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Digital cognitive behavioural therapy for insomnia (*Sleepio*) is associated with gains in quality-adjusted life years.

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Title: Digital cognitive behavioural therapy for insomnia (*Sleepio*) is associated with gains in quality-adjusted life years.

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Abstract (250 words)

Background: Insomnia is common, and difficulty with daytime functioning is a core symptom. Studies show cognitive behavioural therapy (CBT) improves functioning, but evidence is needed on its value for money. Quality-adjusted life years (QALYs), capturing length and quality of life, provide a standard metric by which to judge whether a treatment is worth its cost. Studies have found QALY gains with therapist-delivered and therapist-guided CBT, but most have not reached statistical significance. Estimates of QALY gains with fully automated digital CBT (dCBT) for insomnia are lacking.

Aim: To assess whether dCBT [*Sleepio*] for insomnia is associated with gains in QALYs compared with a sleep hygiene education control.

Design & setting: A secondary analysis of a large effectiveness trial of 1,711 participants from the UK, US and Australia.

Method: EQ-5D scores, NICE's preferred measure of health-related quality of life, were predicted (mapped) from PROMIS-10 Global Health scores and used to determine QALYs from baseline to 24-weeks (controlled), and to 48-weeks (uncontrolled).

Results: At week-24, QALYs were significantly higher for the dCBT group (mean QALYs 0.375 and 0.362 in the dCBT and control groups respectively, mean difference=0.014 [95%CI=0.008, 0.019]), and this difference was maintained over the 48-week study period (0.026 [0.016, 0.036]). The difference of 0.026 QALYs is equivalent to 9.5 days in perfect health.

Conclusion: *Sleepio* is associated with statistically significant gains in QALYs over time compared with control. Findings may be used to power future studies and inform cost-effectiveness analyses of automated dCBT for insomnia scaled to a population level.

How this fits in: *Sleepio,* a fully automated digital cognitive behavioural therapy (CBT) programme for insomnia has been recommended as a clinically effective and cost-effective treatment for insomnia by NICE. Previous studies have found gains in QALYs with therapist-delivered and therapist-guided CBT for insomnia, but in most reports, these gains have not been found to be statistically significant. This is a concern as CBT is recommended as the first line treatment. In this report using data from a large effectiveness trial, we find that *Sleepio* is associated with statistically significant gains in QALYs, equivalent to 9.5 days in perfect health.

Keywords (six and different to title/abstract):
Insomnia; cognitive behavioural therapy, health related quality of life, quality-adjusted life years, sleep, health economics.

Introduction

Insomnia is common with symptoms affecting up to 30% of the population (1). As a disorder, it is characterised by persistent difficulty initiating and/or maintaining sleep, or early-morning awakening with an inability to return to sleep (2). For a diagnosis to be made, individuals must also experience significant impairment to daytime functioning. Typical impacts are upon mood, fatigue, concentration, or memory across different settings (e.g., social, occupational). It has been recognised for some time that insomnia and its consequences negatively impact both physical and mental health dimensions of health-related quality of life (HRQoL) (3,4). Indeed, real-world research suggests that insomnia is associated with a 10% reduction in HRQoL when compared with people who do not have insomnia (4).

Quality-adjusted life years (QALYs), calculated from HRQoL measures, are commonly used in economic evaluations of therapeutic interventions (5). A QALY is a composite measure of length and quality of life that can be used to compare outcomes across a broad range of disease areas and patient groups and are used by the UK National Institute for Health and Care Excellence (NICE) to evaluate whether a treatment represents good value for money (6). In short, QALYs therefore provide a standard metric by which to judge whether a treatment is worth the cost.

Previous studies have used QALYs to evaluate the cost-effectiveness of therapist-delivered and therapist-guided CBT for insomnia. Gains in QALYs have been observed but were not found to be statistically significant (7,8). This is a concern given that CBT is recommended as the first line treatment for insomnia by the British Association of Psychopharmacology (9), and the American College of Physicians (10). *Sleepio*, a fully-automated digital CBT (dCBT) based treatment for insomnia, has been recommended by NICE as cost saving (11) by reducing Primary Care costs through fewer GP appointments and sleeping pills prescribed (12). Patients in England usually receive advice about sleep hygiene education (a set of behavioural recommendations to help promote better sleep (13)) or sleeping pills for their insomnia (14,15). NICE recommends a referral for face-to-face CBT-I but highlighted that this is not routinely available on the NHS for most people with insomnia and so recommends *Sleepio* because it costs less, is scalable to the population and may be non-inferior to face-to-face CBT (11). Given that *Sleepio* has the potential to be a cost-effective treatment for insomnia (16), we were interested to evaluate whether *Sleepio* is associated with statistically significant improvements in QALYs.

In this report, we investigated potential gains in QALYs associated with *Sleepio* using HRQoL data from a published large effectiveness trial comparing *Sleepio* to a sleep hygiene control in 1,711 participants (17). This Digital Insomnia therapy to Assist your Life as well as your Sleep (DIALS) trial observed improvements in insomnia, psychological wellbeing and functional health, which were maintained at 48-weeks follow-up (18). Using these data, we mapped individual participant responses from the PROMIS-10 Global Health Scale to the EQ-5D. The EQ-5D is NICE's preferred measure of HRQoL when calculating QALYs, and encompasses five dimensions of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). Its scores, known as utilities, are based on preferences, so how good or bad each health state is according to the general population (the value set). These utilities were then used to estimate QALYs to evaluate whether dCBT for insomnia resulted in gains to QALYs when compared with a sleep hygiene control.

Methods

We first describe the DIALS trial, and then how we calculated QALYs.

Trial design

This is a secondary analysis of the DIALS trial (ISRCTN 60530898, ethical approval ref: MS-IDREC-C2-2015-024), a large effectiveness clinical trial of 1,711 participants with insomnia recruited online from the UK, US, and Australia. Participants were recruited through online advertisements and contact lists where adults with insomnia volunteered to be involved in research and were randomised to either dCBT (n=853) or sleep hygiene control (n=858) (19). Digital CBT was delivered using *Sleepio*, a fully automated dCBT programme comprising 6 weekly sessions containing cognitive, behavioural, and educational interventions. Content is delivered by an animated personal therapist, and algorithms drive treatment personalisation based on responses to questions and sleep diary data. The study assessed generic HRQoL in participants using the 10-item Patient-Reported Outcomes Measurement Information System: global health scale for physical health (PROMIS-10; (20)) collected in the trial at baseline, 4-, 8-, 24-weeks (both groups), and an uncontrolled follow-up at 36- and 48-weeks for the *Sleepio* group only (18). Items ask generally about overall health, quality of life, physical and mental health, social and physical activities, and fatigue. Items are scored 1 to 5, range: 10-50, with higher scores indicating better overall health.

Calculating Quality-adjusted life years (QALYs)

The EQ-5D is used to generate QALYs, and for this report, individual participant scores from the PROMIS-10 were first mapped to EQ-5D utilities using methods recommended by Thompson et al. (21), building on previous work by Revicki et al. (22). In other words, EQ-5D scores were predicted from PROMIS-10 Global Health scores. Eight items from the PROMIS-10 are used for mapping (general health, physical health, mental health, physical activities, pain (recoded), fatigue, social activities, and emotional problems). Specifically, the model applies equipercentile equating to the predicted values of a linear regression model, where PROMIS-10 items are treated as categorical predictors. Equipercentile equating translates scores from one scale to another by matching their cumulative distribution functions. The mapping by Thompson et al. (21), uses the United States value set for the EQ-5D-3L. The summary index scores (utilities) are then used to compute QALYs.

The QALY profile for each participant from baseline to 24-weeks was estimated, based on the EQ-5D scores, which range from 0 (dead) to 1 (perfect health), and their time points, and the area under the curve of utility measurements was used to calculate the number of QALYs accrued by each participant. QALYs were calculated assuming that each participant's utility changes linearly between each of the time points (baseline, 4-, 8- and 24-weeks). Beyond the controlled comparison to 24-weeks, assumptions were made about the control arm to extend analyses to 48-week using the last observation carried forward. Missing EQ-5D data were first summarised descriptively, and exploratory analyses were conducted to understand possible mechanisms and patterns of missing data. Logistic regressions also explored associations between missingness and baseline variables, and missingness and previously observed EQ-5D scores. We anticipated that multiple imputation would be required to impute missing values. Multiple imputation uses regression to predict *m* values for each missing data cell, based on key (complete and incomplete) variables. In line with guidance, multiple imputation using chained equations was conducted, separately for each treatment group and the number of imputations set to be at least equal to the percentage of incomplete cases (23–25).

Results

We first present the EQ-5D scores (mapped from the PROMIS-10) and QALYs from baseline to 24-weeks, then from 24- to 48-weeks, and finally combine to estimate QALYs from baseline to 48 weeks.

EQ-5D scores and QALYs to 24-weeks

Data completeness and handling of missing data

Overall, 43% of participants (743/1,711) had complete responses to the eight PROMIS-10 Global Health items used to map to the EQ-5D at each timepoint (baseline, 4-, 8-, and 24-weeks). Further details on EQ-5D scores and QALYs to 24-weeks based on observed data can be found in the supplementary material (Table S1). Exploratory analyses of missing data found, in line with the statistical analyses, a number of baseline variables that predict missingness, such as age and gender, and baseline variables which predict QALYs, including baseline EQ-5D. Findings support a missing at random assumption, thus multiple imputation is a flexible and appropriate method for handling the missing data.

Scores from the EQ-5D at 4-, 8-, and 24-weeks were imputed together with baseline EQ-5D, and other baseline variables: age, sex, country, partner status, employment status, smoking status, exercise status, history of heart disease, no comorbidities, other comorbidities and number of comorbidities, separately for each treatment group (see Espie et al., 2019 for details of baseline variables). These baseline variables were included in the regression models since missingness may depend on them. Prediction mean matching with 10 nearest neighbours was used, so based on the variables included, the 10 most similar participants were identified, and the EQ-5D score for one randomly selected participant was assigned to the participant with missing data. The overall percentage of participants with any missing data was 57%, 61% in the dCBT arm and 52% in the control arm. Given this level of missing data, m=61 imputations were conducted.

Results to 24-weeks

Table 1 shows EQ-5D scores and QALYs to 24-weeks in each group, with multiple imputation used to handle missing values. EQ-5D scores are higher in the dCBT arm at each time point, statistically significantly so at weeks 8 and 24. This results in significantly higher QALYs to 24-weeks in the dCBT arm. Note that the maximum number of QALYs that can be gained to 24-weeks by a participant is 0.460 [(24-weeks x 7 days)/365 days in a year].

Insert Table 1 approximately here

EQ-5D scores and QALYs from 24- to 48-weeks

For the dCBT arm, EQ-5D scores at 24-, 36- and 48-weeks were used to calculate QALYs as before and Table S2 in the supplementary material reports the EQ-5D scores and QALYs from 24- to 48-weeks based on observed data. Missing data were imputed in line with methods described above. Given that the control group had access to dCBT from week-24, assumptions had to be made about the EQ-5D scores in the control arm. As mean EQ-5D scores in the control group are the same at weeks-8 and -24 (see Table 1), it was assumed that individual EQ-5D scores at week-24 were carried forward to weeks-36 and -48 for each participant. Table 2 reports the EQ-5D scores and QALYs from 24- to 48-weeks, based on multiple imputation for the dCBT arm, and last observation carried forward for the control arm. This likely underestimates the variability in the control arm (and in the difference between groups). As for baseline to 24-weeks, EQ-5D scores and QALYs from 24- to 48-weeks are significantly higher in the dCBT group.

Insert Table 2 approximately here

QALYs to 48-weeks

Finally, Table 3 combines the previous two analyses, to report QALYs to 48-weeks for both groups. Participants in the dCBT arm had significantly more QALYs overall than the assumed QALYs from participants in the control arm after 48-weeks. The difference of 0.026 QALYs is equivalent to 9.5 days in perfect health when extrapolated to 1 year. It is important to note that we assumed EQ-5D scores, which were used to generate QALYs, were carried forward from the last controlled observation in the study at week-24 to the uncontrolled assessments at week-36 and week-48.

Insert Table 3 approximately here

Discussion

Summary

Fully automated digital CBT (*Sleepio*) for insomnia was associated with statistically significant improvements to QALYs relative to sleep hygiene control over 48-weeks. The difference of 0.026 QALYs is equivalent to 9.5 days in perfect health. Improvements in QALYs are likely due to improved HRQoL with improved insomnia. Results may be used to help power future studies and model the full cost-effectiveness of providing scalable access to first line CBT treatment for insomnia at a national population level.

Strengths and limitations

This study used patient data from a large and well-powered effectiveness trial of dCBT with a long follow-up duration. The mapping undertaken uses equipercentile equating methods, which are preferred over regression-based methods since they avoid the issue of regression to the mean (26). PROMIS-10 items were treated as categorical predictors, not continuous predictors, which was a limitation of previous models. However, a limitation of this work is that the EQ-5D scores results have been estimated from the PROMIS-10 questionnaire rather than measured directly. Furthermore, the mapping by Thompson et al. (21) uses the US value set for the EQ-5D, not the UK value set. In previous work, it has been suggested that the EQ-5D may not be sensitive enough to detect change in quality of life in response to improved symptoms of insomnia and more specific measures of mental health complaints may be considered in future work (7). Further research should now explore whether gains accrue over longer periods of time (12 months+) for both digital and therapist-delivered CBT compared with a control.

Comparison with existing literature

Fully automated dCBT is an effective intervention for insomnia offering sustained benefits to functional health, psychological well-being, and sleep-related quality of life (17,18). This study extends previous findings and demonstrates that automated dCBT is also associated with statistically significant gains in QALYs when compared with a sleep hygiene control over 24-weeks. Gains in QALYs are likely from improved domains of HRQoL and were maintained over time when assessed under assumptions at 48-weeks follow-up. The difference of 0.026 QALYs between-groups is equivalent to 9.5 days in perfect health. Results appear to be the first to demonstrate statistically significant gains to QALYs with an automated dCBT intervention compared with a sleep hygiene control, the most common intervention used in general practice for insomnia management in the UK (14,15). Results may also be useful as they allow researchers to model the cost-effectiveness of dCBT for insomnia when delivered at a population level and compare results with other insomnia treatment options.

Insomnia is associated with reduced HRQoL for domains of physical, mental health, social and emotional functioning (3,4). Successful insomnia treatment can improve functioning associated with HRQoL (3). Symptoms of insomnia, psychological wellbeing and functional health (PROMIS-10) have all been found to improve with dCBT in the participants studied here (17). Findings suggest that gains to insomnia, wellbeing and functional health with dCBT translate to gains in QALYs that are greater than gains from a sleep hygiene control. Results also show that both participants in the dCBT and control group had similar levels of estimated EQ-5D scores at baseline (0.77) and indicate moderate impairment in health status from insomnia disorder. By comparison, mean EQ-5D scores in the UK and US general populations are similar at 0.86 and 0.87, respectively (27). This impairment at

baseline likely reflects reduced HRQoL found previously in those with insomnia (3,4). Previous studies have found gains in QALYs associated with therapist delivered (c.f., Table 2 in Natsky et al. (8) and therapist-guided (7) CBT for insomnia. Improvements to QALYs, however, were statistically significant in only one small study, which examined patients with insomnia and major depressive disorder and mapped QALYs from a depression rating scale (28).

Implications for research and/or practice

It is important to evaluate QALYs associated with dCBT because automated dCBT has the potential to provide access to CBT at a population scale in a cost-effective way. To date, widespread provision of recommended first line CBT for insomnia has not been possible because of a lack of trained therapists. Patients are left with second line sleep medication or ineffective sleep hygiene advice, which is counter to treatment guidelines (9,10). Digital delivery is more scalable and appears to be more cost-effective than therapist delivered CBT as it provides similar benefit at a lower cost (16). *Sleepio* has previously demonstrated cost savings in UK primary care settings, reducing costs by approximately £70.44 per person (12). It is therefore likely to be more cost-effective compared with sleep hygiene advice and face-to-face CBT (estimated by NICE to cost of £542 per person), if priced under £70 per person, as highlighted by NICE in their cost saving recommendation for *Sleepio* (11). Subsequent research should now look to model cost-effectiveness from a societal perspective to further determine pricing. Results may be used to inform future studies that evaluate dCBT with therapist-delivered CBT and medications for insomnia with QALYs for cost-effectiveness in UK settings (16).

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Ethical approval
The DIALS trial (ISRCTN 60530898) obtained ethical approval from the University of Oxford, Medical Sciences Interdivisional Research Ethics Committee ref: MS-IDREC-C2-2015-024.

Competing interests
CBM is employed by Big Health Inc. and is salaried by the company. CAE is the Co-Founder and Chief Scientist of Big Health Inc. and is a shareholder. ALH is employed by Big Health Inc., is salaried by the company and is a shareholder. RS was previously employed by Big Health Inc. EAS has no conflicts of interest.

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Table 1: EQ-5D scores and QALYs to 24-weeks, with multiple imputation used to handle missing values

Outcome	dCBT (*n*=853) Mean (SE)	Control (*n*=858) Mean (SE)	Mean difference (95% CI)
EQ-5D			
Week-0	0.772 (0.004)	0.772 (0.004)	-0.0001 (-0.012, 0.012)
Week-4	0.799 (0.005)	0.785 (0.005)	0.014 (-0.001, 0.028)
Week-8	0.826 (0.005)	0.787 (0.005)	0.039 (0.024, 0.053)*
Week-24	0.820 (0.005)	0.787 (0.005)	0.033 (0.018, 0.048)*
QALYs	0.375 (0.002)	0.362 (0.002)	0.014 (0.008, 0.019)*

dCBT, digital cognitive behavioural therapy; CI, Confidence interval; SE, Standard error
*p<0.05

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Running head (50 characters): Use of the PROMIS-10 to estimate QALYs in dCBT

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Table 2: EQ-5D scores and QALYs from 24- to 48-weeks, with multiple imputation used to handle missing values

Outcome	dCBT (*n*=853) Mean (SE)	Control (*n*=858) Mean (SE)	Mean difference (95% CI)
EQ-5D			
Week-24	0.820 (0.005)	0.787 (0.005)	0.033 (0.018, 0.048)*
Week-36	0.810 (0.006)	0.787 (0.005)	0.023 (0.010, 0.037)*
Week-48	0.817 (0.006)	0.787 (0.005)	0.030 (0.016, 0.043)*
QALYs	0.375 (0.002)	0.362 (0.002)	0.013 (0.007, 0.018)*

dCBT, digital cognitive behavioural therapy; CI, Confidence interval; SE, Standard error
*$p<0.05$

Table 3: QALYs

QALYs	dCBT (*n*=853) Mean (SE)	Control (*n*=858) Mean (SE)	Mean difference (95% CI)
0- to 24-weeks	0.375 (0.002)	0.362 (0.002)	0.014 (0.008, 0.019)*
24- to 48-weeks	0.375 (0.002)	0.362 (0.002)	0.013 (0.007, 0.018)*
0- to 48-weeks	0.750 (0.004)	0.724 (0.003)	0.026 (0.016, 0.036)*

dCBT, digital cognitive behavioural therapy; CI, Confidence interval; SE, Standard error
*p<0.05