score < 5) both amongst the healthy volunteers (4.6 ± 1.4 vs. 2.7 ± 0.7 , $p < 0.01$; Figure 2), and the patients with cirrhosis (5.4 ± 2.0 vs. 3.2 ± 1.6 , $p < 0.001$; Figure 2).

In the healthy volunteers, a STSQS *sleep quality* threshold of > 4 differentiated ‘poor’ from ‘good sleepers’ with a sensitivity of 75% and a specificity of 93% (Figure 3A). In the patients with cirrhosis, a threshold of > 3 discriminated ‘poor’ from ‘good sleepers’ with a sensitivity of 83% and a specificity of 70% (Figure 3B). In the healthy volunteers, the patient-derived threshold of > 3 had a sensitivity of 75% and a specificity of 71%, while in the patients, the healthy volunteer-derived threshold of > 4 had a sensitivity of 72% and a specificity of 81%. The areas under the ROC curves were comparable in the healthy volunteers and the patients with cirrhosis (0.87 [95% confidence interval: 0.62-0.98]; 0.82 [0.72-0.89], $p = 0.73$).

2.2 Sleep timing

On average, 12 (range 9-15) individual, complete sleep diaries were obtained from the healthy volunteers and 12 (3-15) from the patients with cirrhosis. STSQS *sleep timing* data were obtained from 11 (92%) of the healthy volunteers and 35 (100%) of the patients. Approximately 25% of both the healthy controls and the patients misinterpreted the STSQS question on *wake-up time*, and provided one or more wake-up times for the night awakenings, rather than a morning wake-up time; the responses to this individual question could not be utilised.

Sleep timing parameters were generally delayed in the patients compared to the healthy volunteers (Table); *wake-up* and *get-up* times occurred significantly later (sleep diary averages: 7.6 ± 1.7 vs. 6.5 ± 1.5 hr, $p < 0.05$; 8.1 ± 1.8 vs. 6.9 ± 1.6 hr, $p < 0.05$, respectively).

In the healthy volunteers, the estimates of the mean *bed-time*, *sleep latency*, *wake-up time* and *get-up time* obtained from the STSQS did not differ significantly from the average data recorded in the sleep diaries (Table); for example, the mean of the difference in *bed-time* estimates was -0.27 ± 0.26 hr (limits of agreement, -0.79 to 0.25 hr; Table). More variability was observed between estimates in the patients with cirrhosis. Thus, the mean of the difference in *bed-time* was -0.47 ± 0.66 hr (limits of agreement, -1.76 to 0.82 hr; Table). The differences were generally in the same direction in the healthy volunteers and the patients and did not exceed 0.5 hr for time variables (Table). The *number of night awakenings* obtained from the STSQS was slightly overestimated compared to the sleep diaries by both the healthy volunteers and the patients (Table; Figure 4); in the healthy volunteers, there was a positive correlation between the difference and the average of the two estimates ($R = 0.76$, $p < 0.01$), indicating a tendency to overestimate the number of awakenings the more frequent their occurrence (Figure 4).

3. Discussion

3.1 Sleep quality

The prevalence of sleep disturbance in patients with cirrhosis was high, with almost 70% classified as ‘poor sleepers’ using the PSQI. This is in line with previous reports, albeit based on different assessment tools [1-3].

The STSQS *sleep quality* estimates correlated significantly with those obtained using the more complex PSQI questionnaire. Acceptable STSQS *sleep quality* thresholds were identified, which separated individuals classified as ‘poor’ or ‘good sleepers’ on the basis of the PSQI score. Although these thresholds were different in the healthy volunteers (STSQS *sleep quality* >4) and the patients (STSQS *sleep quality* >3), their specificity/sensitivity profiles and the fact that the areas under the two ROC curves were similar suggest that a threshold of ≥ 4 would be acceptable in both populations.

3.2 Sleep timing

In general, patients had delayed sleep habits compared to the healthy volunteers, which is also in line with previous findings [1].

The *sleep timing* estimates obtained from the STSQS did not differ substantially from those obtained from the sleep diaries, varying, on average, by less than 30 minutes. In general, the STSQS provided earlier estimates for *bed-time*, *wake-up time* and *get-up times*, shorter estimates of *sleep latency* and higher estimates of the *number of night awakenings*.

3.3 Strengths and weaknesses of the study

Overall, no difficulties were encountered in use of the STSQS, except in relation to the question ‘*What time do you usually wake-up?*’. This question was misinterpreted by approximately 25% of both the healthy controls and the patients, probably because it immediately followed the question ‘*How many times do you usually wake up?*’ However,

sufficient numbers of subjects answered the question correctly to allow for meaningful comparisons with the wake-up time data obtained from the diaries. Rephrasing the question to read: '*What time do you usually wake-up in the morning?*' would obviate this difficulty.

The patients included in the study were all relatively well and hence the completion rates for the PSQI and the diaries were high. This means that the validity of the STSQS was not tested comprehensively. It is likely that the completion rates of the PSQI and sleep diaries would be much lower in more compromised patients and that, under these circumstances, use of the STSQS might allow capture of otherwise unavailable data. However, this supposition was not tested directly.

No quantitative sleep measures were utilised for validation of the subjective data. While this could be seen as a limitation, *subjective* and *objective* sleep measures are complementary in defining sleep disturbance and quantitative tools are no longer used as the standard against which to judge patients' subjective observations [10]. Thus, the STSQS, a subjective sleep index, was compared exclusively with the subjective sleep measures it is intended to replace.

These minor limitations aside, the main strength of the study is that the proposed tool is comprehensive, despite its simplicity, and likely to be widely applicable. In addition, it is self-explanatory and no scoring is required. These characteristics may facilitate its use amongst physicians managing patients with cirrhosis, who are unlikely to engage with more complex methods for evaluating sleep disturbance.

3.4 Study implications

Although it is known that sleep-wake disturbances severely impinge on the quality of life and psychological well-being of patients with cirrhosis [2, 4] they are under-diagnosed and generally poorly managed. Treatment with common hypnotics, such as benzodiazepines, should be avoided in these patients because impaired hepatic disposition may result in

accumulation and over-sedation and because some patients may show increased cerebral sensitivity to psychoactive medication. However, other measures to aid sleep can and should be considered, including sleep/light hygiene practices and, where indicated, chronotherapy, which involves the timed administration of light and/or melatonin [12]. Further elucidation of the mechanisms of the sleep disturbances in patients with cirrhosis may, in time, result in the development of more specific therapies.

The proposed questionnaire is simple to use and provides information on both sleep quality and sleep timing. Its use might encourage: *i*) the routine assessment of sleep-wake behaviour in patients with cirrhosis; *ii*) simple counselling to improve sleep hygiene, for example enforced wake-up times and exposure to natural light in the morning, particularly in the subset of patients with cirrhosis who exhibit both impaired sleep quality and delayed sleep habits [1, 4, 13]; and *iii*) onward referral to specialist services, if available.

The effects of the measures described to improve sleep disturbances have not been systematically tested in patients with cirrhosis but they have been successfully applied in other contexts [12]; they are certainly worthy of both direct application and further formal investigation.

3.5 Conclusions

The STSQS provided useful estimates of *sleep quality* and *sleep timing* in both healthy volunteers and in patients with cirrhosis. This simple questionnaire could be used as a screening tool to identify individuals whose sleep-wake behaviour requires formal assessment. In addition, it could be used to undertake repeat evaluations in treatment trials.

Figure Legends

Figure 1. Sleep Timing and Sleep Quality Screening questionnaire (STSQS).

Figure 2. Comparison of the mean Sleep Timing Sleep Quality Screening (SQSTS) *sleep quality* scores in subjects classified as ‘good sleepers’ (Pittsburgh Sleep Quality Index [PSQI] ≤ 5) or ‘poor sleepers’ (PSQI >5).

Middle point: mean; boxes: $\pm$ standard error; whiskers: $\pm$ standard deviation

Figure 3. Receiving operator characteristic (ROC) curves indicating ($\square$) the maximum specificity/sensitivity Sleep Quality and Sleep Timing Screening (STSQS) *sleep quality* threshold separating ‘good’ (Pittsburgh Sleep Quality Index [PSQI] ≤ 5) from ‘poor sleepers’ (PSQI >5) in healthy volunteers (**A**) and patients with cirrhosis (**B**).

Figure 4. Bland and Altman plot of the *number of night awakenings* reported on the Sleep Quality and Sleep Timing Screening (STSQS) and in the sleep diaries in the healthy volunteers and in the patients with cirrhosis. The differences and the averages were significantly correlated in the healthy volunteers, who tended to overestimate the number of awakenings on the STSQS, as these increased.

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